

Kaplan's
**Clinical
Hypertension**

**Eleventh
Edition**

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11th edition

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To those such as
Goldblatt and Grollman,
Braun-Menéndez and Page,
Lever and Pickering,
Mancia, Brenner, and Laragh,
Julius, Hansson, and Freis,
and the many others, whose work
has made it possible for us to put
together what we hope will be
a useful book on clinical hypertension.

Hypertension continues to increase in prevalence both in developed and developing countries, thereby expanding its role in cardiovascular and renal morbidity and mortality worldwide.

Two major developments since the 10th edition are (1) percutaneous device-based therapy especially with renal denervation but also carotid baroreceptor pacing and (2) new hypertension guidelines. The surge of publications on both topics has raised more questions than answers and has led to much debate among the experts, which stands to confuse clinicians, patients, and policy makers. What is the future of device-based therapy, which seemed to hold such promise for drug-resistant hypertension? What are the appropriate goals of medication therapy? Do certain groups of patients deserve more intensive or less intensive therapy? We have attempted to address these issues in a fair and balanced manner.

The overall literature about hypertension has grown, perhaps even more than its increased prevalence. A considerable amount of new information is covered in this edition, presented in a manner that we hope enables the reader to grasp its significance and place it in perspective. Almost every page has been revised, using the same goals as reached in previous editions.

- Give more attention to the common problems; the coverage of primary hypertension takes up more than half.
- Cover every form of hypertension at least briefly, providing references for those seeking more information. Additional coverage is provided on topics that have recently assumed greater importance, for example, renal denervation, new hypertension guidelines, and primary aldosteronism.
- Cover the latest published data that we believe are useful to improve diagnosis and treatment.
- Provide enough pathophysiology to permit sound clinical judgment.
- Be objective and identify areas of current controversy.

As before, Dr. Joseph Flynn, head of Pediatric Nephrology at Seattle Children's Hospital, has contributed a chapter on hypertension in childhood and adolescence.

We thank all of the thousands of investigators whose work enables us to compose the 11th edition of this book.

NORMAN M. KAPLAN, M.D.
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Hypertension in the Population at Large

Hypertension continues to be the major risk factor for premature cardiovascular disease (CVD) worldwide (Angeli et al., 2013). Despite steadily increasing understanding of its pathophysiology, the control of hypertension in the United States (U.S.) has improved only minimally in the last decade (Go et al., 2014) while its incidence continues to grow, largely as a consequence of increased longevity. At the same time, levels of blood pressure (BP) above 120/80 mm Hg but below 140/90 mm Hg, i.e., prehypertension, have been found to increase the incidence of stroke (Lee et al., 2011).

The continued clinical importance of hypertension is reflected in the numerous guidelines composed by expert committees published in 2013–2014 (Go et al., 2013; Hackam et al., 2013; James et al., 2014; Mancia et al., 2013; Shimamoto et al., 2014; Weber et al., 2014). As useful as these are, they need to be integrated with guidelines for other cardiovascular (CV) risks. As written by Peterson et al. (2014): “There is an important need to create a national consensus group to draft an updated comprehensive practice guideline that would harmonize the hypertension guideline with other CV risk guidelines and recommendations, thereby resulting in a more coherent overall CV prevention strategy. This group should include representatives from multiple specialties and primary care disciplines, should follow the Institute of Medicine recommendations for guideline development, and should cover the full range of CV care topics, to develop an integrated approach for prevention, detection, and evaluation, along with treatment goals. Individual recommendations from discrete guidelines—such as for hypertension, cholesterol, and obesity—do not reflect the integrated care needed for many patients seen in practice.”

Although most of this book addresses hypertension in the U.S. and other developed countries, it should

be noted that CVDs are the leading cause of death worldwide, more so in the economically developed countries, but also in the developing world (Angeli et al., 2013). As Lawes et al. (2008) note: “Overall about 80% of the attributable burden (of hypertension) occurs in low-income and middle-income economies.”

In turn, hypertension is, overall, the major contributor to the risks for CVDs. In the U.S., hypertension is by far the most prevalent attributable risk factor for CVD mortality, estimated to contribute 40.6% of the total (Go et al., 2014). When the total global impact of known risk factors on the overall burden of disease is calculated, 54% of stroke and 47% of ischemic heart disease (IHD) are attributable to hypertension (Lawes et al., 2008). Of all the potentially modifiable risk factors for myocardial infarction in 52 countries, hypertension is exceeded only by smoking (Danaei et al., 2009).

The growing prevalence of hypertension has been documented in the ongoing survey of a representative sample of the adult U.S. population, the National Health and Nutrition Examination Survey (NHANES), as rising from 24.4% of the adult population in 1990 to 29.1% in 2012 (Nwankwo et al., 2013).

The striking impact of aging was seen among participants in the Framingham Heart Study: Among those who remained normotensive at either age 55 or 65 (providing two cohorts) over a 20-year follow-up, hypertension developed in almost 90% of those who were now aged 75 or 85 (Vasan et al., 2002).

The impact of aging and the accompanying increased prevalence of hypertension on both stroke and IHD mortality has been clearly portrayed in a meta-analysis of data from almost one million adults in 61 prospective studies by the Prospective Studies Collaboration (Lewington et al., 2002). As seen in Figure 1-1, the absolute risk for IHD mortality was

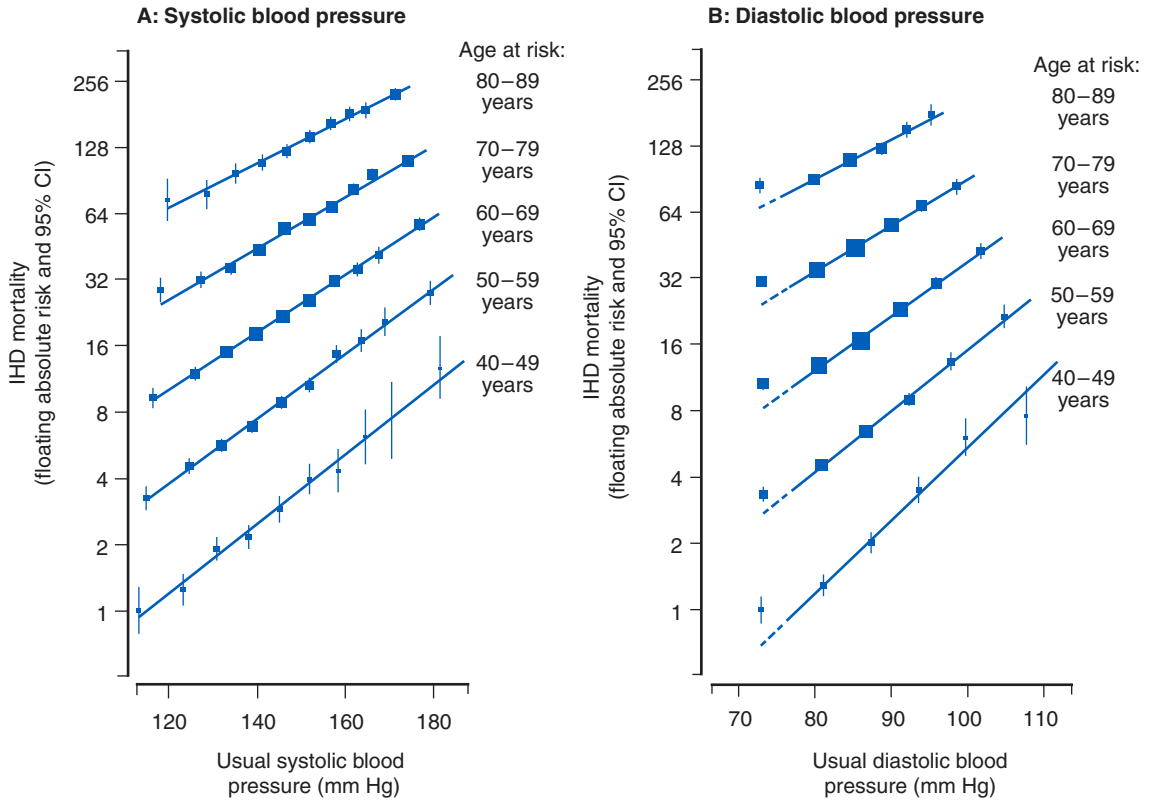


FIGURE 1-1 • Ischemic heart disease (IHD) mortality rate in each decade of age plotted for the usual systolic (A) and diastolic (B) BPs at the start of that decade. Data from almost one million adults in 61 prospective studies. (Modified from Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–1913.)

increased at least twofold at every higher decade of age, with similar lines of progression for both systolic and diastolic pressure in every decade.

Fortunately, there has been a steadily improving rate of control of hypertension in the U.S. (Table 1-1). However, the rates of adequate control remain lower

in both black and Mexican-American men than among non-Hispanic white males in the U.S. (Go et al., 2014). Moreover, the rate of improved control has been slower over the last decade worldwide (Mancia, 2013). And of even greater concern, even when hypertensives are treated down to an optimal

TABLE 1-1

Trends in Awareness, Treatment, and Control of High Blood Pressure in U.S. Adults (Over Age 20) 1976–2004

National Health and Nutrition Examination Survey (%)

	1976–1980	1988–1991	1991–1994	2000–2004	2005–2006	2011–2012
Awareness	51	73	68	70	79	83
Treatment	31	55	54	59	61	76
Control ^a	10	29	27	34	45	52

The data are for adults aged 18 and over with systolic pressure ≥ 140 mm Hg and/or diastolic pressure ≥ 90 mm Hg.

^aControl is defined as a systolic pressure below 140 mm Hg and a diastolic pressure below 90 mm Hg.

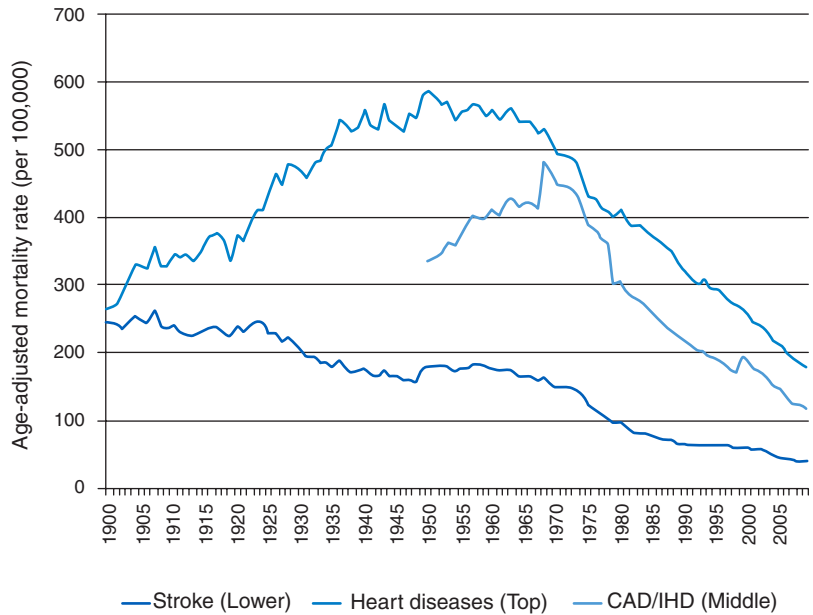


FIGURE 1-2 • Stroke and heart disease mortality rates per 100,000 population for the U.S., 1900–2005, standardized to the U.S. 2000 standard population. (Reproduced from Lackland DT, Roccella EJ, Deutsch AF, et al. Factors influencing the decline in stroke mortality: A statement from the American Heart Association/American Stroke Association. *Stroke* 2014;45(1):315–353.)

level, below 120/80 mm Hg, they continue to suffer a greater risk of stroke than do normotensives with similar optimal BP levels (Asayama et al., 2009).

Nonetheless, as shown in Figure 1-2, impressive reductions in mortality from both coronary disease and stroke have continued, even if these are largely attributable to improved management after they occur rather than decreases in their incidence (Vaartjes et al., 2013).

On the other hand, the ability to provide protection against stroke and heart attack by antihypertensive therapy in those who have hypertension has been overwhelmingly documented (Blood Pressure Lowering Treatment Trialists' Collaboration, 2008). There is no longer any argument as to the benefits of lowering BP, though there is insufficient evidence to document the benefit of treating otherwise healthy people with BP from 140/90 to 160/100 mm Hg, i.e., stage 1 hypertension (Diao et al., 2012) giving rise to papers such as “Waste and Harm in the Treatment of Mild Hypertension” (Heath, 2013). Meanwhile, the unraveling of the human genome gave rise to the hope that gene manipulation or transfer could prevent hypertension. As of now, that hope seems extremely unlikely beyond the very small number of patients with monogenetic defects that have been discovered, since at least 28 genes have been shown to contribute to BP variation (Arnett and Claas, 2012).

This book summarizes and analyses the works of thousands of clinicians and investigators worldwide who have advanced our knowledge about the

mechanisms behind hypertension and who have provided increasingly effective therapies for its control. Despite their continued efforts, however, hypertension will almost certainly not ever be conquered totally, because it is one of those diseases that, in the words of a *Lancet* editorialist over 20 years ago (Anonymous, 1993):

...afflict us from middle age onwards [that] might simply represent “unfavorable” genes that have accumulated to express themselves in the second half of our lives. This could never be corrected by any evolutionary pressure, since such pressures act only on the first half of our lives: once we have reproduced, it does not greatly matter that we grow “sans teeth, sans eyes, sans taste, sans everything.”

Since hypertension likely cannot be prevented by genetic manipulations, the need for improvements in lifestyle that would reduce population-wide levels of BP as little as 2 mm Hg such as moderate reduction in sodium (The Executive Board of the World Hypertension League, 2014) would provide major improvements in CV health (Go et al., 2014).

In this chapter, the overall problems of hypertension for the population at large are considered. We define the disease, quantify its prevalence and consequences, classify its types, and describe the current status of detection and control. In the remainder of the book, these generalities will be amplified into practical ways to evaluate and treat hypertension in its various presentations.

CONCEPTUAL DEFINITION OF HYPERTENSION

As seen in Figure 1-1, mortality from IHD begins to rise from the lowest levels recorded in the overall population, 115/75 mm Hg, to a doubling of mortality at 140/90 mm Hg. Therefore, why is “hypertension” universally considered to begin at 140/90 mm Hg? That number apparently arose from actuarial data from the 1920s showing a doubling of mortality from CVD at that level (Society of Actuaries, 1959). The arbitrariness of that view was challenged by Sir George Pickering who decried the search for an arbitrary dividing line between normal and high BP. In 1972, he restated his argument: “There is no dividing line. The relationship between arterial pressure and mortality is quantitative; the higher the pressure, the worse the prognosis.” He viewed arterial pressure “as a quantity and the consequence numerically related to the size of that quantity” (Pickering, 1972).

However, as Pickering realized, physicians feel more secure when dealing with precise criteria, even if the criteria are basically arbitrary. To consider a BP of 138/88 mm Hg as normal and one of 140/90 mm Hg as high is obviously arbitrary, but medical practice requires that some criteria be used to determine the need for workup and therapy. The criteria should be established on some rational basis that includes the risks of disability and death associated with various levels of BP as well as the ability to reduce those risks by lowering the BP. As stated by Rose (1980): “The operational definition of hypertension is the level at which the benefits... of action exceed those of inaction.”

Even this definition should be broadened, because action (i.e., making the diagnosis of hypertension at any level of BP) involves risks and costs as well as benefits, and inaction may provide benefits. These are summarized in Table 1-2. Therefore, the conceptual definition of hypertension should be that level of BP at which the benefits (minus the risks and costs) of action exceed the risks and costs (minus the benefits) of inaction.

Most elements of this conceptual definition are fairly obvious, although some, such as interference with lifestyle and risks from biochemical side effects of therapy, may not be. Let us turn first to the major consequence of inaction, the increased incidence of premature CVD, because that is the prime, if not the sole, basis for determining the level of BP that is considered abnormal and is called *hypertension*.

TABLE 1-2

Factors Involved in the Conceptual Definition of Hypertension

Action	Benefits	Risks and Costs
Action	Reduce risk of CVD, debility, and death	Assume psychological burdens of “the hypertensive patient” Interfere with QOL
	Decrease monetary costs of catastrophic events	Require changes in lifestyle Add risks and side effects from therapy Add monetary costs of health care
Inaction	Preserve “nonpatient” role	Increase risk of CVD, debility, and death
	Maintain current lifestyle and QOL	
	Avoid risks and side effects of therapy	Increase monetary costs of catastrophic events
	Avoid monetary costs of health care	

Risks of Inaction: Increased Risk of CVD

The risks of elevated BP have been determined from large-scale epidemiologic surveys. As seen in Figure 1-1, the Prospective Studies Collaboration (Lewington et al., 2002) obtained data on each of 958,074 participants in 61 prospective observational studies of BP and mortality. Over a mean time of 12 years, mortality during each decade of age at death was related to the estimated usual BP at the start of that decade. The relation between usual systolic and diastolic BP and the absolute risk for IHD mortality is shown in Figure 1-1. From ages 40 to 89, each increase of 20 mm Hg systolic BP or 10 mm Hg diastolic BP is associated with a twofold increase in mortality rates from IHD and more than a twofold increase in stroke mortality. These proportional differences in vascular mortality are about half as great in the 80 to 89 decade as they are in the 40 to 49 decade, but the annual absolute increases in risk are considerably greater in the elderly. As is evident from the straight lines in Figure 1-1, there is no evidence of a threshold wherein BP is not directly related to risk down to as low as 115/75 mm Hg.

As the authors conclude: “Not only do the present analyses confirm that there is a continuous relationship with risk throughout the normal range of usual BP, but they demonstrate that within this range the usual BP is even more strongly related to vascular mortality than had previously been supposed.” They conclude that a 10 mm Hg higher than usual systolic BP or 5 mm Hg higher than usual diastolic BP would, in the long term, be associated with about a 40% higher risk of death from stroke and about a 30% higher risk of death from IHD.

These data clearly incriminate levels of BP below the level usually considered as indicative of hypertension, i.e., 140/90 mm Hg or higher. Data from the closely observed participants in the Framingham Heart Study confirm the increased risks of CVD with BP levels previously defined as *normal* (120 to 129/80 to 84 mm Hg) or *high-normal* (130 to 139/85 to 89 mm Hg) compared to those with *optimal* BP (<120/80 mm Hg) (Vasan et al., 2001).

A similar relation between the levels of BP and CVDs has been seen worldwide (Lim et al., 2012) with an even stronger association for stroke (Feigin

et al., 2014). Some of these differences in risk and BP levels can be explained by obvious factors such as socioeconomic differences and variable access to health care (Victor et al., 2008; Wilper et al., 2008).

Beyond the essential contribution of BP per se to CV risk, a number of other associations may influence the relationship.

Gender and Risk

The Prospective Studies Collaboration found the age-specific associations of IHD mortality with BP to be slightly greater for women than for men and concluded that “for vascular mortality as a whole, sex is of little relevance” (Lewington et al., 2002). In the U.S., women over age 65 have a higher prevalence of hypertension than do men (Go et al., 2014).

Race and Risk

As shown in Figure 1-3, U.S. blacks tend to have higher rates of hypertension than do nonblacks (Go et al., 2014), and overall hypertension-related

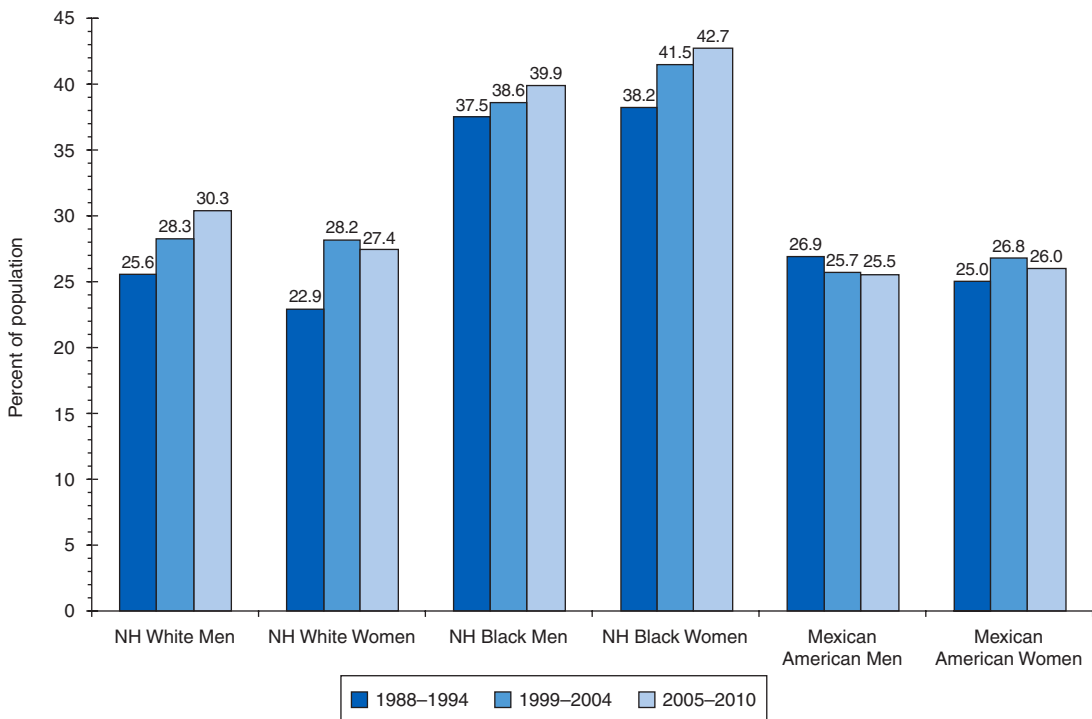


FIGURE 1-3 • Age-adjusted prevalence trends for high BP in adults ≥ 20 years of age by race/ethnicity, sex, and survey (National Health and Nutrition Examination Survey: 1988–1994, 1999–2004, and 2005–2010). NH indicates non-Hispanic. Source: National Center for Health Statistics and National Heart, Lung and Blood Institute. On behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. (From Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: A report from the American Heart Association. *Circulation* 2014;129:e28–e292.)

mortality rates, particularly for stroke, are higher among blacks (Lackland et al., 2014).

The greater risk of hypertension among blacks suggests that more attention must be given to even lower levels of hypertension among this group, but there seems little reason to use different criteria to diagnose hypertension in blacks than in whites. The special features of hypertension in blacks are discussed in more detail in Chapter 4.

The relative risk of hypertension differs among other racial groups as well. In particular, hypertension rates in U.S. Hispanics of Mexican origin are lower than those in whites (Go et al., 2014). In keeping with their higher prevalence for obesity and diabetes, U.S. Hispanics have lower rates of control of hypertension than do whites or blacks (Go et al., 2014).

Age and Risk: The Elderly

The number of people older than 65 years is rapidly increasing and, in less than 25 years, one of every five people in the U.S. will be over age 65. Systolic BP rises progressively with age (Go et al., 2014) (Fig. 1-4), and elderly people with hypertension are at greater risk for CVD.

Pulse Pressure

As seen in Figure 1-5, systolic levels rise progressively with age, whereas diastolic levels typically start to fall beyond age 50 (Burt et al., 1995). Both of these changes reflect increased aortic stiffness and pulse-wave velocity with a more rapid return of the reflected

pressure waves, as is described in more detail in Chapter 3. It therefore comes as no surprise that the progressively widening of pulse pressure is a prognosticator of CV risk, as both the widening pulse pressure and most of the risk come from the same pathology—atherosclerosis and arteriosclerosis (Protogerou et al., 2013).

Isolated Systolic Hypertension

As expected from Figure 1-5, most hypertension after age 50 is isolated systolic hypertension (ISH), with a diastolic BP of less than 90 mm Hg. In an analysis based on the NHANES III data, Franklin et al. (2001a) found that ISH was the diagnosis in 65% of all cases of uncontrolled hypertension seen in the entire population and in 80% of patients older than 50. It should be noted that, unlike some reports that define ISH as a systolic BP of 160 mm Hg or greater, Franklin et al. (2001a) appropriately used 140 mm Hg or higher.

ISH in the elderly is associated with increased morbidity and mortality from coronary disease and stroke. However, as older patients develop CVD and cardiac pump function deteriorates, systolic levels often fall and a U-shaped curve of CV mortality becomes obvious: Mortality increases both in those with systolic BP of less than 120 mm Hg and in those with systolic BP of more than 140 mm Hg. Similarly, mortality is higher in those 85 years of age or older if their systolic BP is lower than 140 mm Hg or their diastolic BP is lower than 70 mm Hg, both indicative of poor overall health (van Bommel et al., 2006).

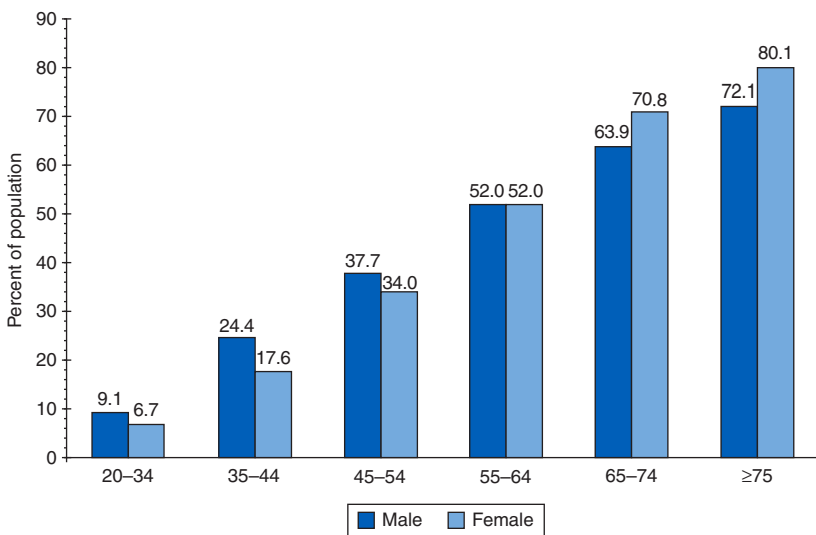


FIGURE 1-4 • Prevalence of high BP in adults ≥20 years of age by age and sex (National Health and Nutrition Examination Survey: 2007–2010). Hypertension is defined as systolic BP ≥140 mm Hg or diastolic BP ≥ 90 mm Hg, if the subject said “yes” to taking antihypertensive medication, or if the subject was told on two occasions that he or she had hypertension. Source: National Center for Health Statistics and National Heart, Lung, and Blood Institute. (From Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: A report from the American Heart Association. *Circulation* 2014;129:e28–e292.)

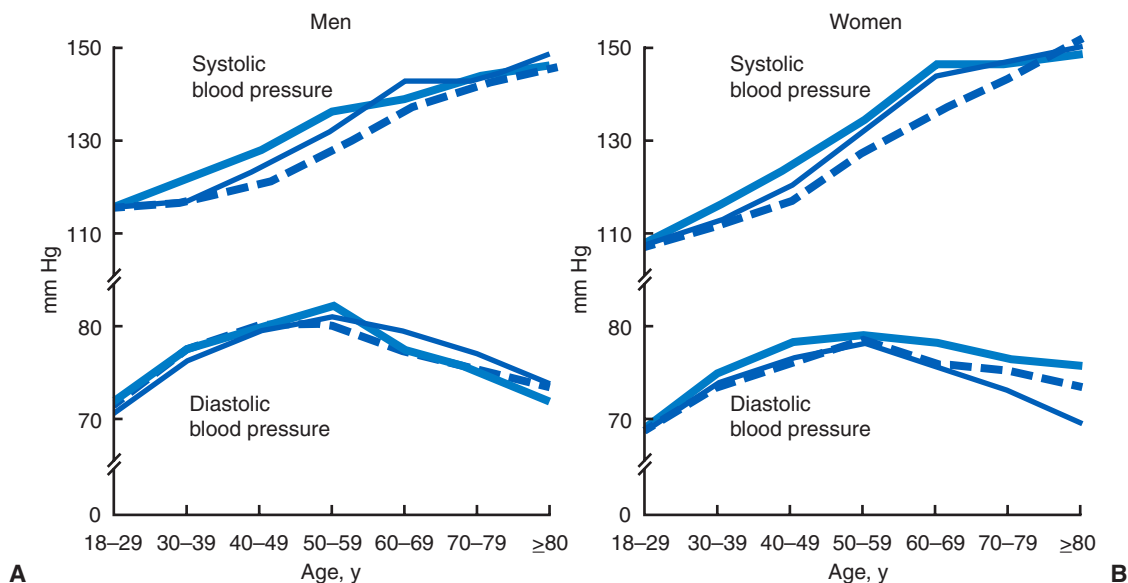


FIGURE 1-5 • Mean systolic and diastolic BPs by age and race or ethnicity for men and women in the U.S. population 18 years of age or older. *Thick solid line*, non-Hispanic blacks; *dashed line*, non-Hispanic whites; *thin solid line*, Mexican Americans. Data from the NHANES III survey. (Modified from Burt VL, Whelton P, Roccella EJ, et al. Prevalence of hypertension in the U.S. adult population. Results from the Third National Health and Nutrition Examination Survey, 1988–1991. *Hypertension* 1995;25:305–313.)

Isolated Diastolic Hypertension

In people under age 45, ISH is exceedingly rare, but isolated diastolic hypertension (IDH), i.e., systolic below 140 mm Hg and diastolic 90 mm Hg or higher, may be found in 20% or more (Franklin et al., 2001a). Peters et al. (2013) found a 30% increased CV mortality compared with normotensive patients among 850 subjects with even transient IDH who were followed for 29 years and Niiranen et al. (2014) observed a 1.95 relative hazard of CV events compared with normotensives among 114 subjects with IDH identified by home BP measurements over an 11.2 year follow-up. Therefore, patients with IDH should be given anti-hypertensive therapy to reduce their CV risks.

Relative Versus Absolute Risk

The risks of elevated BP are often presented as relative to risks found with lower levels of BP. This way of looking at risk tends to exaggerate its degree as seen in Figure 1-6. When the associations among various levels of BP to the risk of having a stroke were examined in a total of 450,000 patients followed up for 5 to 30 years, there was a clear increase in stroke risk with increasing levels of diastolic BP (Prospective Studies Collaboration, 1995). In *relative* terms, the increase in risk was much greater in the younger group (<45 years), going from 0.2 to 1.9, which is almost a 10-fold increase in relative risk compared to

the less than twofold increase in the older group (10.0 to 18.4). But, it is obvious that the *absolute* risk is much greater in the elderly, with 8.4% (18.4 to 10.0) more

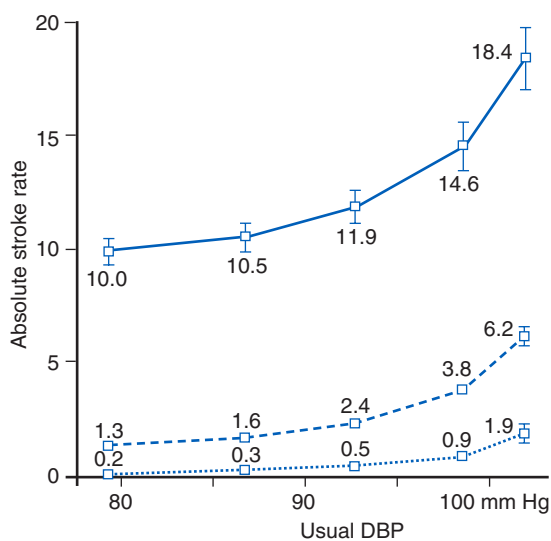


FIGURE 1-6 • The absolute risks for stroke by age and usual diastolic BP in 45 prospective observational studies involving 450,000 individuals with 5 to 30 years of follow-up during which 13,397 participants had a stroke. *Dotted line*, less than 45 years old; *dashed line*, 45 to 65 years old; *solid line*, ≥65 years old. (Modified from Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective cohorts. *Lancet* 1995;346:1647–1653.)

having a stroke with the higher diastolic BP while only 1.7% (1.9 to 0.2) more of the younger were afflicted. The importance of this increased risk in the young with higher BP should not be ignored, but the use of the smaller change in absolute risk rather than the larger change in relative risk seems more appropriate when applying epidemiologic statistics to individual patients.

The distinction between the risks for the population and for the individual is important. For the population at large, risk clearly increases with every increment in BP, and levels of BP that are accompanied by significantly increased risks should be called *high*. As Stamler et al. (1993) note: “Among persons aged 35 years or more, most have BP above optimal (<120/<80 mm Hg); hence, they are at increased CVD risk, i.e., the BP problem involves most of the population, not only the substantial minority with clinical hypertension.” However, for individual patients, the absolute risk from slightly elevated BP may be quite small. Therefore, more than just the level of BP should be used to determine risk. Sussman et al. (2013) provide statistical evidence that “benefit-based tailored treatment” that uses estimated CVD event reduction by other risk factors as well provides better protection against CVD and more quality-adjusted life-years than does the currently used “treatment to target” approach.

Benefits of Action: Decreased Risk of CVD

The major benefit listed in Table 1-2 that is involved in a conceptual definition of hypertension is the level at which it is possible to show the benefit of reducing CVD by lowering the BP. Inclusion of this factor is predicated on the assumption that it is of no benefit—and, as we shall see, is potentially harmful—to label a person hypertensive if nothing will be done to lower the BP.

Natural Versus Treatment-Induced BP

Before proceeding, one caveat is in order. As noted earlier, less CVD is seen in people with low BP, who are not receiving antihypertensive therapy. However, that fact cannot be used as evidence to support the benefits of therapy, because naturally low BP offers a degree of protection not provided by a similarly low BP resulting from antihypertensive therapy.

The available evidence supports that view: Morbidity and mortality rates, particularly those of coronary disease, continue to be higher in patients who are undergoing antihypertensive drug treatment than in

untreated people with similar levels of BP. This has been shown for coronary disease in follow-up studies of multiple populations (Andersson et al., 1998; Clausen & Jensen, 1992; Okin et al., 2012; Thürmer et al., 1994) and in Japanese for strokes (Asayama et al., 2009). This issue is covered in more detail in Chapter 5.

In contrast to these data, considerable experimental, epidemiologic, and clinical evidences indicate that reducing elevated BP is beneficial, particularly in high-risk patients (Bakris et al., 2014; Blood Pressure Lowering Treatment Trialists’ Collaboration, 2008; Lackland et al., 2014).

Rationale for Reducing Elevated BP

Table 1-3 presents the rationale for lowering elevated BP. The reduction in CVD and death (listed last in the table) has been measured to determine the BP level at which a benefit is derived from antihypertensive therapy as covered in Chapter 5.

During the past 40 years, controlled therapeutic trials have included patients with diastolic BP levels as low as 90 mm Hg. Detailed analyses of these trials are presented in Chapter 5. For now, it is enough to say that there is no question that protection against CVD has been documented for reduction of diastolic BP levels that start at or above 95 mm Hg, but there is continued disagreement about whether protection has been shown for those whose diastolic BP starts at or above 90 mm Hg who are otherwise at low risk. Similarly, protection for the elderly with ISH has been documented with a systolic BP ≥ 160 mm Hg or higher, but there are no data for the large elderly population between 140 and 160 mm Hg. Therefore,

TABLE 1-3
Rationale for the Reduction of Elevated BP

1. Morbidity and mortality as a result of CVDs are directly related to the level of BP
2. BP rises most in those whose pressures are already high
3. In humans, there is less vascular damage where the BP is lower: beneath a coarctation, beyond a renovascular stenosis, and in the pulmonary circulation
4. In animal experiments, lowering the BP has been shown to protect the vascular system
5. Antihypertensive therapy reduces CVD and death

TABLE 1-4

Features of Recent Guidelines

Blood Pressure (mm Hg)	NICE (2011)	Mancia et al. (2013) ESH/ESC	Weber et al. (2014) ASH/ISH	Go et al. (2013) AHA/ACC/CDC	James et al. (2014) Hypertension guidelines, U.S. "JNC 8"
Definition of hypertension	≥140/90 and daytime ABPM (or home BP ≥135/85)	≥140/90	≥140/90	≥140/90	Not addressed
Drug therapy in low-risk patients after nonpharmacologic treatment	≥160/100 or daytime ABPM ≥ 150/95	≥140/90	≥140/90	≥140/90	<60 y <140/90 ≥60 y ≥150/90
Blood pressure targets	<140/90 ≥80 y <150/90	<140/90 Elderly < 80 y SBP 140–150 SBP < 140 in fit patients Elderly ≥80 y SBP 140–150	<140/90 ≥80 y <150–90	<140/90 Lower targets may be appropriate in some patients, including the elderly	<60 y <140/90 ≥60 y <150/90
Blood Pressure target in patients with diabetes	Not addressed	<140/85	<140/90	<140/90 Lower targets may be considered	<140/90

expert committees have disagreed about the minimum level of BP at which drug treatment should begin.

In particular, as seen in Table 1-4, the British guidelines (National Institute for Health and Clinical Excellence (UK) (NICE), 2011) are more conservative than are those from the U.S., which recommend 140/90 mm Hg (Go et al., 2013; Weber et al., 2014). However, the report written by the majority of members of the JNC-8 committee recommends a level of 150 mm Hg for all over age 60 (James et al., 2014). A four-person minority of the JNC-8 committee strongly support maintenance of the current 140-mm Hg level for all below age 80 (Wright et al., 2014).

These disagreements have highlighted the need to consider more than the level of BP in making that decision. As is noted in Chapter 5, the consideration of other risk factors, target organ damage, and symptomatic CVD allows a more rational decision to be made about whom to treat.

Prevention of Progression of Hypertension

Another benefit of action is the prevention of progression of hypertension, which should be looked on as a surrogate for reducing the risk of CVD. Evidence of

that benefit is strong, based on data from multiple, randomized, placebo-controlled clinical trials as shown in Chapter 4, Table 4-2. In such trials, the number of patients whose hypertension progressed from their initially less severe degree to more severe hypertension, defined as BP greater than 200/110 mm Hg, increased from only 95 of 13,389 patients on active treatment to 1,493 of 13,342 patients on placebo (Moser & Hebert, 1996).

As seen in Figure 1-7, the progressively lower frequency distribution of systolic BP in the U.S. population from 1959 to 2010 is shown by Lackland et al. (2014) to be largely a consequence of improved treatment of hypertension. The mean systolic BP has fallen from 131 mm Hg in 1960 to 122 mm Hg in 2008 (Lackland et al., 2014).

Short time trials of antihypertensive therapy have not shown prevention of progression in patients with prehypertension (Julius et al., 2006; Luders et al., 2008).

Risks and Costs of Action

The decision to label a person hypertensive and begin treatment involves assumption of the role of a patient, changes in lifestyle, possible interference with the

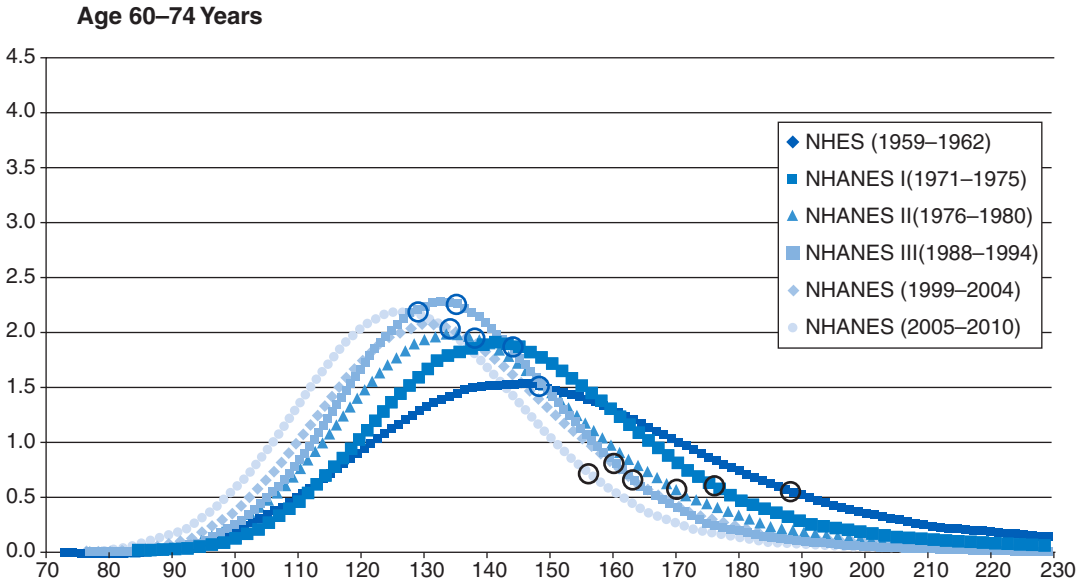


FIGURE 1-7 • Smoothed weighted frequency distribution, median, and 90th percentile of systolic BP: U.S., 1959 to 2010. Age 60 to 74 years. NHANES indicates National Health and Nutrition Examination Survey; and NHES, National Health Examination Surveys. (Lackland DT, Roccella EJ, Deusch AF et al. Factors influencing the decline in stroke mortality: A Statement From the American Heart Association/American Stroke Association. *Stroke* 2014;45:315–353.)

quality of life (QOL), risks from biochemical side effects of therapy, and financial costs. As is emphasized in the next chapter, the diagnosis should not be based on one or only a few readings since there is often an initial white-coat effect that frequently dissipates after a few weeks, particularly when readings are taken out of the office.

Assumption of the Role of a Patient and Worsening QOL

Merely labeling a person hypertensive may cause negative effects as well as enough sympathetic nervous system activity to change hemodynamic measurements (Rostrup et al., 1991). The adverse effects of labeling were identified in an analysis of health-related QOL measures in hypertensives who participated in the 2001–2004 NHANES (Hayes et al., 2008). Those who knew they were hypertensive had significantly poorer QOL measures than did those who were hypertensive with similar levels of BP but were unaware of their condition. QOL measures did not differ by the status of hypertension control. Fortunately, hypertensive people who receive appropriate counseling and comply with modern-day therapy usually have no impairment and may have improvements in overall QOL measures (Zygmuntowicz et al., 2013).

Risks from Biochemical Side Effects of Therapy

Biochemical risks are less likely to be perceived by the patient than are the interferences with QOL, but they may actually be more hazardous. These risks are discussed in detail in Chapter 7. For now, only two will be mentioned: Hypokalemia, which develops in 5% to 20% of diuretic-treated patients, and elevations in blood triglyceride and glucose levels, which may accompany the use of β -blockers.

Overview of Risks and Benefits

Obviously, many issues are involved in determining the level of BP that poses enough risk to mandate the diagnosis of hypertension and to call for therapy, despite the potential risks that appropriate therapy entails. An analysis of issues relating to risk factor intervention by Brett (1984) clearly defines the problem:

Risk factor intervention is usually undertaken in the hope of long-term gain in survival or quality of life. Unfortunately, there are sometimes trade-offs (such as inconvenience, expense, or side effects), and something immediate must be sacrificed. This tension between benefits and liabilities is not necessarily resolved by appealing to statements of

medical fact, and it is highlighted by the fact that many persons at risk are asymptomatic. Particularly when proposing drug therapy, the physician cannot make an asymptomatic person feel any better, but might make him feel worse, since most drugs have some incidence of adverse effects. But how should side effects be quantitated on a balance sheet of net drug benefit? If a successful anti-hypertensive drug causes impotence in a patient, how many months or years of potentially increased survival make the side effect acceptable? There is obviously no dogmatic answer; accordingly, global statements such as “all patients with asymptomatic mild hypertension should be treated” are inappropriate, even if treatment were clearly shown to lower morbidity or mortality rates.

On the other hand, as noted in Figure 1-1, the risks related to BP are directly related to the level, progressively increasing with every increment of BP. Therefore, the argument has been made that, with currently available antihypertensive drugs, which have few, if any, side effects, therapy should be provided even at BP levels lower than 140/90 mm Hg to prevent both the progression of BP and target organ damages that occur at “high-normal” levels (Julius, 2000). The benefit of lowering BP in normotensive patients with known CVD has been documented (Thompson et al., 2011) but there is little evidence for treatment of normotensives at low risk.

An even more audacious approach toward the prevention of CV consequences of hypertension has been proposed by the English epidemiologists Wald and Law (2003) and Law et al. (2009). They recommend a “Polypill” composed of low doses of a statin, a diuretic, an ACEI, a β -blocker, folic acid (subsequently deleted), and aspirin to be given to all people from age 55 on and everyone with existing CVD, regardless of pretreatment levels of cholesterol or BP. Wald and Law concluded that the use of the Polypill in this manner would reduce IHD events by 88% and stroke by 80%, with one-third of people benefiting and gaining an average 11 years of life free from IHD or stroke. They estimated side effects in 8% to 15% of people, depending on the exact formulation. In a more recent analysis, the use of their currently devised Polypill was estimated to provide a 46% reduction in CHD and a 62% reduction in stroke (Law et al., 2009). In a 15-month open-label study of a Polypill in 2004 subjects with known CVD or at high risk of developing CVD, Thom et al. (2013) found small but statistically significant reductions in systolic BP and LDL cholesterol. However, as editorialized by Gaziano (2013),

“Although the potential remains for use of various polypills in certain settings, the precise advantage of this strategy remains largely unproven.”

OPERATIONAL DEFINITIONS OF HYPERTENSION

Seventh Joint National Committee Criteria

In keeping with the data shown in Figure 1-1, the 2003 Seventh Joint National Committee report (JNC-7) introduced a new classification—prehypertension—for those whose BPs range from 120 to 139 mm Hg systolic and/or 80 to 89 mm Hg diastolic, as opposed to the JNC-6 classification of such levels as “normal” and “high-normal” (Chobanian et al., 2003) (Table 1-5). In addition, the former stages 2 and 3 have been combined into a single stage 2 category, since management of all patients with BP above 160/100 mm Hg is similar.

Classification of BP

Prehypertension

The JNC-7 report (Chobanian et al., 2003) states

Prehypertension is not a disease category. Rather it is a designation chosen to identify individuals at high risk of developing hypertension, so that both patients and clinicians are alerted to this risk and encouraged to intervene

TABLE 1-5

Changes in Blood Pressure Classification

JNC 6 Category	SBP/DBP	JNC 7 Category
Optimal	<120/80	Normal
Normal	120–129/80–84	Prehypertension
Borderline	130–139/85–89	Prehypertension
Hypertension	\geq 140/90	Hypertension
Stage 1	140–159/90–99	Stage 1
Stage 2	160–179/100–109	Stage 2
Stage 3	\geq 180/110	Stage 2

The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of high Blood Pressure. *Arch Intern Med* 1997;157:2413–2416; The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 2003;289:2560–2571.

and prevent or delay the disease from developing. Individuals who are prehypertensive are not candidates for drug therapy on the basis of their level of BP and should be firmly and unambiguously advised to practice lifestyle modification in order to reduce their risk of developing hypertension in the future.... Moreover, individuals with prehypertension who also have diabetes or kidney disease should be considered candidates for appropriate drug therapy if a trial of lifestyle modification fails to reduce their BP to 130/80 mm Hg or less.... The goal for individuals with prehypertension and no compelling indications is to lower BP to normal with lifestyle changes and prevent the progressive rise in BP using the recommended lifestyle modifications.

The guidelines from Europe (Mancia et al., 2013) and Canada (Hackam et al., 2013) continue to classify BP below 140/90 mm Hg as normal or high-normal. However, the JNC-7 classification seems appropriate, recognizing the significantly increased risk for patients with above-optimal levels. Since for every increase in BP by 20/10 mm Hg the risk of CVD doubles, a level of 135/85 mm Hg, with a double degree of risk, is better called prehypertension than high-normal.

Not surprisingly, considering the bell-shaped curve of BP in the U.S. adult population (Fig. 1-7), the number of people with prehypertension is even greater than those with hypertension, 37% versus 29% of the adult population (Lloyd-Jones et al., 2009).

It should be remembered that—despite an unequivocal call for health-promoting lifestyle modifications and no antihypertensive drug for such prehypertensives—the labeling of prehypertension could cause anxiety and lead to the premature use of drugs that have not yet been shown to be protective at such low levels of elevated BP. Americans are pill happy, and their doctors often acquiesce to their requests even when they know better. So, time will tell: Are Americans too quick or is the rest of the world too slow?

Systolic Hypertension in the Elderly

In view of the previously noted risks of isolated systolic elevations, JNC-7 recommended that, in the presence of a diastolic BP of less than 90 mm Hg, a systolic BP level of 140 mm Hg or higher is classified as ISH. Although risks of such elevations of systolic BP in the elderly have been clearly identified (Franklin et al., 2001b), the value of therapy to reduce systolic levels that are between 140 and 160 mm Hg in the elderly has not been documented (Diao et al., 2012).

Labile Hypertension

As ambulatory readings have been recorded, the marked variability in virtually everyone's BP has become obvious (see Chapter 2). In view of the usual variability of BP, the term *labile* is neither useful nor meaningful.

PREVALENCE OF HYPERTENSION

As previously noted, the prevalence of hypertension is increasing worldwide, in developed countries because of increasing longevity with its burden of systolic hypertension and in developing countries because of increasing obesity, diabetes, and dyslipidemia related to urbanization (Danaei et al., 2013).

Prevalence in the U.S. Adult Population

The best sources of data for the U.S. population are the previously noted NHANES surveys, which examine a large representative sample of the U.S. adult population aged 18 and older. The presence of hypertension has been defined in the NHANES as having a measured systolic BP of 140 mm Hg or higher or a measured diastolic BP of 90 mm Hg or higher, or taking antihypertensive drug therapy. In the latest NHANES from 2011 to 2012, the data show a definite increase in the overall prevalence of hypertension in the U.S. to a total of 29.1% (Nwankwo et al., 2013). As seen in Figure 1-4, the prevalence rises in both genders with increasing age. As seen in Figure 1-3, the prevalence among U.S. blacks is higher than in whites and Mexican Americans in both genders and at all ages. Part of the lower overall rates in Mexican Americans reflects their younger average age. With age adjustment, Mexican Americans had prevalence rates similar to U.S. whites.

These increases in prevalence over the past 10 years are attributed to a number of factors, including the following:

- An increased number of hypertensives who live longer as a result of improved lifestyles or more effective drug therapy
- The increased number of older people
- The increase in obesity
- An increased rate of new-onset hypertension not attributable to older age or obesity; the prevalence rates increased in all groups except those aged 18 to 29

Populations Outside the U.S.

Increases in the prevalence of hypertension, particularly in low- and middle-income countries (Lim et al., 2012) have been accompanied by increases in strokes (Feigin et al., 2014).

INCIDENCE OF HYPERTENSION

Much less is known about the incidence of newly developed hypertension than about its prevalence. The Framingham study provides one database wherein the incidence of hypertension in the Framingham cohort over 4 years was directly related to the prior level of BP, body mass index, smoking, and hypertension in both parents (Parikh et al., 2008).

The best currently available published data are from a prospective cohort study of 4,681 subjects, black and white, men and women aged 18 to 30 years at baseline in 1985–1986 in four U.S. cities who were repeatedly examined over 25 years in the CARDIA study (Allen et al., 2014). The primary end-point at 25 years was the association of BP trajectories and the presence of coronary artery calcification (CAC). Five distinct trajectories were identified. The odds of having a CAC score of 100 Housefield units were closely related to the trajectory. The odds, adjusted for baseline and 25-year BP, rose progressively from the low-stable group to 1.44 for the moderate-stable group, 1.86 for the moderate-increasing, 2.28 for the elevated-stable, and 3.70 for the elevated-rising. The authors conclude: “Blood pressure trajectories throughout young adulthood vary, and higher BP trajectories were associated with an increased risk of CAC in middle age. Long-term trajectories in BP may assist in more accurate identification of individuals with subclinical atherosclerosis.”

In an accompanying editorial, Sarafidis and Bakris (2014) wrote: “The study by Allen and colleagues presents a novel approach for assessing coronary heart disease and CVD risk, and the data provide an important perspective to support a preventive approach to reduce coronary heart disease risk by demonstrating (1) the existence of widely different BP trajectories ranging from young adulthood through middle age and (2) the relationship of increasing BP trajectories within groups that are African American, are obese, or have diabetes. Further research is warranted to explore the associations of BP trajectories

with development of advancing chronic kidney disease and heart failure and to provide novel tools for risk prediction to guide interventions for lowering BP in everyday practice.”

CAUSES OF HYPERTENSION

The list of causes of hypertension (Table 1-6) is quite long; however, the cause of about 90% of the cases of hypertension is unknown, i.e., primary or “essential.” The proportion of cases secondary to some identifiable mechanism has been debated considerably, as more specific causes have been recognized. Claims that one cause or another is responsible for up to 20% of all cases of hypertension repeatedly appear from investigators who are particularly interested in a certain category of hypertension, and therefore see only a highly selected population. In truth, the frequency of various forms in an otherwise unselected population of hypertensives is unknown.

POPULATION RISK FROM HYPERTENSION

Now that the definition of hypertension and its classification have been provided, along with various estimates of its prevalence, the impact of hypertension on the population at large can be considered. As noted, for the individual patient, the higher the level of BP, the greater the risk of morbidity and mortality. However, for the population at large, the greatest burden from hypertension occurs among people with only minimally elevated pressures, because there are so many of them. This burden can be seen in Figure 1-8, where 12-year CV mortality rates observed with each increment of BP are plotted against the distribution of the various levels of BP among the 350,000 35- to 57-year-old men screened for the Multiple Risk Factor Intervention Trial (National High Blood Pressure Education Program Working Group, 1993). Although the mortality rates climb progressively, most deaths occur in the much larger proportion of the population with minimally elevated pressures. By multiplying the percentage of men at any given level of BP by the relative risk for that level, it can be seen that more CV mortality will occur in those with a diastolic BP of 80 to 84 mm Hg than among those with a diastolic BP of 95 mm Hg or greater.

TABLE 1-6

Types and Causes of Hypertension

Systolic and Diastolic Hypertension	Foods Containing Tyramine and Monoamine Oxidase Inhibitors
<p>Primary, essential, or idiopathic</p> <p>Identifiable causes</p> <p>Renal</p> <ul style="list-style-type: none"> Renal parenchymal disease Acute glomerulonephritis Chronic nephritis Polycystic disease Diabetic nephropathy Hydronephrosis <p>Renovascular disease</p> <ul style="list-style-type: none"> Renal artery stenosis Other causes of renal ischemia <p>Renin-producing tumors</p> <p>Renoprival</p> <p>Primary sodium retention: Liddle syndrome, Gordon syndrome</p> <p>Endocrine</p> <ul style="list-style-type: none"> Acromegaly Hypothyroidism Hyperthyroidism Hypercalcemia (hyperparathyroidism) Adrenal disorders <ul style="list-style-type: none"> Cortical disorders <ul style="list-style-type: none"> Cushing syndrome Primary aldosteronism Congenital adrenal hyperplasia Medullary tumors: pheochromocytoma Extra-adrenal chromaffin tumors 11-β-hydroxysteroid dehydrogenase <ul style="list-style-type: none"> Deficiency or inhibition (Licoric) <p>Carcinoids</p> <p>Exogenous hormones</p> <ul style="list-style-type: none"> Estrogen Glucocorticoids Mineralocorticoids Sympathomimetics Erythropoietin 	<p>Coarctation of the aorta and aortitis</p> <p>Pregnancy-induced</p> <p>Neurologic disorders</p> <ul style="list-style-type: none"> Increased intracranial pressure Central sleep apnea Quadriplegia Acute porphyria Familial dysautonomia Lead poisoning Guillain-Barré syndrome <p>Acute stress (including surgery)</p> <ul style="list-style-type: none"> Psychogenic hyperventilation Hypoglycemia Burns Alcohol withdrawal Sickle cell crisis After resuscitation Perioperative <p>Increased intravascular volume</p> <p>Alcohol</p> <p>Nicotine</p> <p>Cyclosporine, tacrolimus</p>
	<p>Systolic hypertension</p> <ul style="list-style-type: none"> Arterial rigidity Increased cardiac output Aortic valvular insufficiency Arteriovenous fistula, patent ductus Thyrotoxicosis Paget disease of bone Beriberi

Strategy for the Population

This disproportionate risk for the population at large from relatively mild hypertension bears strongly on the question of how to achieve the greatest reduction in the risks of hypertension. In the past, most effort has been directed at the group with the highest levels of BP. However, this “high-risk” strategy, as effective as it may be for those affected, does little to reduce total morbidity and mortality if the “low-risk” patients,

who make up the largest share of the population at risk, are ignored (Rose, 1985).

Many more people with mild hypertension are now being treated actively and intensively with anti-hypertensive drugs. Particularly since short-term anti-hypertensive drug therapy has not prevented the progression of hypertension (Julius et al., 2006; Luders et al., 2008), a more effective strategy as emphasized by Rose (1992) would be to lower the BP level of the entire population, as might be accomplished by

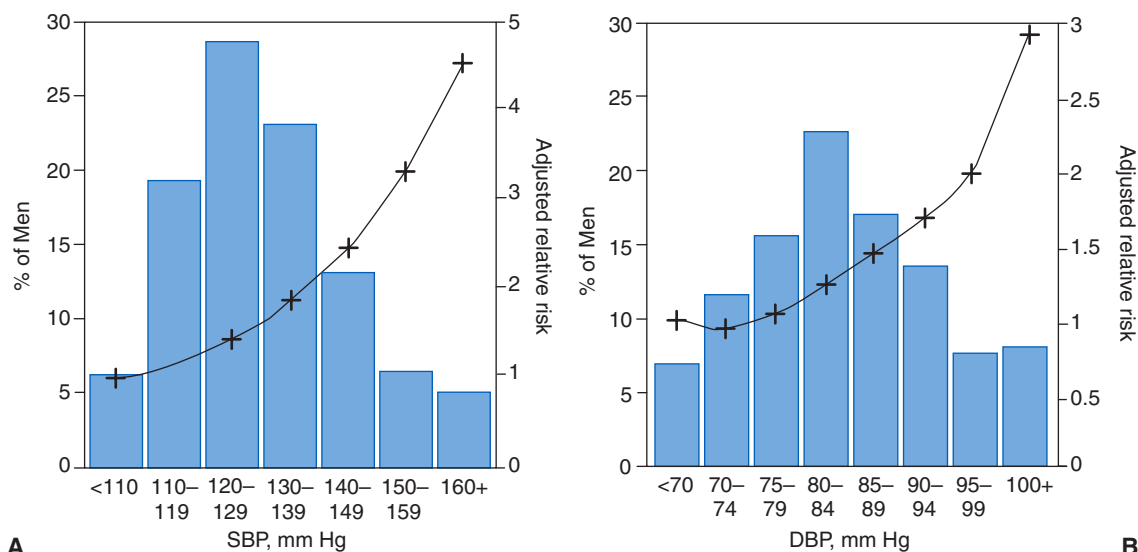


FIGURE 1-8 • A: Percentage distribution of SBP for men screened for the MRFIT who were 35 to 57 years old and had no history of myocardial infarction ($n = 347,978$) (bars) and corresponding 12-year rates of cardiovascular mortality by SBP level adjusted for age, race, total serum cholesterol level, cigarettes smoked per day, reported use of medication for diabetes mellitus, and imputed household income (using census tract for residence) (curve). **B:** Same as part (A), showing the distribution of DBP ($n = 356,222$). (Modified from National High Blood Pressure Education Program Working Group. *Arch Intern Med* 1993;153:186–208.)

reduction of sodium intake (The Executive Board of the World Hypertension League, 2014). Rose estimated that lowering the entire distribution of BP by only 2 to 3 mm Hg would be as effective in reducing the overall risks of hypertension as prescribing current antihypertensive drug therapy for all people with definite hypertension.

This issue was eloquently addressed by Stamler (1998):

The high-risk strategy of the last 25 years—involving detection, evaluation, and treatment (usually including drug therapy) of tens of millions of people with already established high BP—useful as it has been, has serious limitations: It is late, defensive, mainly reactive, time-consuming, associated with adverse effects (inevitable with drugs, however favorable the mix of benefit and risk), costly, only partially successful, and endless. It offers no possibility of ending the high BP epidemic.

However, present knowledge enables pursuit of the additional goal of the primary prevention of high BP, the solution to the high BP epidemic. For decades, extensive concordant evidence has been amassed by all research disciplines showing that high salt intake, obesity, excess alcohol intake, inadequate potassium intake, and sedentary lifestyle all have adverse effects on population BP levels.

This evidence is the solid scientific foundation for the expansion in the strategy to attempt primary prevention of high BP by improving lifestyles across entire populations.

PREVENTION

The broader approach is almost certainly correct on epidemiologic grounds. However, the needed changes in lifestyle cannot be achieved on an individual basis (Woolf, 2008). They require broad, societal changes. Health care providers can play a role, as described in Chapter 7. But the main tasks must be assumed by others, including

- City planners to provide sidewalks and bicycle paths
- School administrators to require physical activity in school time and to get rid of soft drinks and candy bars
- Food processors and marketers to quit preparing and pushing high-calorie, high-fat, high-salt products
- Television programmers to quit assaulting young children with unhealthy choices
- Parents to take responsibility for their children's welfare
- Adults to forgo instant pleasures (Krispy Crèmes) for future benefits

► Society to protect immature young adults—old enough to die in Iraq—who will surely continue to smoke, drink, and have unprotected sex. Ways to help include enforcing selling restrictions on cigarettes and alcohol, providing chaperones at student drinking parties, ensuring availability of condoms and morning-after pills. Adults may not like what hot-blooded young people do, but “just saying no” is not enough.

Until (and if) such nirvana arrives, it may take active drug therapies, either in the slow, measured approach being taken by Julius et al. (2006) or the broad, unmeasured use of a Polypill as formulated by Wald and Law (2003) and Law et al. (2009). However it may be accomplished, we need to keep the goal of prevention in mind as we consider the overall problems of hypertension for the individual patient in the ensuing chapters.

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Measurement of Blood Pressure

We are witnessing an evolving transition in the measurement of blood pressure (BP). Over more than 100 years since indirect measurement was described and after more than 75 years when the practitioners' office was the sole site for BP measurement, home, self-recorded BP monitoring has been recognized to be the most accurate, inexpensive, and available way to diagnose and manage hypertension. As will be noted, both office readings and automatic, ambulatory monitoring (ABPM) will continue to have their place, but home readings have taken their place at the top of the hierarchy of BP measurement. The prediction of Thomas Pickering and coworkers in 2008 has been validated and the obsolescence of office measurements recognized (Sebo et al, 2014; Stergiou & Parati, 2012).

Much of this evolution arises by the recognition that various sources of variability have placed insurmountable hurdles to the adequacy of office readings.

VARIABILITY OF BLOOD PRESSURE

Variability of the BP has been recognized from the very beginning of BP measurement, but its presence and importance have been highlighted by the availability of noninvasive automatic BP monitoring.

The multiple types of variability are portrayed in Figure 2-1 (Parati & Bilo, 2012). These authors note: "It is clear that blood pressure variations (BPVs) over different time periods may reflect the impact of very different physiologic factors" (see Fig. 2-1). Very short-term BP changes (over seconds or minutes) may reflect central and reflex autonomic modulation, as well as changes in arterial properties. BPV over 24 hours heavily depends also on a subject's activity, including

sleep–wakefulness cycle. Visit-to-visit variability may in turn be driven, among other factors, by changes in antihypertensive treatment, by the inconstant accuracy of office BP measurements, by the degree of patient therapeutic adherence, and by seasonal changes, either through the direct physiologic effects of ambient temperature or through improper modifications in therapy in response to changing weather conditions (Modesti et al., 2013).

The typical short-term variability of the BP through the 24-hour day is easily recognized by ABPM (Fig. 2-2). This printout of readings taken in a single patient every 15 minutes during the day and every 30 minutes at night displays the large fluctuations in daytime readings, the typical dipping during sleep, and the abrupt increase on arising.

The adverse consequences of not recognizing and dealing with this variability are obvious: Individual patients may be falsely labeled as hypertensive or normotensive. If falsely labeled as normotensive, needed therapy may be denied. If falsely labeled as hypertensive, the label itself may provoke ill effects (Hamer et al., 2010) and unnecessary therapy will likely be given.

Sources of Variation in Office Readings

Variability in office BP readings may arise from problems involving the observer (measurement variation) or factors working within the patient (biologic variation).

Measurement Variations

An impressively long list of factors that can affect the immediate accuracy of office measurements has been compiled by Reeves (1995) (Table 2-1). These errors

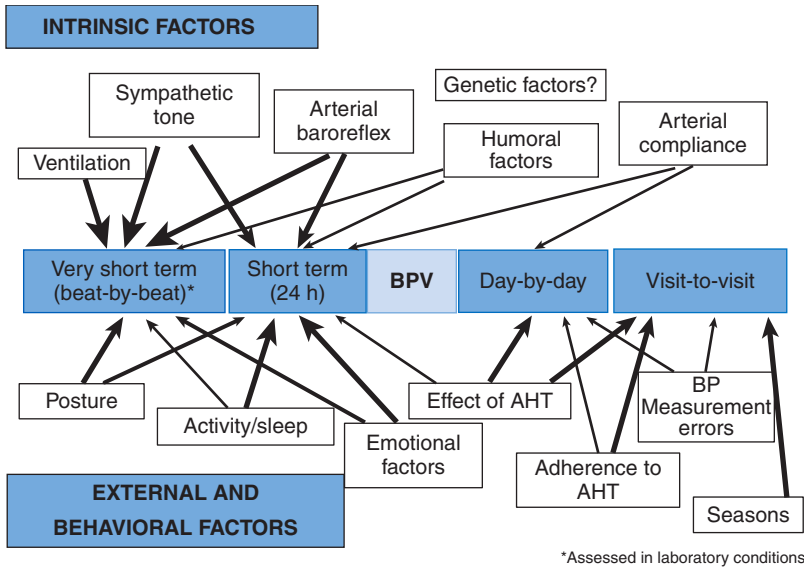


FIGURE 2-1 • Different types of BPV and the complex network of their possible determinants (arrow width reflects the likely strength of relationship based on available evidence). AHT, antihypertensive treatment; BPV, blood pressure variability. (Adapted from Parati G, Bilo G. Calcium antagonist added to angiotensin receptor blocker: A recipe for reducing blood pressure variability?: Evidence from day-by-day home blood pressure monitoring. *Hypertension* 2012;59:1091–1093.)

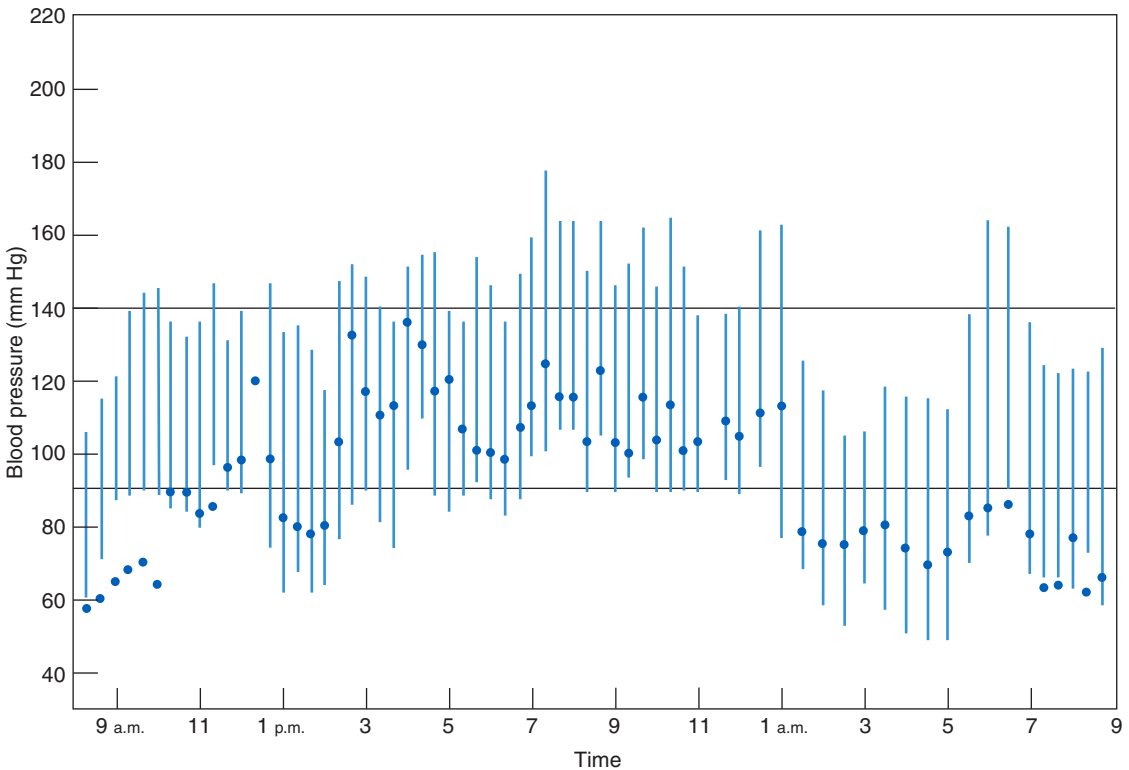


FIGURE 2-2 • Computer printout of BPs obtained by ABPM over 24 hours, beginning at 9 a.m., in a 50-year-old man with hypertension receiving no therapy. The patient slept from midnight until 6 a.m. Solid circles, heart rate in beats per minute. (From Zachariah PK, Sheps SG, Smith RL. Defining the roles of home and ambulatory monitoring. *Diagnosis* 1988;10:39–50, with permission.)

TABLE 2-1

Factors Affecting the Immediate Accuracy of Office BP Measurements

Increases BP	Decreases BP	No Effect on BP
Examinee	Examinee	Examinee
Soft Korotkoff sounds	Soft Korotkoff sounds	Menstrual phase
Pseudohypertension	Recent meal	Chronic caffeine ingestion
White-coat reaction	Missed auscultatory gap	Cuff self-inflation
Paretic arm (due to stroke)	High stroke volume	Examinee and examiner
Pain, anxiety	Setting, equipment	Discordance in gender or race
Acute smoking	Noisy environs	Examination
Acute caffeine	Faulty aneroid device	Thin shirtsleeve under cuff
Acute ethanol ingestion	Low mercury level	Bell vs. diaphragm
Distended bladder	Leaky bulb	Cuff inflation per se
Talking, signing	Examiner	Hour of day (during work hours)
Setting, equipment	Reading to next lowest 5 or	
Cold environment	10 mm Hg, or expectation bias	
Leaky bulb valve	Impaired hearing	
Examination	Examination	
Cuff too narrow	Resting for too long	
Arm below heart level	Arm above heart level	
Too-short rest period	Too rapid deflation	
Arm, back unsupported	Excess bell pressure	
Parallax error	Parallax error (aneroid)	
Using phase IV (adult)		

Modified from Reeves RA. Does this patient have hypertension? *JAMA* 1995;273:1211–1218.

are more common than most practitioners realize (Keenan et al., 2009), and regular, frequent retraining of personnel is needed to prevent them.

Biologic Variations

Biologic variations in BP may be either random or systematic. Random variations are uncontrollable but can be reduced simply by repeating the measurement as many times as needed. Systematic variations are introduced by something affecting the patient and, if recognized, are controllable; however, if not recognized, they cannot be reduced by multiple readings. For example, Modesti et al. (2013), using ABPM in 1,897 subjects, found the daytime systolic BP was negatively related to the subjects' environmental temperature, nighttime BP was positively related to daylight hours, and the morning surge was negatively related to daylight hours.

As seen in Figure 2-2, considerable differences in readings can be seen at different times of the day, whether or not the subject is active. Beyond these, between-visit variations in BP can be substantial. Even after three office visits, the standard deviation of the difference in BP from one visit to another in 32 subjects

was 10.4 mm Hg for systolic BP and 7.0 mm Hg for diastolic BP (Watson et al., 1987).

Types of Variation

As seen in Figure 2-1, variability in BP arises from different sources: Short term, daytime, diurnal, and seasonal. The overriding influence of activity on daytime and diurnal variations was well demonstrated in a study of 461 untreated hypertensive patients whose BP was recorded with an ambulatory monitor every 15 minutes during the day and every 30 minutes at night over 24 hours (Clark et al., 1987). In addition, five readings were taken in the clinic before and another five after the 24-hour recording. When the mean diastolic BP readings for each hour were plotted against each patient's mean clinic diastolic BP, considerable variations were noted, with the lowest BPs occurring during the night and the highest near midday (Fig. 2-3A). The patients recorded in a diary the location at which their BP was taken (e.g., at home, work, or other location) and what they were doing at the time, selecting from 15 choices of activity. When the effects of the various combinations of location

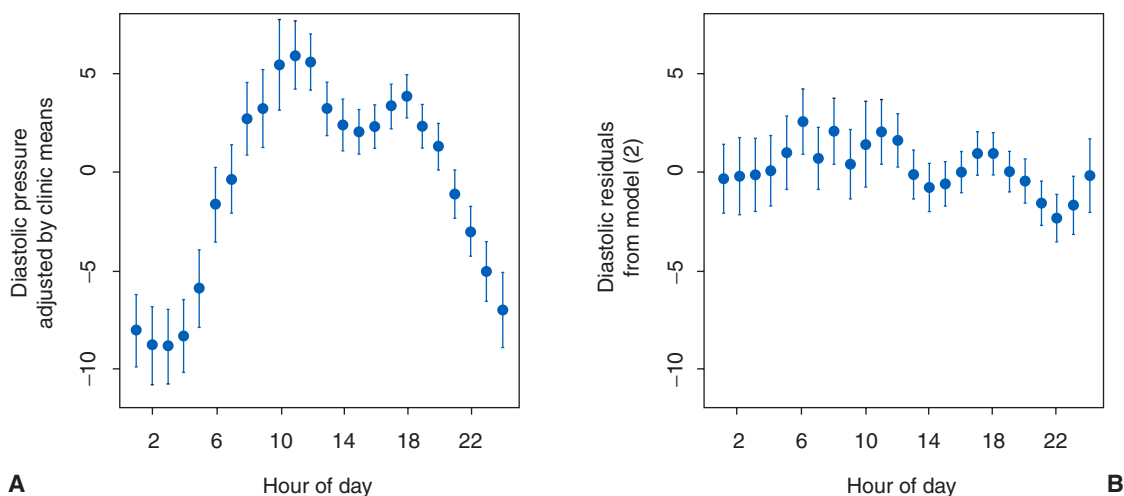


FIGURE 2-3 • **A:** Plot of diastolic BP readings adjusted by individual clinic means. **B:** Plot of the diastolic BP hourly mean residuals after adjustments for various activities by a time-of-day model. The hourly means (solid circles) \pm 2 standard errors of the mean (vertical lines) are plotted versus the corresponding time of day. (Modified from Clark LA, Denby L, Pregibon D, et al. A quantitative analysis of the effects of activity and time of day on the diurnal variations of blood pressure. *J Chronic Dis* 1987;40:671–679.)

and activity on the BP were analyzed, variable effects relative to the BP recorded while relaxing were seen (Table 2-2). When the estimated effects of the various combinations of location and activity were subtracted

from the individual readings obtained throughout the 24-hour period, little residual effect related to the time of day was found (Fig. 2-3B). To be sure, BP usually falls during sleep, and a morning surge is typical, but beyond these, there is no circadian rhythm of BP (Peixoto & White, 2007).

TABLE 2-2

Average Changes in BP Associated with Commonly Occurring Activities, Relative to BP while Relaxing

Activity	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Meetings	+20.2	+15.0
Work	+16.0	+13.0
Transportation	+14.0	+9.2
Walking	+12.0	+5.5
Dressing	+11.5	+9.5
Chores	+10.7	+6.7
Telephone	+9.5	+7.2
Eating	+8.8	+9.6
Talking	+6.7	+6.7
Desk work	+5.9	+5.3
Reading	+1.9	+2.2
Business (at home)	+1.6	+3.2
Television	+0.3	+1.1
Relaxing	0.0	0.0
Sleeping	-10.0	-7.6

Data adapted from Clark LA, Denby L, Pregibon D, et al. A quantitative analysis of the effects of activity and time of day on the diurnal variations of blood pressure. *J Chronic Dis* 1987;40:671–679.

Additional Sources of Variation

It is important to minimize the changes in BP that arise because of variations within the patient. Even little things can have an impact: Both systolic BP and diastolic BP may rise 10 mm Hg or more with a distended urinary bladder (Faguis & Karhuvaara, 1989) or during ordinary conversation (Le Pailleur et al., 1998). Just the presence of a medical student in the room was found to increase the BP by an average of 6.4/2.4 mm Hg (Matthys et al., 2004). Those who are more anxious or elated tend to have higher levels (Ogedegbe et al., 2008). Particularly in the elderly, eating may lower the BP (Smith et al., 2003). Two common practices may exert significant pressor effects: Smoking (Groppelli et al., 1992) or drinking caffeinated beverages (Hartley et al., 2004).

The BP may vary between the two arms, and it should preferably be taken simultaneously in both arms on initial exam, with the higher arm used in subsequent measurements. In the few patients with subclavian artery stenoses causing a steal phenomenon, even higher differences are found.

Prognostic Implications of Variability

Additional insights into the mechanisms and consequences of both short-term and long-term BPV have been provided by another leader of the Milan group, Giuseppe Mancia (2012). In examining short-term BPV, i.e., over 24 hours, Mancia (2012) notes that the main reason for the reduction in variability with antihypertensive therapy is the reduction of the BP. More importantly, BPV within 24 hours has been found to be an independent predictor of the incidence of cardiovascular events (Kikuya et al., 2008; Parati et al., 1987). However, Mancia (2012) notes a number of limitations of the measurement of short-term BPV that will require measurement of beat-to-beat ambulatory BP noninvasively, a requirement that may be difficult to fulfill.

As to long-term variability, Mancia (2012) observes that “little is known about the factors responsible for the BP differences that have been observed between visits spaced by months or years in observational and antihypertensive drug trials” but notes that “these differences have been shown to have a prognostic value as in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) reported by Rothwell et al. (2010a,b): the lower within-individual visit-to-visit variability seen in the amlodipine-treated group compared to that seen in the atenolol-treated group “account for the disparity in observed effects on risk of stroke” (Rothwell et al., 2010a). They conclude that “visit-to-visit variability in systolic BP and maximum SBP are strong predictors of stroke, independent of mean SBP” (Rothwell et al., 2010b). When individual variation in SBP was analyzed from data in 389 trials, these authors found a pattern of variation with various antihypertensive drug classes that was associated with the risk of stroke independently of effects on mean SBP (Fig. 2-4) (Webb et al., 2010).

Support for this effect of BPV was forthcoming both for the risk of stroke (Shimbo et al., 2012; Zhang et al., 2011) and decline in cognitive function in older subjects (Sabayan et al., 2013). However, in keeping with Mancia’s (2012) view of multiple limitations on the validity of BPV for risk assessment, the results of two studies have shown that mean systolic BP and not variability predict outcomes: Schutte et al. (2012) in a prospective study of 2,944 patients given antihypertensive therapy for 12 years, Asayama et al. (2013) in 2,421 patients treated for 12 years.

Additional evidence of the impact of long-term blood pressure variability (BPV) has been provided by Hastie et al. (2013) who examined the levels of office BPV in 14,522 subjects during the 1st year of treatment, during years 1 to 5, during years 5 to 10, and after 10 years. Higher long-term and ultra-long-term BPV were associated with increased cardiovascular mortality, including patients with mean systolic BP less than 140 mm Hg in all time frames. Surprisingly, they found no association with stroke mortality.

These data confirm the need to maintain as little BPV as possible in the long-term treatment of hypertension. As seen in Figure 2-4, diuretics and calcium channel blockers provide the least degree of variability, likely part of the reason they are more effective in protection against stroke.

Blood Pressure During Sleep and on Awakening

Normal Pattern

The usual fall in BP at night is largely the result of sleep and inactivity rather than the time of day (Sayk et al., 2007). The usual falls in BP and heart rate that occur with sleep reflect a decrease in sympathetic nervous tone. In healthy young men, plasma catecholamine

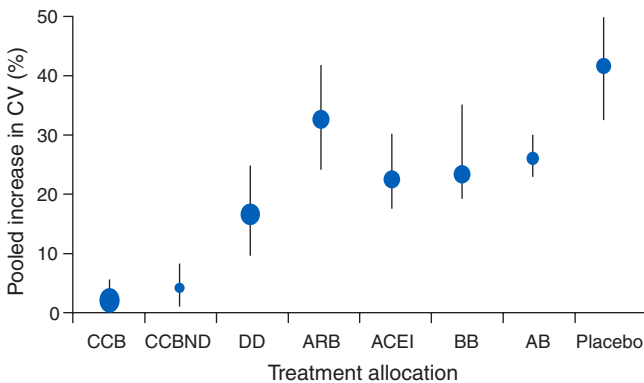


FIGURE 2-4 • Changes in group variation in systolic BP at follow-up compared with baseline and percentage increase in coefficient of variation. Error bars represent the 95%. CCB, calcium channel blocker; CCBND, nondihydropyridine calcium channel blocker; DD, nonloop diuretic drug; ARB, angiotensin-2-receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; BB, β blocker; AB, α -1 blocker. (Adapted from Webb AJ, Fischer U, Mehta Z, Rothwell PM. Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: A systematic review and meta-analysis. *Lancet* 2010;375:906–915.)

levels fell during rapid-eye-movement sleep, whereas awakening immediately increased epinephrine, and subsequent standing induced a marked increase in norepinephrine (Dodt et al., 1997).

Two features of the pattern of BP portrayed in 24-hour ABPM—the degree of fall in the BP during sleep, i.e., “dipping,” and the degree of rise of BP upon awakening and rising, i.e., the “morning surge”—have been extensively examined for their relation to hypertensive organ damage and cardiovascular morbidity and mortality. Fortunately, the pattern of nocturnal dipping may be recognized by home monitoring devices that are more accessible and less expensive than 24-hour ABPM devices. Two devices have been used to obtain three measurements of sleep-time BP: the Omron HEM-5001 (Ishikawa et al., 2012) and the MicrolifeWatchBNP (Stergiou et al., 2012c).

The Degree of Dipping

The nocturnal dip in pressure is normally distributed with no evidence of bimodality in both normotensive and hypertensive people (Staessen et al., 1997). The separation between “dippers” and “nondippers” is, in a sense, artifactual. However, most investigators such as Ivanovic et al. (2013) have used these criteria in comparison to the average daytime level:

- Normal = average decrease of BP greater than 10% and less than 20%
- extreme dippers = greater than 20% fall
- nondippers = less than 10% fall
- reverse dippers = higher than daytime average (Ivanovic et al., 2013)

What appears to be nondipping may be simply a consequence of getting up to urinate (Perk et al., 2001) or a reflection of obstructive sleep apnea (Peltari et al., 1998), or simply poor sleep quality (Sherwood et al., 2011). Moreover, the degree of dipping during sleep can be affected by the amount of dietary sodium in those who are salt sensitive: Sodium loading attenuates these individuals’ dipping, whereas sodium reduction restores their dipping status (Uzu et al., 1999). Among 325 African French, those who excreted a large portion of urinary sodium during the day had more dipping at night (Bankir et al., 2008). Furthermore, dipping is more common among people who are more physically active during the day (Cavelaars et al., 2004).

Associations with Nondipping

A number of associations have been noted with nondipping. These include

- Older age (Staessen et al., 1997)
- Cognitive dysfunction (Van Boxtel et al., 1998) and psychological stress (Clays et al., 2012)
- Diabetes (Björklund et al., 2002)
- Obesity (Kotsis et al., 2005)
- African Americans (Sherwood et al., 2011) and Hispanics (Rodriguez et al., 2013)
- Impaired endothelium-dependent vasodilation (Higashi et al., 2002)
- Diastolic dysfunction (Ivanovic et al., 2013)
- Left ventricular hypertrophy (Cuspidi et al., 2004)
- Early atherosclerosis (Vasunta et al., 2012) and coronary artery calcification (Coleman et al., 2011)
- Intracranial hemorrhage (Tsigoulis et al., 2005)
- Loss of renal function (Kanno et al., 2013) and albuminuria (Syrseloudis et al., 2011)
- Mortality from cardiovascular disease (Redon & Lurbe, 2008)

Associations with Excessive Dipping

Just as a failure of the BP to fall during sleep may reflect or contribute to cardiovascular damage, there may also be danger from too great a fall in nocturnal BP. Floras (1988) suggested that nocturnal falls in BP could induce myocardial ischemia in hypertensives with left ventricular hypertrophy and impaired coronary vasodilator reserve, contributing to the J-curve of increased coronary events when diastolic BP is lowered below 65 mm Hg (see Chapter 5).

The first objective evidence for this threat from too much dipping was the finding by Kario et al. (1996) that more silent cerebrovascular disease (identified by brain magnetic resonance imaging) was found among extreme dippers who had a greater than 20% fall in nocturnal systolic BP. Subsequently, Kario et al. (2001), in a 41-month follow-up of 575 elderly hypertensives, found the lowest stroke risk to be at a sleep diastolic BP of 75 mm Hg, with an increased risk below 75 mm Hg that was associated with their intake of antihypertensive drugs. Too great a fall in nocturnal pressure may also increase the risk of anterior ischemic optic neuropathy and glaucoma (Pickering et al., 2008). These findings serve as a warning against late evening or bedtime dosing of drugs that have a substantial antihypertensive effect in the first few hours after intake.

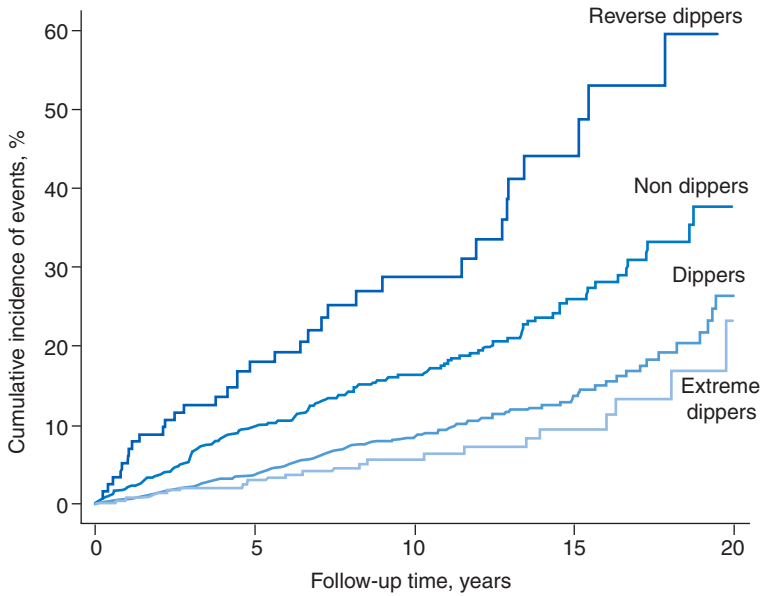


FIGURE 2-5 • Kaplan-Meier curves reporting the cumulative incidence of cardiovascular disease in the four categories of dipping pattern. (Adapted from Verdecchia P, Angeli F, Mazzotta G, et al. Day-night dip and early-morning surge in blood pressure in hypertension: Prognostic implications. *Hypertension* 2012;60:34–42.)

It should be noted that, regardless of the pattern of dipping, the presence of nocturnal hypertension, defined as a BP greater than 120/70 mm Hg, is associated with an increased incidence of cardiovascular events even among patients who have normotensive daytime BP levels (Li & Wang, 2013) or normal nocturnal dipping (Cuspidi et al., 2012).

A typical relation between various dipping patterns and cardiovascular events is shown in Figure 2-5, the data obtained from a cohort of 3,012 initially untreated hypertensive patients followed for a mean of 8.4 years (Verdecchia et al., 2012).

Early Morning Surge

The BP abruptly rises, i.e., surges, upon arising from sleep, whether it be in the early morning (Gosse et al., 2004) or after a midafternoon siesta (Bursztyrn et al., 1999), and the degree of surge may vary on repeated measurements (Wizner et al., 2008). As amply described, the early morning hours after 6 a.m. are accompanied by an increased prevalence of all cardiovascular catastrophes as compared to the remainder of the 24-hour period (Muller, 1999). Early morning increases have been noted for stroke (Foerch et al., 2008), cardiac arrest (Soo et al., 2000), rupture of the abdominal aorta (Manfredini et al., 1999), and epistaxis (Manfredini et al., 2000), possibly by destabilizing atherosclerotic plaques (Marfella et al., 2007) within the thickened resistance arteries (Rizzoni et al., 2007).

The belief that these early morning events are directly related to the early morning rise in BP has been repeatedly emphasized by Kario (2010). As the threshold for “pathologic” morning surge, Kario and coinvestigators found increased risk only in subjects in the upper 10th percentile of systolic BP, a rise of 55 mm Hg or more (Kario, 2010). In an analysis of data from 5,695 subjects followed for a median of 11.4 years, Li et al. (2010) also observed an increase in events only among the subjects in the upper 10th percentile of SBP, a level of 37 mm Hg or more. Thus, a “pathologic” morning surge appears to be a very high level of increased SBP.

Conversely, data from two more recent studies do not confirm a relation between any level of morning surge and either cardiovascular events (Verdecchia et al., 2012) or all-cause mortality (Israel et al., 2011). Israel et al. (2011) found a greater morning surge in nondipping subjects to be associated with *decreased* all-cause mortality, concluding that “an increase in morning BP over nocturnal level probably represents a healthier form of circadian variation.” Verdecchia et al. (2012), in their study of 3,012 initially untreated hypertensives followed for a mean of 8.4 years, found that “a blunted morning BP surge was an independent predictor of cardiovascular events whereas an excessive BP surge did not portend an increased risk of events.” Both authors emphasize that their findings likely relate to the degree of nocturnal dipping: The greater the day–night dip, the

greater the morning BP surge. Therefore, as noted before, the degree of BP dipping seems to be the best prognostic indicator.

White-Coat Effect

Measurement of the BP may invoke an alerting reaction, a reaction that is only transient in most patients but persistent in some. It usually is seen more often in people who have a greater rise in BP under psychological stress (Palatini et al., 2003), but the majority of people have higher office BP than out-of-office BP (O'Brien et al., 2003).

Environment

There is a hierarchy of alerting: Least at home, more in the clinic or office, and most in the hospital. Measurements by the same physician were higher in the hospital than in a health center (Enström et al., 2000). To reduce the alerting reaction, patients should relax in a quiet room and have multiple readings taken with an automatic device (Myers, 2012a).

Measurer

Figure 2-6 demonstrates that the presence of a physician usually causes a rise in BP that is sometimes very impressive (Mancia et al., 1987). The data in Figure 2-6 were obtained from patients who had an intra-arterial recording. When the intra-arterial readings were stable, the BP was measured in the non-catheterized arm by both a male physician and a female nurse, half of the time by the physician first and the other half by the nurse first. The patients had not met the personnel but had been told that they would be coming. When the physician took the first readings, the BPs rose an average of 22/14 mm Hg and as much as 74 mm Hg systolic. The readings were approximately half that much above baseline at 5 and 10 minutes. Similar rises were seen during three subsequent visits. When the nurse took the first set of readings, the rises were only half as great as those noted by the physician, and the BP usually returned to near-baseline when measured again after 5 and 10 minutes. The rises were not related to patient age, gender, overall BP variability, or BP levels. These marked differences are not limited to handsome Italian doctors or their excitable patients. Similar nurse–physician differences have been repeatedly noted elsewhere (Little et al., 2002).

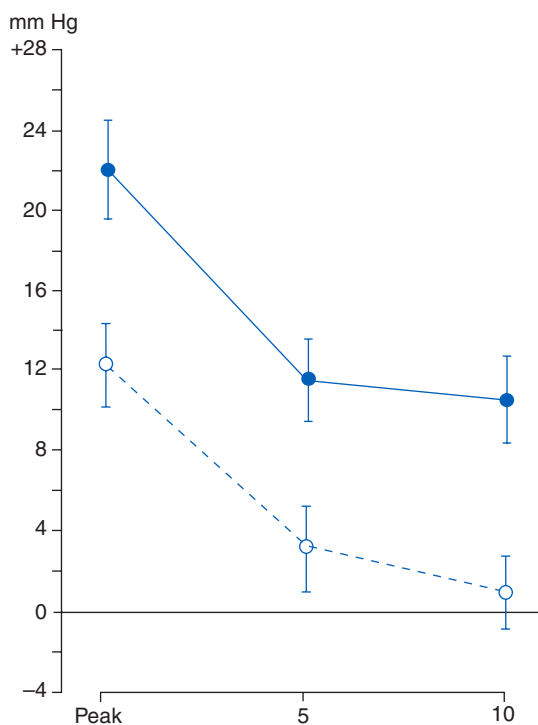


FIGURE 2-6 • Comparison of maximum (or peak) rises in systolic BP in 30 subjects during visits with a physician (solid line) and a nurse (dashed line). The rises occurring at 5 and 10 minutes into the visits are shown. Data are expressed as mean (\pm standard error of the mean) changes from a control value taken 4 minutes before each visit. (Modified from Mancia G, Paroti G, Pomidossi G, et al. Alerting reaction and rise in blood pressure during measurement by physician and nurse. *Hypertension* 1987;9:209–215.)

A large amount of data indicate a marked tendency in most patients for BP to fall after repeated measurements, regardless of the time interval between readings (Verberk et al., 2006). These findings, then, strongly suggest that nurses and not physicians should measure the BP and that at least three sets of readings should be taken before the patient is labeled hypertensive and the need for treatment is determined (Graves & Sheps, 2004).

White-Coat Hypertension

As will be noted, *white-coat hypertension* (WCH) has been variably defined. The most commonly accepted definition is an average of multiple daytime out-of-office BPs of less than 135/85 mm Hg in the presence of usual office readings above 140/90 mm Hg (O'Brien et al., 2003; Verdecchia et al., 2003).

Most patients have higher BP levels when taken in the office than when taken out of the office, as

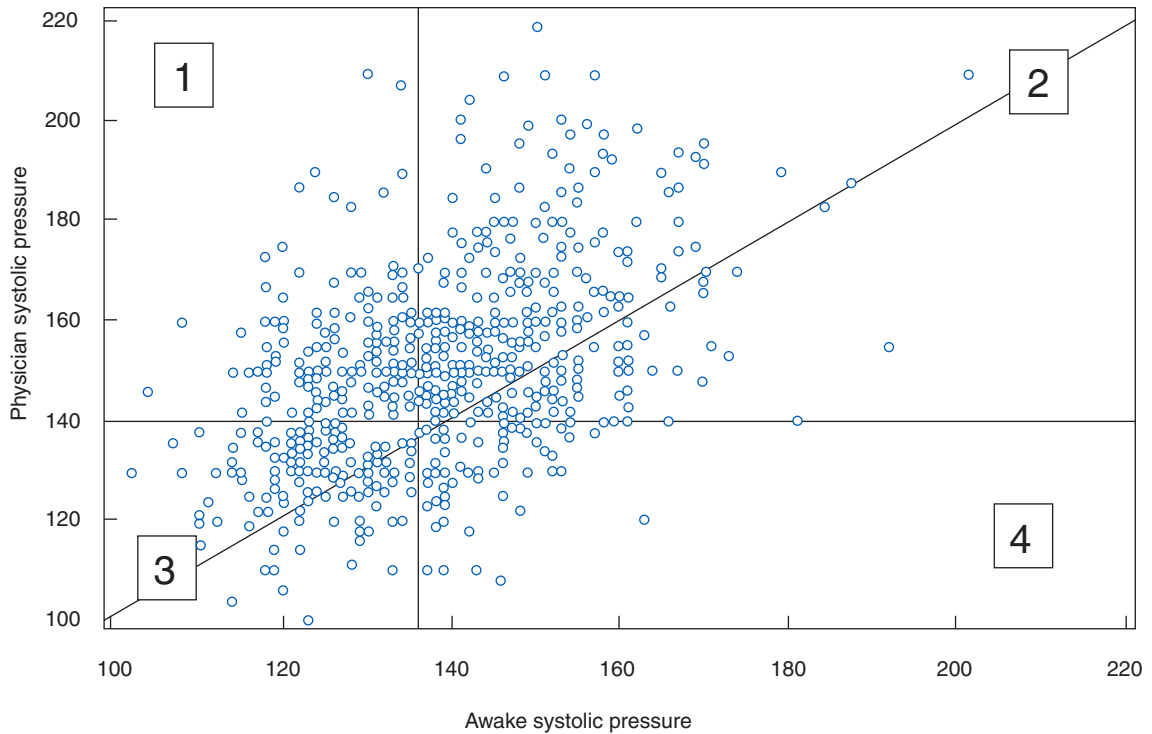


FIGURE 2-7 • Plot of clinic systolic and daytime ambulatory BP readings in 573 patients. 1, Patients with WCH; 2, patients with sustained hypertension; 3, patients with normal BP; 4, patients whose clinic BP underestimates ambulatory BP. The majority of sustained hypertensives and normotensives had higher clinic pressures than awake ambulatory pressures. (Adapted from Pickering TG. Ambulatory monitoring and the definition of hypertension. *J Hypertens* 1992;10:401–409.)

shown in a comparison between the systolic BPs obtained by a physician versus the average daytime systolic BPs obtained by ambulatory monitors (Pickering, 1996) (Fig. 2-7). In the figure, all the points above the diagonal line represent higher office readings than out-of-office readings, indicating that a majority of patients demonstrate the white-coat effect.

Whereas most patients exhibiting a white-coat effect also had elevated out-of-office readings, so that they are hypertensive in all settings (Fig. 2-7, group 2), a smaller but significant number of patients had normal readings outside the office—i.e., WCH (Fig. 2-7, group 1)—whereas another group had normal office readings but elevated outside readings (Fig. 2-7, group 4). As will be described, such *masked* hypertension has received increasing attention. Pickering et al. (1988) had previously found that among 292 untreated patients with persistently elevated office readings over an average of 6 years, the out-of-office readings recorded by a 24-hour ambulatory monitor were normal in 21%. Since that observation, the prevalence of WCH has been found to be approximately 15% in multiple groups of patients with office hypertension

(Dolan et al., 2004). To ensure the diagnosis, more than one ABPM should be obtained (Cuspidi et al., 2007).

It is important to avoid confusion between the white-coat effect and white-coat hypertension. As Pickering (1996) emphasized, “White coat hypertension is a measure of BP level, whereas the white coat effect is a measure of change. A large white coat effect is by no means confined to patients with white coat hypertension and indeed is often more pronounced in patients with severe hypertension.”

As interest in WCH has grown, a number of its features have become apparent, including the following:

- The prevalence depends largely on the level of the office readings: The less the elevation, the lower the prevalence of WCH since there is less spread between the lower limit of office hypertension (>140/90 mm Hg) and the upper limit of WCH (<135/85 mm Hg).
- The prevalence of WCH may be reduced if the office readings are based on at least five separate visits or by the process of ambulatory BP measurement described by Myers (2012a) (refer section, Automated Office BP Measurement, page 14).

- ▶ Only daytime ambulatory readings have been used to define WCH, but O'Brien et al. (2013) state that “because of the contribution of asleep BP as a predictor of outcome, it seems illogical to exclude this period from consideration....an alternative definition of WCH might encompass patients with office readings at least 140/90 mm Hg and a mean 24-hour BP less than 130/80 mm Hg.”
- ▶ Multiple self-obtained home readings are as good as ambulatory readings to document WCH (Den Hond et al., 2003). However, neither necessarily reflect the extent of the pressor effect of the doctor's visit (Saladini et al., 2012).
- ▶ The prevalence rises with the age of the patient (Mansoor et al., 1996) and is particularly high in elderly patients with isolated systolic hypertension (Jumabay et al., 2005).
- ▶ Women are more likely to have WCH (Dolan et al., 2004).
- ▶ Some patients considered to have resistant or uncontrolled hypertension on the basis of office readings instead have WCH and, therefore, in the absence of target organ damage, may not need more intensive therapy (Redon et al., 1998). However, most treated hypertensives with persistently high office readings also have high out-of-office readings, so their inadequate control cannot be attributed to the white-coat effect (Mancia et al., 1997). Moreover, Franklin et al. (2012a) found patients with isolated systolic hypertension who when treated continue to display the white-coat effect remained at a two-fold greater risk for cardiovascular events than seen in untreated normotensives. Franklin et al. (2012a) refer to these patients as having “treated normalized hypertension” whereas Myers (2012b) prefers the term “pseudoresistant treated hypertension.”

Beyond these features, two more important and interrelated issues remain: What is the natural history of WCH and what is its prognosis?

Natural History

Too few patients have been followed long enough to be sure of the natural history of WCH. Pickering et al. (1999) found that only 10% to 30% become hypertensive over 3 to 5 years. Mancia et al. (2009) found that 43% of patients with WCH developed sustained hypertension after 10 years. As noted, the magnitude of the white-coat effect varies considerably, so multiple ABPMs are needed to ensure the diagnosis (Muxfeldt et al., 2012).

Prognosis

Less uncertainty remains about the risks of WCH as more patients are followed for longer times. In an analysis of data from four prospective cohort studies from the United States (U.S.), Italy, and Japan, which used comparable methodology for 24-hour ABPM in 1,549 normotensives and 4,406 essential hypertensive patients, the prevalence of WCH was 9% (Verdecchia et al., 2005). Over the first 6 years of follow-up, the risk of stroke in a multivariate analysis was a statistically insignificant 1.15 in the WCH group versus 2.01 in the ambulatory hypertensive group compared to the normotensive group. However, the incidence of stroke began to increase after the 6th year in the WCH group and, by the 9th year, crossed the hazard curve of the ambulatory hypertensive group.

Pierdomenico et al. (2008) followed 305 people with normal BP, 399 with WCH, and 1,333 with sustained hypertension for 14 years. Event-free survival rates were the same in the normotensives and WCHs until the 10th year when it fell among the WCHs but still remained much higher than seen in the sustained hypertensives. Similar data were reported by Ben-Dov et al. (2008) in an even larger group of treated WCHs compared to those with sustained hypertension. On the other hand, Franklin et al. (2012a) found that over a mean follow-up of 10.6 years, the 334 subjects with isolated systolic hypertension and the white-coat effect who remained untreated had the same cardiovascular risk as seen among the 5,271 untreated normotensives.

Before clinical events are seen, WCHs have been found to have increased arterial stiffness (Sung et al., 2013) and thickness (Puato et al., 2008). Obviously, close follow-up of patients diagnosed with WCH is mandatory (Muxfeldt et al., 2012). At the least, they should be encouraged to modify their lifestyle in an appropriate manner and continue to monitor their BP status.

Masked Hypertension

As seen in the lower right portion of Figure 2-7, labeled as no. 4, some patients have normal office BP (<140/90) but elevated ambulatory readings (>135/85). These “masked” hypertensives may comprise a significant portion, 10% or more, of the general population (O'Brien et al., 2013). Higher daytime ambulatory BPs than office readings were found in 41% of 1,814 subjects aged 75 years or older with a normal office BP

(Cacciolati et al., 2011). Such patients have increased rates of cardiovascular morbidity, almost as high as seen in those with both clinic and ambulatory hypertension (Ben-Dov et al., 2008; Bobrie et al., 2008; Pierdomenico & Cuccurullo, 2011).

Since by definition these patients have normal office BP readings, the only way to exclude masked hypertension is to obtain out-of-office readings on every patient. Though only a few home readings are usually needed (Mallion et al., 2004), most patients cannot get them. Therefore, the search should be narrowed to those more likely to be higher out of the office. These include patients with diabetes (Franklin et al., 2013), unexplained tachycardia (Grassi et al., 2007), left ventricular hypertrophy (Hanninen et al., 2013), or obstructive sleep apnea (Baguet et al., 2008).

Patients on antihypertensive therapy usually have a lesser fall, averaging 30% less, in ambulatory BPs than in office measurements (Mancia & Parati, 2004), often showing a pattern of masked hypertension. However, they should not be called “masked” because they were hypertensive before therapy. O'Brien et al. (2013) prefer the term “masked uncontrolled hypertension.” Diabetic patients display this mimicry more often than do nondiabetics (Franklin et al., 2013).

OFFICE MEASUREMENT OF BLOOD PRESSURE

Despite the presence of inadequacies that are inherent in the current performance of office readings, they will continue to be widely used so they will be fully described. As will be noted, a possible way to rescue their use has been described (Myers, 2012a). Moreover, fewer than half of U.S. hypertensives have home monitors (Ostchega et al., 2013) and in many places even rudimentary offices remain the only site available for BP measurement.

Under the best of circumstances, all of the previously described causes of variability are difficult to control. Even under carefully controlled conditions, all indirect measures are different from those obtained intra-arterially, averaging about 5 mm Hg lower for systolic and 10 mm Hg higher for diastolic (Smulyan & Safar, 2011). Use of the guidelines shown in Table 2-3 will prevent most preventable measurement errors. More details are provided in a report by experts (Stergiou et al., 2012a).

Patient and Arm Position

The patient should be seated comfortably with the arm supported and positioned at the level of the heart (Fig. 2-8). Measurements taken with the arm hanging at the patient's side averaged 10 mm Hg higher than those taken with the arm supported in a horizontal position at heart level (Netea et al., 2003). When sitting upright on a table without support, readings may be as much as 10 mm Hg higher because of the isometric exertion needed to support the body and arm. Systolic readings are approximately 8 mm Hg higher in the supine than in the seated position even when the arm is at the level of the right atrium (Netea et al., 2003).

Differences Between Arms

As noted earlier in this chapter, initially the BP should preferably be measured in both arms simultaneously to ascertain the differences between them; if the reading is higher in one arm, that arm should be used for future measurements. In two meta-analyses of BP measurement data, some including patients referred because of suspicion of peripheral vascular disease (PVD), a difference of 10 mm Hg or more was found in 15% to 20% of patients and was associated with an increased prevalence of PVD and mortality (Clark et al., 2012; Verberk et al., 2011). Much lower BP in the left arm is seen in patients with subclavian steal caused by reversal of flow down a vertebral artery distal to an obstructed subclavian artery, as noted in 9% of 500 patients with asymptomatic neck bruits (Bornstein & Norris, 1986). The BP may be either higher or lower in the paretic arm of a stroke patient (Dewar et al., 1992).

Standing Pressure

Readings should be taken immediately on standing and after standing at least 2 minutes to check for spontaneous or drug-induced postural changes, particularly in the elderly and in diabetics. If no fall in BP is seen in patients with suggestive symptoms, the time of quiet standing should be prolonged to at least 5 minutes. In most people, systolic BP falls and diastolic BP rises by a few millimeters of mercury on changing from the supine to the standing position. In the elderly, significant postural falls of 20 mm Hg or more in systolic BP are more common, occurring in approximately 10% of ambulatory people older than 65 years and in more than half of frail nursing-home residents, particularly in those with elevated supine systolic BP (Gupta & Lipsitz, 2007).

TABLE 2-3

Guidelines for Measurement of BP in the Office

Patient Conditions

Posture

- Initially, particularly in those >65 years old or, with diabetes, or receiving antihypertensive therapy, check for postural changes by taking readings after 5 min supine, then immediately and 2 min after standing
- For routine follow-up, the patient should sit quietly with the arm bared and supported at the level of the heart and the back resting against a chair. The length of time before measurement is uncertain, but most guidelines recommend at least 1 min.

Circumstances

- No caffeine or smoking within 30 min preceding the reading
- A quiet, warm setting

Equipment

Cuff size

- The bladder should encircle at least 80% of the circumference and cover two-thirds of the length of the arm
- A too-small bladder may cause falsely high readings

Manometer

- Either a mercury, recently calibrated aneroid or validated electronic device
- Since mercury is hazardous, oscillometric devices are being used increasingly, and they do not require listening for Korotkoff sounds

Stethoscope

- The bell of the stethoscope should be used, avoiding excess pressure

Infants

- Use ultrasound (e.g., the Doppler method)

Technique

Number of readings

- On each occasion, take at least two readings, separated by as much time as is practical; if readings vary >5 mm Hg, take additional readings until two are close
- For diagnosis, obtain three sets of readings at least 1 wk apart
- Initially, take pressure in both arms preferably simultaneously; if the pressures differ, use the arm with the higher pressure
- If the arm pressure is elevated, take the pressure in one leg, particularly in patients <30 years old

Performance

- Inflate the bladder quickly to a pressure 20 mm Hg above the systolic pressure, recognized by the disappearance of radial pulse, to avoid an auscultatory gap
- Deflate the bladder 3 mm Hg/s
- Record the Korotkoff phase I (appearance) and phase V (disappearance)
- If the Korotkoff sounds are weak, have the patient raise the arm and open and close the hand 5–10 times, then inflate the bladder quickly

Recordings

- Note the pressure, patient position, the arm, and the cuff size (e.g., 140/90, seated, right arm, and large adult cuff, respectively)

Leg Pressure

If the arm reading is elevated, particularly in a patient younger than 30, the BP should be taken in one leg to rule out coarctation of the aorta.

Sphygmomanometer

Independent evaluations of BP device accuracy and performance are available at www.dableducational.org,

but there are no obligatory standards which must be met. Significant errors of both mercury and aneroid manometers were found in more than 5% of readings in physicians' offices (Niyonsenga et al., 2008).

As mercury manometers are being phased out because of the toxic potential of mercury spills and with the inaccuracies of aneroid manometers, automated oscillometric devices are increasingly being used, which should improve the accuracy of readings.

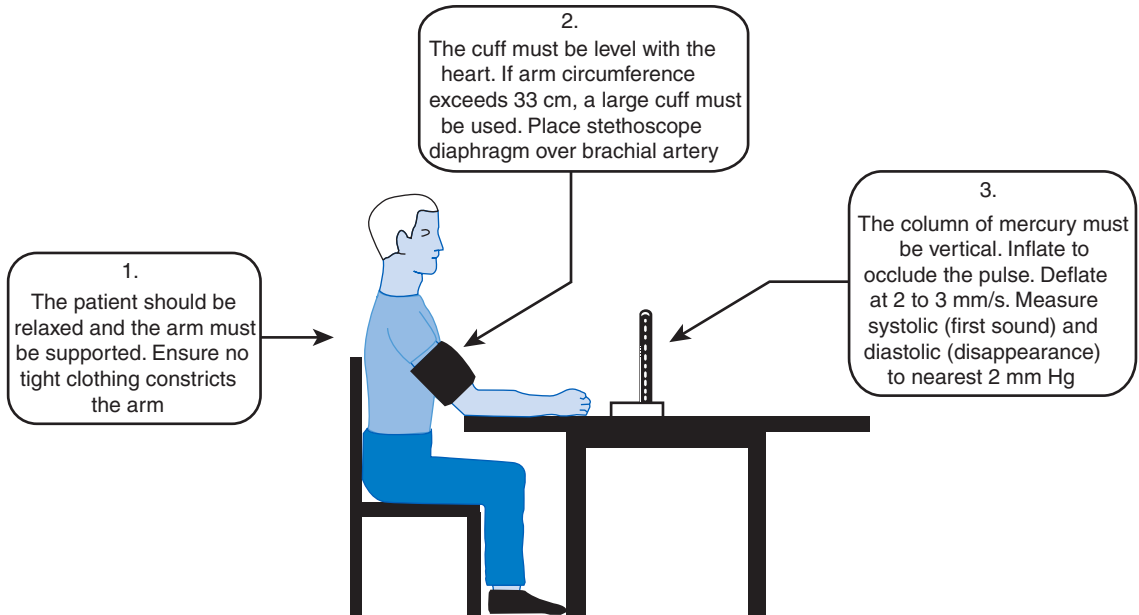


FIGURE 2-8 • Technique of BP measurement recommended by the British Hypertension Society. (From British Hypertension Society. Standardization of blood pressure measurement. *J Hypertens* 1985;3:29–31. Reproduced with permission)

Bladder Size

The width of the bladder should be equal to approximately two-thirds the distance from the axilla to the antecubital space; a 16-cm-wide bladder is adequate for most adults. The bladder should be long enough to encircle at least 80% of the arm. Erroneously high readings may occur with the use of a bladder that is too short (Aylett et al., 2001) and erroneously low readings with a bladder that is too wide (Bakx et al., 1997).

Most sphygmomanometers sold in the U.S. have a cuff with a bladder that is 12 cm wide and 22 cm long, which is too short for patients with an arm circumference greater than 26 cm, whether fat or muscular (Aylett et al., 2001). The British Hypertension Society (BHS) recommends longer cuff size (12 × 40 cm) for obese arms (O'Brien et al., 2003). The American Heart Association recommends progressively larger cuffs with larger arm circumference:

- Arm circumference 22 to 26 cm, 12 × 22 cm cuff (small adult)
- Arm circumference 27 to 34 cm, 16 × 30 cm cuff (adult)
- Arm circumference 35 to 44 cm, 16 × 36 cm cuff (large adult)
- Arm circumference 45 to 52 cm, 16 × 42 cm cuff (adult thigh)

Children require smaller cuffs depending on their size.

Cuff Position

With mercury manometers, if the bladder within the cuff does not completely encircle the arm, particular care should be taken to ensure that the bladder is placed over the brachial artery. The lower edge of the cuff should be approximately 2.5 cm above the antecubital space. In extremely obese people, a thigh cuff may be used with the wide bladder folded on itself if necessary, or the bladder may be placed on the forearm and the sounds heard over the radial artery.

Manometer

Oscillometric devices are rapidly taking over the home market and are becoming standard in offices and hospitals. Fortunately, their accuracy and reliability are improving, and more have passed the protocols of the U.S. Association for the Advancement of Medical Instrumentation (AAMI) and the BHS. Web sites (www.dableducational.com and bhsec.org/blood_pressure.list.stm) have been established to provide all of the available information needed about the devices being marketed.

The oscillometric devices detect initial (systolic) and maximal (mean arterial pressure) oscillations in the brachial artery and calculates the diastolic BP based on proprietary algorithms. In general, the readings obtained by auscultatory and oscillometric devices are closely correlated. In a large population wherein both oscillometric devices (Omron HEM-907XL) and mercury manometers were compared, the mean differences were less than 2 mm Hg except in obese subjects requiring the extra-large cuff where the systolic difference averaged 3.1 mm Hg (Ostchega et al., 2012).

The oscillometric devices are easier and faster to use, and they minimize the common terminal digit preference wherein the last number is rounded off to 0 or 5. Some of the electronic devices inflate automatically, which is especially useful for patients with arthritis. Others have a printer attached, and some can have the data downloaded after storing a number of readings. Devices are available for automatic transmission of data to a central location (Møller et al., 2003). An adequate device can be purchased for less than \$40. To ensure its proper use and accuracy, the electronic device should be checked by having the patient use it on one arm while the pressure is simultaneously taken in the office with a sphygmomanometer on the other arm.

If at least three measurements are taken, oscillometric devices provide accurate readings in patients with atrial fibrillation (Pagonas et al., 2013).

Automated Office BP Measurement

Martin Myers (2012a) has proposed a way to improve the accuracy of office readings by “an automated office blood pressure (AOBP)” procedure, which requires five readings, taken at 1-minute intervals, with a fully automatic oscillometric device while the patient sits alone, undisturbed. Myers et al. (2010) provide evidence that the average of these five readings closely approximates those obtained both during the awake portion of 24-hour ambulatory monitoring and multiple self-recorded home readings. This procedure virtually eliminates the white-coat effect and reduces the prevalence of masked hypertension as well (Myers et al., 2012).

As attractive as this procedure is, it does require a dedicated space in the office and an automated device that may cost \$600.

Meanwhile, a low-cost solar-powered device (Omron HEM-SOLAR) has been developed, which should be useful for low-resource settings (Parati et al., 2010a).

Another Technology

A new manometric device has been developed by Fujikawa et al. (2013), which uses a triple cuff and measures changes in pulse arrival time rather than oscillations in the cuff as it deflates. This technique may be a more accurate way to measure BP.

Wrist and Finger Devices

Wrist oscillometric devices are particularly useful for obese people whose upper arm is too large for accurate readings. They must be kept at the level of the heart. At least three of them have been shown to be accurate (dableducational.com).

Finger devices measure the pressure in the finger by volume-clamp plethysmography. The Finapres finger cuff may be used for continuous BP monitoring under carefully controlled conditions (Silke & McAuley, 1998), but it is not suitable for intermittent readings. Home finger units are not recommended for self-monitoring (Pickering et al., 2008).

Automated Devices in the Community

The automated oscillometric devices increasingly found in pharmacies usually provide accurate readings but may be inaccurate in people who are either obese or very thin (Van Durme et al., 2000). For those who cannot use more accurate (and more easily validated) home devices, readings obtained by such an automated machine are better than nothing, but patients should not be managed solely on the basis of these readings.

Technique for Measuring Blood Pressure

As noted in Table 2-3, the pressure in the bladder should be raised at least 20 mm Hg above the systolic level, as indicated by the disappearance of the radial pulse, because there may be an auscultatory gap (a temporary disappearance of the sound after it first appears), which is related to increased arterial stiffness.

The cuff should be deflated at a rate of 2 to 4 mm Hg per second; either a slower or faster rate may cause falsely higher readings (Bos et al., 1992). However, most oscillometric devices are set for more rapid deflation.

By auscultation, disappearance of the sound (phase V) is a more sensitive and reproducible end

point than muffling (phase IV) (De Mey, 1995). In some patients with a hyperkinetic circulation, e.g., anemia or pregnancy, the sounds do not disappear, and the muffled sound is heard well below the expected diastolic BP, sometimes near zero. This phenomenon can also be caused by pressing the stethoscope too firmly against the artery. If arrhythmias are present, additional readings with an auscultatory device may be required to estimate the average systolic and diastolic BP (Lip et al., 2001).

Pseudohypertension

As written by Franklin et al. (2012b): “The term ‘pseudohypertension’ in the elderly is misleading; it suggests a benign condition secondary to a false elevation in oscillometric or auscultatory DBP as compared to intra-arterial DBP, whereas, when white-coat hypertension and white-coat effect without target organ damage are ruled out, the finding of isolated systolic hypertension with widened pulse pressure is associated with considerable cardiovascular risk.”

Ways to Amplify the Sounds

With auscultation, the loudness and sharpness of the Korotkoff sounds depend in part on the pressure differential between the arteries in the forearm and those beneath the bladder. To increase the differential and thereby increase the loudness of the sounds, either the amount of blood in the forearm can be decreased or the capacity of the vascular bed can be increased. The amount of blood can be decreased by rapidly inflating the bladder, thereby shortening the time when venous outflow is prevented but arterial inflow continues, or by raising the arm for a few seconds to drain venous blood before inflating the bladder. The vascular bed capacity can be increased by inducing vasodilation through muscular exercise, specifically by having the patient open and close the hand 10 times before the bladder is inflated. If the sounds are not heard well, the balloon should be emptied and reinflated; otherwise, the vessels will have been partially refilled and the sounds thereby muffled.

Taking Blood Pressure in the Thigh

A large (thigh) cuff should be used to avoid factitiously elevated readings. With the patient lying prone and the leg bent and cradled by the observer, the observer listens with the stethoscope for the Korotkoff

sounds in the popliteal fossa. This should be done as part of the initial workup of every young hypertensive, in whom coarctation is more common. Normally, the systolic BP is higher and the diastolic BP a little lower at the knee than in the arm because of the contour of the pulse wave (Smulyan & Safar, 2011).

Taking Blood Pressure in Children

If the child is calm, the same technique that is used with adults should be followed; however, smaller, narrower cuffs must be used (see Chapter 16). If the child is upset, the best procedure may be simply to determine the systolic BP by palpating the radial pulse as the cuff is deflated. In infants, ultrasound is usually used.

Recording of Findings

Regardless of which method is used to measure BP, notation should be made of the conditions so that others can compare the findings or interpret them properly. This is particularly critical in scientific reports, yet many articles about hypertension fail to provide this information.

Blood Pressure During Exercise

An exaggerated response of BP during or immediately after graded exercise, stress testing has been found to predict the development of hypertension in normotensives (Holmqvist et al., 2012) and their subsequent morbidity or mortality from cardiovascular disease (Schultz et al., 2013). Different upper limits for a normal response to exercise have been used in various series, but an exaggerated response to a systolic level above 200 mm Hg at a 100 W workload increases the likelihood of the onset of hypertension from twofold to fourfold over the subsequent 5 to 10 years as compared with that seen with nonexaggerated responses.

Pulse Pressure

Pulse pressure is the difference between the systolic and diastolic BP levels. Among the 13,340 participants in an ongoing study with 18 years of follow-up, pulse pressure was the greatest contributor for the risk of heart failure and all-cause mortality whereas systolic BP was most closely associated with coronary heart disease and stroke (Cheng et al., 2013). Moreover, in the HYVET trial of patients 80 years or

older, wider pulse pressure was closely associated with the risk of dementia (Peters et al., 2013).

Importance of Office Blood Pressures

Even if all the guidelines listed in Table 2-3 are followed, routine office measurements of BP by sphygmomanometry will continue to show considerable variability. However, before discounting even single casual BP readings, recall that almost all the data on the risks of hypertension described in Chapter 1 are based on only one or a few office readings taken in large groups of people. There is no denying that such data have epidemiologic value, but a few casual office readings are usually not sufficient to determine the status of an individual patient. Two actions minimize variability. First, at least two readings should be taken at every visit, as many as needed to obtain a stable level with less than a 5-mm Hg difference; second, at least three and, preferably, more sets of readings, weeks apart, should be taken unless the initial value is so high, e.g., greater than 180/120 mm Hg, that immediate therapy is needed.

Although multiple carefully taken office readings may be as reliable as those taken by ambulatory monitors, out-of-office readings provide additional data, both to confirm the diagnosis and, more important, to document the adequacy of therapy.

HOME MEASUREMENTS

The current emphasis on home BP measurements has been reached for a number of reasons, including these:

- The availability of inexpensive and reliable devices (www.dableducational.com)
- The elucidation of the optimal schedule for home readings (Niiranen et al., 2011)
- The establishment of thresholds for home-obtained readings for ascertainment of cardiovascular risk (Niiranen et al., 2013)
- The recognition of the comparability of home readings and ambulatory monitors and the superiority of both of them over office readings (Stergiou & Bliziotis, 2011; Ward et al., 2012)
- The finding that home monitoring is one of the few ways to improve adherence to antihypertensive therapy (Bosworth et al., 2011)
- The availability of techniques to ensure the accurate translation of home readings either by memory in the device or by telemonitoring (Omboni et al., 2013)

When home devices have been documented to measure BP during sleep (Ishikawa et al., 2012) and these devices become widely available, one of the remaining rationales for ABPM will no longer be needed. Moreover, as Zanchetti (2011) has noted, home readings may be the most practical way to assess BP variability.

These recommendations are currently advised (Parati et al, 2010b):

- HBPM should become a routine component of BP measurement in all patients with known or suspected hypertension. However, fewer than half of the hypertensives in the U.S. have a home device (Ostchega et al., 2013).
- Patients should be advised to purchase oscillometric monitors that measure BP on the upper arm with an appropriate cuff size and that have been shown to be accurate according to the standard international protocols. They should be shown how to use them by their health care providers.
- Two to three readings should be taken while the subject is resting in the seated position, both in the morning and at night, over a period of 1 week. A total of ≥ 12 readings are recommended for making clinical decisions (Niiranen et al., 2011).
- HBPM is indicated in patients with newly diagnosed or suspected hypertension, in whom it may distinguish between WCH and sustained hypertension. In patients with prehypertension, HBPM may be useful for detecting masked hypertension.
- HBPM is recommended for evaluating the response to any type of antihypertensive treatment and may improve adherence.
- The target HBPM goal for treatment is less than 130/85 mm Hg (Niiranen et al., 2013).
- HBPM is useful in the elderly (Cushman et al., 2012), in whom both BP variability and the white-coat effect are increased; in patients with diabetes (Eguchi et al., 2012), in whom adequate BP control is of paramount importance; and in pregnant women, children, and patients with kidney disease.
- HBPM has the potential to improve the quality of care while reducing costs and should be reimbursed (Pickering et al., 2008).

A few patients cannot overcome their anxiety over measuring their own BP, a continuing alerting reaction. Others become overly concerned, despite prior advice, over an occasional high reading. For a few, the stress is beyond the benefit, and they should be advised to give the device to a relative or sell it to a neighbor.

AMBULATORY MONITORING

ABPM has been available for over 30 years and was shown to have prognostic value in 1983 (Perloff et al., 1983). While ABPM is not currently available to most clinicians, the recent recommendation by the U.K. National Institute for Health and Clinical Excellence (NICE) that ABPM be used to establish the diagnosis and thereby guide the institution of antihypertensive therapy in all patients found to have an elevated office BP (Ritchie et al., 2011) will likely stimulate the availability and use of the procedure.

The NICE recommendation was accompanied by two publications. The first validated the improved sensitivity and specificity of ABPM over both office and home measurements (Hodgkinson et al., 2011). The other examined the cost-efficiency of ABPM after the initial finding of an elevated office reading, concluding that using ABPM in this manner “would reduce misdiagnosis and save costs” by reducing the number of incorrectly diagnosed and treated patients (Lovibond et al., 2011).

The ability of ABPM to provide better evidence for both the diagnosis of hypertension and the prognosis of patients has been validated in various types of patients, including those with chronic renal disease (Minutolo et al., 2011), cognitive decline (Celle et al., 2012), silent cerebrovascular disease (Hara et al., 2012), and atrial fibrillation (Stergiou et al., 2012b). Moreover, 6-hour daytime ABPM has been reported to correlate closely with 24-hour monitoring in both children (King-Schultz et al., 2012) and adults (Ernst et al., 2011). Therefore, the ability of such shorter intervals to diagnose and establish the adequacy of therapy could reduce the inconvenience of the 24-hour procedure (Wolak et al., 2013).

For these and other reasons, ABPM has been recommended for use in the NHANES surveys of the U.S. population (Giles et al., 2012) and for assessing the effects of drugs on BP (O'Brien & Turner, 2013). A European Society of Hypertension position paper provides a complete analysis of the use of ABPM (O'Brien et al., 2013). The recommended thresholds for ABPM are shown in Table 2-4.

Despite its obvious attractions, there are some problems with ABPM. First, it is expensive and not paid for by most U.S. third-party payers. Second, many devices lack adequate accuracy (Hodgkinson et al., 2013) even though there are 13 recommended devices on the *dableducational* Web site. Third, it may be possible to measure sleep-time BP with less expensive and easier to use devices (Ishikawa et al., 2012).

TABLE 2-4

Recommended Thresholds for ABPM in Adults

24-Hour average	≥130/80 mm Hg
Awake (daytime) average	≥135/85 mm Hg
Asleep (nighttime) average	≥120/70 mm Hg

Adapted from O'Brien E, et al. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013;31:1731-1768.

The advice of Palatini (2012) seems appropriate: “Obtaining information on clinic, self-measured, and 24-hour BP may represent the optimal clinical procedure... Whenever possible, it is advisable that clinic, home, and ambulatory BPs are used for the diagnosis and management of hypertension.”

CENTRAL BLOOD PRESSURE

Beyond ABPM, newer techniques may be moving from investigation into clinical practice: Measurement of pulse wave velocity and central BP, noninvasively, using a number of commercially available devices (Cameron, 2013). Most recent studies have utilized a high-fidelity micromanometer to record radial or carotid artery waveforms, using a generalized transfer function to generate a corresponding central (ascending aortic) pressure waveform (Salvi et al., 2013) (Fig. 2-9).

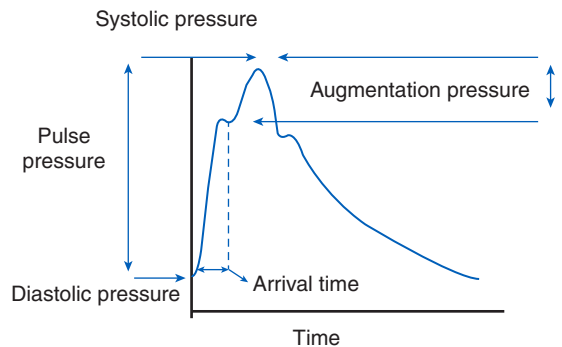


FIGURE 2-9 • Central pressure waveform. The height of the late systolic peak above the inflection defines the augmented pressure, and the ratio of augmented pressure to PP defines the augmentation index (in percentage). (Reprinted from Agabiti-Rosei E, Mancia G, O'Rourke MF, et al. Central blood pressure measurements and antihypertensive therapy: A consensus document. *Hypertension* 2007;50:154-160, with permission.)

A detailed description of pulse wave reflections and velocity, arterial stiffness, and much more about this emerging area of hypertension is provided in Chapter 3. For now, measurement of central BP will remain an interesting investigative tool but will likely not move into clinical practice since much of the information it provides is provided by pulse pressure and other measures of arterial stiffness (Winston et al., 2013). Nonetheless, as the cost of the equipment comes down and proof of its superiority over peripheral (brachial) measurements becomes even more persuasive (Williams et al., 2013), measurement of central BP may be the next advance in clinical hypertension.

Heart Rate

With all the deserved attention to BP measurements, the heart rate and its variability have been shown to add to the assessment of cardiovascular risk (Julius et al., 2012)

Ankle–Brachial Index

Ankle–brachial index is used to identify and quantify PVD. Currently, the procedure is performed by measuring systolic BP at the ankle and arm with a Doppler device, with values less than 0.9 indicating PVD and increased cardiovascular risk. Verberk et al. (2012) recommend the use of oscillometric BP monitors as a reliable and practical alternative to the Doppler technique.

CONCLUSION

Despite all the reasons that home and ambulatory measurements are better than office readings, for now, office sphygmomanometry will continue to be widely used for diagnosing and monitoring hypertension. Home readings are being more widely used, both to confirm the diagnosis and to provide better assurance of appropriate therapy. Ambulatory monitoring should be increasingly available and used. Central BP measurement may become the next major advance.

We next turn to the mechanisms responsible for elevated BP in 90% of those with hypertension, i.e., those with primary (essential) hypertension.

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Primary Hypertension: Pathogenesis (with a Special Section on Renal Denervation and Carotid Baroreceptor Pacing)

Despite decades of research and debate, we still have no unifying mechanism—and thus no single therapeutic target—for primary human hypertension. A strong case can be made that neural, renal, hormonal, and vascular mechanisms are all involved and conspire in a myriad of ways to produce hypertension. Over 60 years ago, Irvine Page proposed his mosaic theory of hypertension (Page, 1949), which states that several factors—including genes, environment, hemodynamics, humoral, endocrine, neural, adaptive, and anatomical—interact to raise blood pressure (BP). In the past two decades, it has become clear that inflammation and production of reactive oxygen species (ROS) are two common cellular and molecular events underlying many of Page’s hypertensive factors operating at the systems biology level (Harrison, 2013a). In the past 4 years since the last edition of this book, percutaneous intervention—by renal denervation (RDN) or baroreceptor pacing—is the most exciting, and also the most perplexing, development in hypertension, reawakening great interest in neural mechanisms and in the mosaic theory.

GENERAL CONSIDERATIONS

Before diving into specific theories and data, some general considerations are in order. In particular, the pathogenesis of primary hypertension has been difficult to unravel for several reasons:

- The relevance of rodent models to human disease is uncertain (Rice, 2012; Seok et al., 2013), and methods are limited for testing mechanistic hypotheses in humans.
- The dichotomy between normotension and hypertension is arbitrary because BP is a quantitative trait, showing a continuous positive relation with cardiovascular (CV) risk (Lewington et al., 2002). Thus, many experts—beginning with Sir Thomas Pickering (Pickering, 1964) and including members of the American Society of Hypertension (ASH) Working Group (Giles et al., 2005)—have argued that high BP per se is not even a disease. The same argument can be made for high serum cholesterol levels, and yet we know much more about the molecular mechanisms of hyperlipidemia than hypertension. The search for causation is not necessarily futile, but it is difficult.
- The difficulty begins with taking an accurate snapshot of a person’s “usual” BP. As discussed in Chapter 2, a person’s BP varies more from moment to moment and from day to day than any other routine measurement in clinical medicine. The within-subject variability further blurs the distinction between normal and abnormal, between normotension and hypertension.
- BP is a complex trait influenced by both environmental factors, which are well characterized, and genetic factors, which are poorly characterized. After initial excitement over the Human Genome

Project, hypertension has been far more resistant to genetic dissection than dyslipidemia and atherosclerosis. After expenditure of hundreds of millions of research dollars, many negative studies and many false-positive association studies engendered a sense of futility. But lately, a few leads have emerged, some withstanding the scrutiny of independent replication in multiple study samples.

- All clinical research designs have their limitations. Cross-sectional case–control studies of normotensives versus hypertensives have a hard time distinguishing causality from compensation. Once BP is even mildly elevated, other CV risk factors coexist along with remodeling of cardiac and vascular smooth muscle. The horse is out of the barn. Normotensive children of hypertensive parents offer one approach to identify pathogenic factors that precede the onset of hypertension and thus may be causal. However, large samples are needed to detect small effects. Clinic-based studies suffer from recruitment bias for health care–seeking individuals who do not reflect the greater disease burden in the general population, especially minority populations who have been underrepresented in clinical research (Victor et al., 2004). Observational studies cannot prove causation. Too often mechanistic inferences are

derived from post hoc analyses of randomized controlled trials (RCTs) that were not designed to interrogate disease mechanisms and where the sponsor had a financial or economic interest in the outcome.

- Primary hypertension can no longer be considered a single disease entity but rather can be subdivided into several different hemodynamic subsets, including diastolic hypertension in middle-aged persons and isolated systolic hypertension (ISH) in older persons. Obesity-related hypertension seems to be a different entity from hypertension in lean persons. More rigorously defined phenotypes hopefully will pave the way to a better mechanistic understanding of the genesis and progression of hypertension in specific segments of the population and identify individuals who can benefit from personalized medicine. This is an elusive holy grail.

It is impossible to describe the contributions of so many past and present investigators in the confines of a single chapter. The ensuing discussion will explain basic concepts in broad strokes and, wherever possible, emphasize recent data from translational studies in human subjects. We will begin with systemic hemodynamics and then discuss disease mechanisms, human genetics, and environmental modifiers (Fig. 3-1).

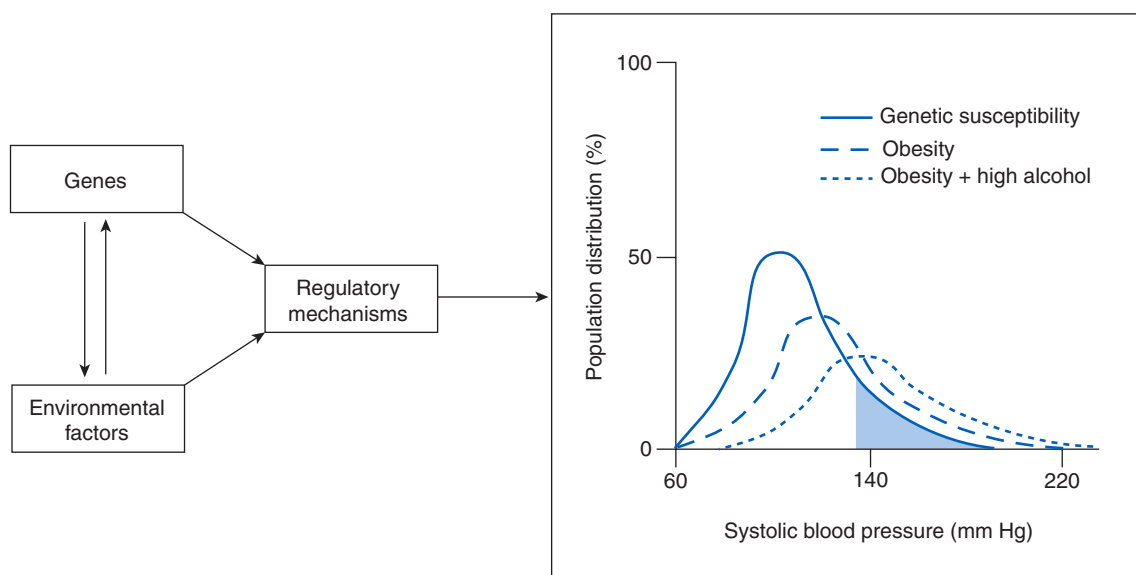


FIGURE 3-1 • Interaction among genetic and environmental factors in the development of hypertension. The left side of the figure shows that genes and environment interact to affect multiple hypertensive mechanisms. The right side of the figure depicts schematically the cumulative effects of genetic and environmental factors on population-level BP, which is normally distributed. The solid line shows the theoretic BP distribution caused by genetic susceptibility alone; the shaded area indicates systolic BP in the hypertensive range. Broken lines and dotted lines indicate populations in which one (obesity) or two (obesity plus high alcohol intake) environmental factors have been added. (Modified from Carretero OA, Oparil S. Essential hypertension. *Circulation* 2000;101:329–335.)

HEMODYNAMIC SUBTYPES

Mounting evidence from the Framingham Heart Study investigators and others indicates that human hypertension can be divided into at least three separate hemodynamic subtypes that vary by age.

Systolic Hypertension in Teenagers and Young Adults

Typically associated with hypertension in the elderly (see below), Isolated Systolic Hypertension in Older Adults also is the main type in young adults (17 to 25 years of age). The key hemodynamic abnormalities are increased cardiac output and a stiff aorta, both presumably reflecting an overactive sympathetic nervous system. The prevalence may reach as high as 25% in young men (particularly tall athletes), but only affects 2% of young women. Several recent studies show that young persons with ISH have elevated central systolic BP (by the SphygmoCor method) as well as brachial systolic BP, indicating significantly increased hemodynamic burden (Franklin et al., 2012). Thus, ISH in youth may predispose to diastolic hypertension in middle age.

Diastolic Hypertension in Middle Age

When hypertension is diagnosed in middle age, the most common BP pattern is elevated diastolic pressure with systolic pressure being either normal (isolated diastolic hypertension) or elevated (combined systolic/diastolic hypertension) (Franklin et al., 2005). This is classic “essential hypertension.” Isolated diastolic hypertension is more common in men and often associated with middle-age weight gain and the metabolic syndrome (Franklin et al., 2006). Without treatment, isolated diastolic hypertension often progresses to combined systolic/diastolic hypertension.

The fundamental hemodynamic fault is an elevated systemic vascular resistance coupled with an inappropriately “normal” cardiac output. Vasoconstriction at the level of the resistance arterioles (100 to 200 μm in diameter) results from increased neurohormonal drive and an autoregulatory reaction of vascular smooth muscle to an expanded plasma volume, the latter due to impairment in the kidneys' ability to excrete sodium (Stolarz-Skrzypek et al., 2013).

Isolated Systolic Hypertension in Older Adults

After age 55, ISH (systolic BP > 140 mm Hg and diastolic BP < 90 mm Hg) is the most common form (Franklin, 2012). In developed countries, systolic pressure rises steadily with age; in contrast, diastolic pressure rises until about age 55 and then falls progressively thereafter (Burt et al., 1995). The resultant widening of pulse pressure indicates stiffening of the central aorta, reduced aortic diameter, and a more rapid return of reflected pulse waves from the periphery, causing an augmentation of systolic aortic pressure (McEnery et al., 2014). Accumulation of collagen (which is poorly distensible) adversely increases its ratio to elastin in the aortic wall.

ISH may represent an acceleration of this age-dependent stiffening process (Franklin, 2012), although systolic BP and pulse pressure do not rise with age in the absence of urbanization (e.g., cloistered nuns) (Timio et al., 1999). ISH is more common in women and is a major risk factor for diastolic heart failure, which also is more common in women (Franklin et al., 2006). Most cases of ISH arise de novo after age 60 and are not the result of “burned out” middle-age diastolic hypertension (Franklin, 2012). Compared with young or middle-aged adults with optimal BP, those with BP in the prehypertensive range are more likely to develop ISH after age 60 (Franklin et al., 2005).

Many neurohormonal, renal, and vascular mechanisms interact to varying degrees in driving these different hemodynamic patterns of hypertension.

NEURAL MECHANISMS AND PERCUTANEOUS INTERVENTION: CAROTID BARORECEPTOR PACING AND RENAL DENERVATION

Two types of percutaneous intervention—a surgically implanted carotid baroreceptor pacemaker and catheter-based renal denervation (RDN) (see Chapter 7)—have rekindled great interest in neural mechanisms of clinical hypertension. Figure 3-2 shows the major central and reflex mechanisms thought to drive sympathetic overactivity in human hypertension (Martin & Victor, 2011). These include, among others, resetting of the baroreceptors and activation of renal sensory nerves termed “renal afferents.”

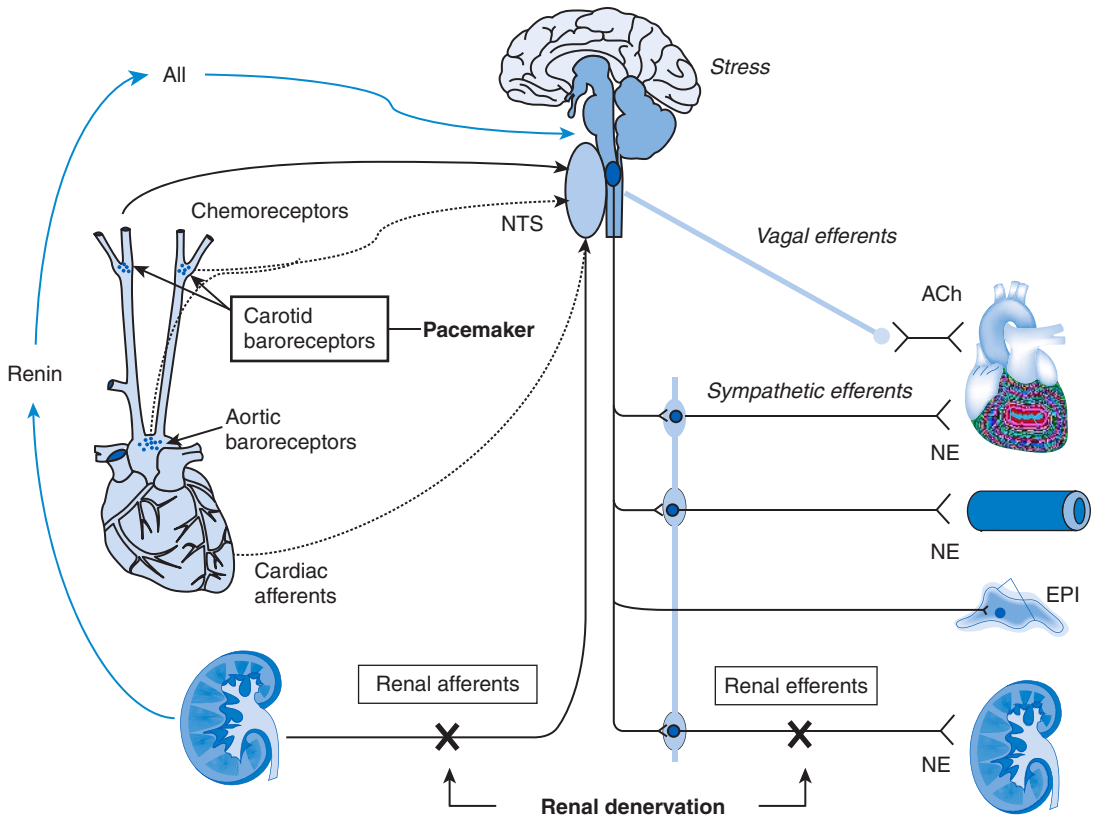


FIGURE 3-2 • Sympathetic neural mechanisms of BP regulation and treatment targets of carotid baroreceptor pacing and RDN. Note that aortic baroreceptors, which also influence BP, are not paced. Also note that RDN affects afferent and efferent renal nerves. Dotted arrows represent inhibitory neural influences, and solid arrows represent excitatory neural influences on sympathetic outflow to the heart, peripheral vasculature, and kidneys. A II, angiotensin II; ACh, acetylcholine; EPI, epinephrine; NE, norepinephrine; NTS, nucleus tractus solitarius. (Modified from Martin EA, Victor RG. Premise, promise, and potential limitations of invasive devices to treat hypertension. *Curr Cardiol Rep* 2011;13:86–92.)

Figure 3-2 also specifies the mechanisms targeted by the device-based therapies. Despite impressive results in unblinded Phase 2A and Phase 2B trials, in blinded pivotal Phase 3 RCTs thus far primary efficacy end points were not met with either device (Bhatt et al., 2014; Bisognano et al., 2011; Medtronic, 2014).

Carotid Baroreceptor Pacemaker

The Rheos system (CVRx, Inc., Minneapolis, MN) is a surgically implanted carotid baroreceptor pacemaker. Under general anesthesia, electrode wires are implanted around the carotid sinus nerves in the neck and connected to the pacemaker generator placed in a subcutaneous pocket in the chest. Electrical stimulation of the carotid sinus nerves sends afferent neural signals that the brainstem interprets as a rise in BP, evoking a reflex reduction in BP. The efferent arm of this reflex arc involves decreased efferent sympathetic

nerve activity (SNA) to the heart, which slows heart rate; to the peripheral circulation, which lowers systemic vascular resistance; and to the kidney, which reduces renin release and increases renal sodium excretion. Activation of the Rheos device acutely decreases SNA, BP, and heart rate and may avert acute hypertensive crisis (Fig. 3-3) (Mohaupt et al., 2007). While the carotid sinus and aortic arch baroreceptors buffer acute increases in BP, we lack data regarding the durability of the antihypertensive action of continuous carotid baroreceptor stimulation. This question was addressed by the Rheos Pivotal Trial, a randomized, double-blind, placebo-controlled study of carotid baroreceptor pacing in patients with drug-resistant hypertension (Bisognano et al., 2011).

In the Rheos trial, 265 patients with resistant hypertension and baseline BP averaging 169/101 mm Hg (despite treatment of most patients with five or more BP medications) underwent implantation of the Rheos

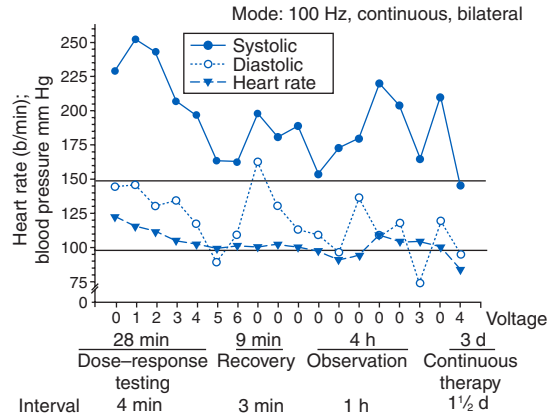


FIGURE 3-3 • Management of a hypertensive crisis with a carotid baroreceptor pacemaker. *Left panel*, chest roentgenogram after implantation showing the electrodes placed around both carotid sinuses and the stimulator that is somewhat larger than a conventional pacemaker. *Right panel*, BP measurements of the patient during a hypertensive crisis are shown. Systolic BP decreased >45 mm Hg, and diastolic BP decreased 50 mm Hg. Thereafter, the device was shut off, and BP increased over 4 hours. Continuation of the stimulus resulted in BP decreases to the previous stimulation values. Voltage is indicated on the x axis. The stimulation was bilateral with a continuous square-wave pattern at a frequency of 100 Hz and a pulse width of 480 μ s. (Modified from Mohaupt MG, Schmidli J, Luft FC. Management of uncontrollable hypertension with a carotid sinus stimulation device. *Hypertension* 2007;50:825–828.)

device and subsequently randomization (2:1) 1 month after implantation to immediate initiation of bilateral carotid baroreceptor pacing (Group A) or delayed initiation until the 6-month visit (Group B); all patients received open-label baroreceptor pacing for another 6 months. The results were largely negative, but mixed. There were no group differences at 6 or 12 months in the coprimary end points of percentage of subjects in whom systolic BP decreased by at least 10 mm Hg (54% for Group A and 46% for Group B; $p = \text{NS}$); and 9% of patients developed transient or permanent facial nerve injury. Yet, a post hoc analysis showed that 42% of Group A patients and 24% of Group B patients achieved systolic BP control (systolic BP ≤ 140 mm Hg) at 6 months ($p = 0.005$), with just over 50% of both groups achieving systolic BP control at 12 months (at which point Group B had received baroreceptor pacing for 6 months). The reduction in BP was associated with a small initial decrease in estimated glomerular filtration rate (eGFR) (Alnima et al., 2013). More research should determine if efficacy and safety can be improved by additional technical refinements or if offsetting responses from aortic baroreceptors, which are not paced, inherently limits this approach. A second-generation minimally invasive unilateral carotid nerve pacing system (Barostim neo) has yielded encouraging preliminary results for safety and efficacy (Alnima et al., 2013; Hoppe et al., 2012). A United States (U.S.) pivotal trial of Barostim neo is underway (ClinicalTrials.gov Identifier NCT01679132).

Catheter-Based Renal Denervation

Rodent studies implicate a major role for the renal sympathetic nerves in the development of hypertension (Guyenet, 2006), but the importance of the renal nerves in causing human hypertension previously had not been studied directly. As shown by Dibona (2005), in rats, renal sympathetic nerves cause renal vasoconstriction and vascular hypertrophy via $\alpha 1$ receptors, stimulate renin release via $\beta 1$ receptors, and enhance renal sodium and water reabsorption via $\alpha 1$ receptors (Fig. 3-4). Thus, catheter-based RDN is an exciting novel intervention for hypertension. The renal nerves, which are located on the adventitial surface of the renal arteries, are destroyed by radiofrequency current via an intraluminal catheter. Under conscious sedation, the Symplicity catheter is advanced into each renal artery, and four to six discrete low-power radiofrequency treatments are applied along the length of each artery.

The final 3-year follow-up data from the open-label uncontrolled Symplicity HTN-1 trial in 88 patients with severe drug-resistant hypertension show impressive sustained reductions in office BP averaging $-36/-14$ mm Hg, but ambulatory BP was not assessed (Krum et al., 2014). In that study, RDN did not prevent a decline in eGFR, but, without a control group, this decline may be less than or greater than that caused by hypertension alone without RDN.

In the unblinded Symplicity HTN-2 trial (Renal Denervation in Patients With Uncontrolled

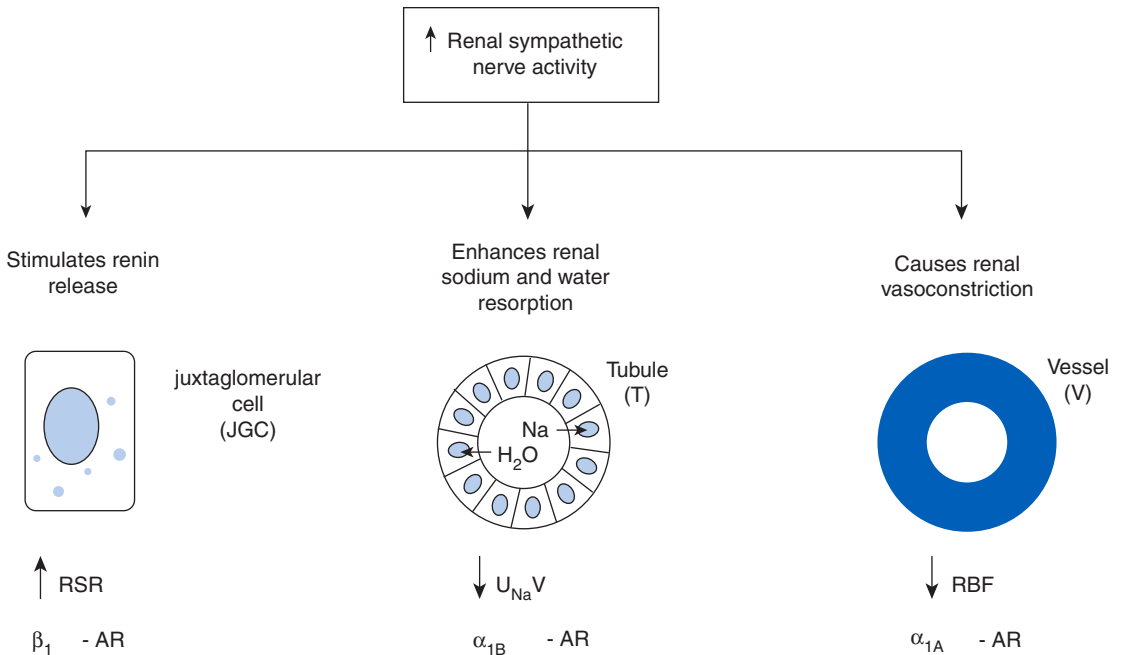


FIGURE 3-4 • Effects of increased RSNA on the three renal neuroeffectors: the juxtaglomerular cell (JGC) with increased renin secretion rate (RSR) via stimulation of the β_1 adrenoceptors (AR), the renal tubular epithelial cells (T) with increased renal tubular sodium reabsorption and decreased urinary sodium excretion (U_{Na^+V}) via stimulation of α_{1B} AR, and the renal vasculature (V) with decreased renal blood flow (RBF) via stimulation of α_{1A} AR. (From DiBona GF. Physiology in perspective: The Wisdom of the Body. Neural control of the kidney. *Am J Physiol Regul Integr Comp Physiol* 2005;289:R633–R641.)

Hypertension) (Esler et al., 2010), 106 non-U.S. patients with drug-resistant hypertension and baseline BP 178/97 mm Hg despite treatment with an average of 5 or more BP medications randomly underwent RDN while continuing prior drug therapy or continued prior drug therapy alone. Patients who met initial screening criteria were excluded if systolic BP fell below 160 mm Hg on a second screening or if they had unfavorable renal anatomy. The primary end point was the change from baseline in seated office-based measurement of systolic BP at 6 months. Office-based BP fell dramatically: by $-32/-12$ mm Hg in the active treatment group, versus no change in the control group. The 24-hour ambulatory BP, measured in less than half of patients, fell less dramatically: by $-11/-7$ mm Hg in the active treatment group, versus no change in the control group. No major adverse events occurred.

Subsequently, post hoc analyses of the Symplicity HTN-1 and HTN-2 data and smaller studies have suggested multiple ancillary benefits of RDN. These include improvement in glycemic control (Mahfoud et al., 2011), sleep apnea (Witkowski et al., 2011), and quality of life (Lambert et al., 2012); regression of left ventricular hypertrophy (LVH) (Brandt et al., 2012a); reduction in central aortic stiffness

(Brandt et al., 2012b); and reduced ventricular rate in patients with atrial fibrillation (Linz et al., 2013). Presumably, these diverse benefits derive not from destruction of efferent renal sympathetic nerve fibers but rather from destruction of renal afferent (sensory) nerves—thereby causing a global reflex decrease in sympathetic outflow to multiple tissues and vascular beds (Thompson et al., 2011) (Fig. 3-5).

Based on these unblinded data, RDN already has been approved for clinical use in Europe, Australia, and Asia (see Chapter 7) with published clinical practice guidelines (Schmieder et al., 2012). However, the blinded pivotal U.S. Symplicity HTN-3 trial did not show a significant reduction of systolic BP in patients with resistant hypertension 6 months after renal artery denervation as compared with a sham control (Bhatt et al., 2014).

In Symplicity HTN-3, 535 patients with Stage 2 drug-resistant hypertension with baseline office systolic BP 179 mm Hg and 24-hour ambulatory systolic BP 159 mm Hg despite treatment with 5 BP medications all underwent renal angiography under conscious sedation and were randomized (2:1) in the catheterization lab to either actual or sham RDN with both the patient and the research staff being blinded

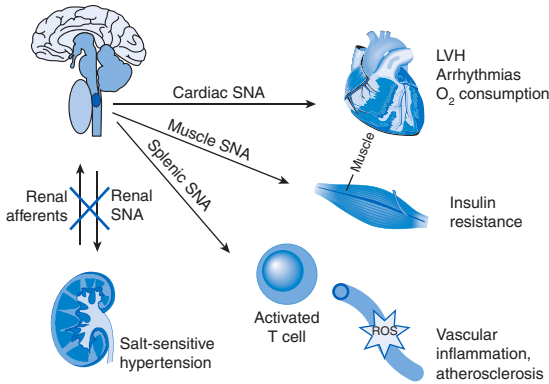


FIGURE 3-5 • Conceptual framework by which denervation of renal afferents explains ancillary benefits of catheter-based RDN. In patients with drug-resistant hypertension, overactivity of efferent RSNA contributes to salt-sensitive hypertension, whereas overactivity of excitatory renal sensory (afferent) nerves triggers sustained reflex increases in cardiac SNA (leading to LVH, arrhythmias, and increased oxygen consumption), in skeletal muscle SNA (leading to insulin resistance), and in splenic SNA (activating T cells, which are honed to vascular smooth muscle, stimulating ROS that promote vascular inflammation and atherosclerosis).

to condition assignment. The primary end point was the change in office systolic BP after 6 months. The priority secondary end point was the reduction in 24-hour systolic BP assessed by ambulatory BP monitoring in all patients. After 6 months, office systolic BP fell by -14 ± 24 mm Hg (mean \pm SD) in the RDN group versus -12 ± 26 mm Hg in the sham group ($p = 0.26$); 24-hour ambulatory systolic BP fell by -7 ± 15 mm Hg in the RDN group versus -5 ± 17 mm Hg in the sham group (Bhatt et al., 2014).

Potential explanations for the negative Symplicity HTN-3 trial and the difficulty showing an overall treatment benefit of RDN with 24-hour ambulatory BP monitoring include the following:

- Patient selection.** The large standard deviations around the mean reductions in BP in Symplicity HTN-1, 2, and 3 show large interindividual variability in the response (Messerli & Bangalore, 2014). The sympathetics will not be overactive in all patients with resistant hypertension. Indeed, subgroup analyses showed statistically significant but small intervention effects in patients younger but not those older than 65 and in nonblack but not black patients. Renal norepinephrine (NE) spillover is most consistently elevated in young hypertensives (ages 20 to 39) but is indistinguishable from normotensive levels in older hypertensives aged 60 to 79 years (Parati & Esler, 2012).

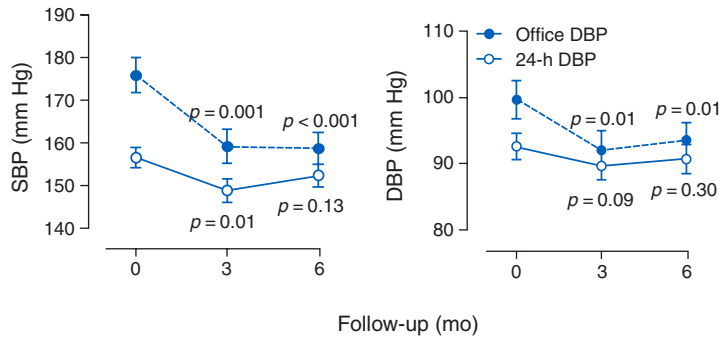
Also, 25% of the study population comprised black patients, in whom renal and vascular mechanisms could be more important than neurogenic mechanisms. RDN would have little effect if the sympathetics are not overactive.

- Incomplete denervation.** There is no point-of-care verification procedure to prove the completeness of RDN before the patient leaves the catheterization laboratory. Because the catheter is in the lumen of the renal artery, the thermal energy produced has to cross the arterial wall to reach the nerves located in the adventitia and perivascular fat. Incomplete denervation is of particular concern with renal afferents; in animal studies, 100% destruction of afferents is needed to attenuate a BP-raising reflex but near-complete deafferentation has almost no effect because of redundancy in afferent inputs into the central nervous system (CNS).

- Trial design issues.** Protocol violation on medication compliance by participating physicians and patients is a likely confounder because the patients in these trials were on an average of 5 BP medications, including adrenergic blockers and central sympatholytics as well as mineralocorticoid receptor (MR) antagonists, which also seem to have central sympatholytic effects. That BP showed zero decline in the unblinded control group of Symplicity HTN-2 is a red flag, because BPs always improve in patients randomized to blinded control groups in hypertension trials—including Symplicity HTN-3—because of the Hawthorne effect and regression to the mean. These nonspecific factors explain why patients with the highest baseline BP show the greatest reduction in BP after RDN, a finding that provides no mechanistic insight. Also, a recent small pilot study suggests that intensive medication management can be more effective than RDN and thus is the appropriate active comparator for future outcome trials (Fadl Elmula et al., 2014).

- White-coat hypertension.** White-coat hypertension is common and invalidates office BP as a primary outcome measure when evaluating any therapy based on a neural mechanism. Six-month registry data from 47 patients who had RDN for clinical indications in Europe show that office BP fell by $-18/-7$ mm Hg (from 175/98 to 158/91 mm Hg, $p = 0.01$) but 24-hour BP showed a much smaller and statistically nonsignificant change of $-6/-4$ mm Hg (from 157/92 to 151/88, $p = 0.3$) with much interindividual variation (Fig. 3-6) (Persu et al., 2013). Clearly, ambulatory BP—both awake and sleeping

FIGURE 3-6 • European registry data on conventional office and 24-h ambulatory BP values at baseline and at 3 and 6 months after RDN in 47 patients. SBP and DBP indicate systolic and diastolic BP, respectively. *p*-Values denote the significance compared with baseline in unadjusted analyses. (Data from Persu A, Jin Y, Azizi M, et al. Blood pressure changes after renal denervation at 10 European expert centers. *J Hum Hypertens* 2013;28:150–156.)



BPs—must replace office BP as the primary outcome in future studies of RDN, carotid pacing, and related intervention.

Thus, future RDN trials are likely to focus on younger hypertensives. Much more work is needed to create a point-of-care end point, to better understand the relative contributions of renal efferent versus afferent nerves to the mechanism of action of RDN, and, most importantly, to identify which patients will most likely benefit from RDN and which will not. In this regard, it is worth recalling that, in the 1940s, less than one-third of severely hypertensive patients showed a substantial improvement in BP with total surgical thoracic/lumbar/splanchnic sympathectomy plus celiac ganglionectomy (Fig. 3-7) (Grimson et al., 1949).

In the meantime, the recent RDN studies certainly have refocused much attention on neural mechanisms of hypertension. Previously, the sympathetic nervous system was implicated mainly in the initiation of hypertension, but not in its maintenance. These studies also implicate a greatly expanded role for renal afferents, formerly thought to contribute mainly to renal parenchymal hypertension and cyclosporine-induced hypertension (Converse et al., 1992; Zhang et al., 2000). To put this rapidly growing and now perplexing field in perspective, the following is a detailed discussion of neural mechanisms of hypertension.

Overview of the Sympathetic Nervous System

Pioneering work by Julius and coworkers and others indicate that hypertension is often initiated by adrenergically driven increases in cardiac output (a “hyperdynamic” circulation) but sustained by subsequent vasoconstriction, vascular remodeling, and autoregulation—leading to increased vasoconstriction

with an inappropriately normal cardiac output (Julius et al., 1991). In young adults, primary hypertension consistently associates with increased heart rate and cardiac output, plasma and urinary NE levels, regional NE spillover, peripheral postganglionic sympathetic nerve firing (determined by microelectrode recordings), and alpha-adrenergic receptor-mediated vasoconstrictor tone in the peripheral circulation (Martin & Victor, 2011). Sympathetic overactivity occurs in early primary hypertension and in several other forms of established human hypertension, including hypertension associated with obesity, sleep apnea, early type 2 diabetes mellitus and prediabetes, chronic kidney disease (CKD), heart failure, and immunosuppressive therapy with calcineurin inhibitors such as cyclosporine. In these conditions, central sympathetic outflow can result from deactivation of inhibitory neural inputs (e.g., baroreceptors), activation of excitatory neural inputs (e.g., carotid body chemoreceptors, renal afferents), or circulating angiotensin II (Ang II), which activates pools of excitatory brainstem neurons with a poorly formed blood–brain barrier.

As shown in Figure 3-2, multiple central and reflex mechanisms are involved in the neural control of BP.

Baroreceptors

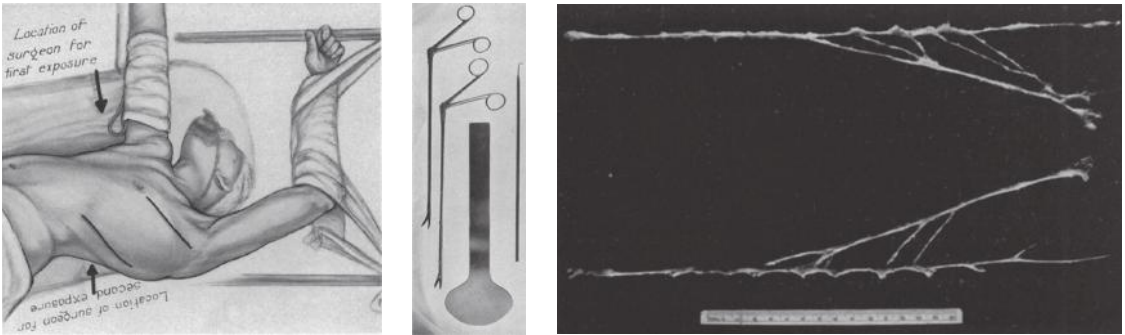
The major inhibitory reflexes arise in the (1) high-pressure arterial baroreceptors of the carotid sinus and aortic arch and (2) low-pressure cardiopulmonary baroreceptors of the heart and great veins. The activation of these baroreceptors, by increased BP or increased cardiac filling pressure, respectively, sends inhibitory signals to the CNS via the nucleus tractus solitarius (NTS) and evokes reflex increases in efferent parasympathetic and decreases in efferent sympathetic activity, causing bradycardia and peripheral vasodilation that buffer the increases in BP (Guyenet, 2006).

In hypertension, the baroreceptors reset to defend a higher level of BP. Baroreflex control of sinus node function is abnormal even in mild hypertension, but baroreflex control of systemic vascular resistance and BP is well preserved until diastolic function is impaired (Grassi et al., 2009). Complete baroreflex failure causes labile hypertension, most often seen in throat cancer survivors as a late complication of radiation therapy, which causes a gradual destruction of the baroreceptor nerves (Huang et al., 2013). Partial baroreceptor dysfunction is common in elderly hypertensive patients and typically manifests with a triad of

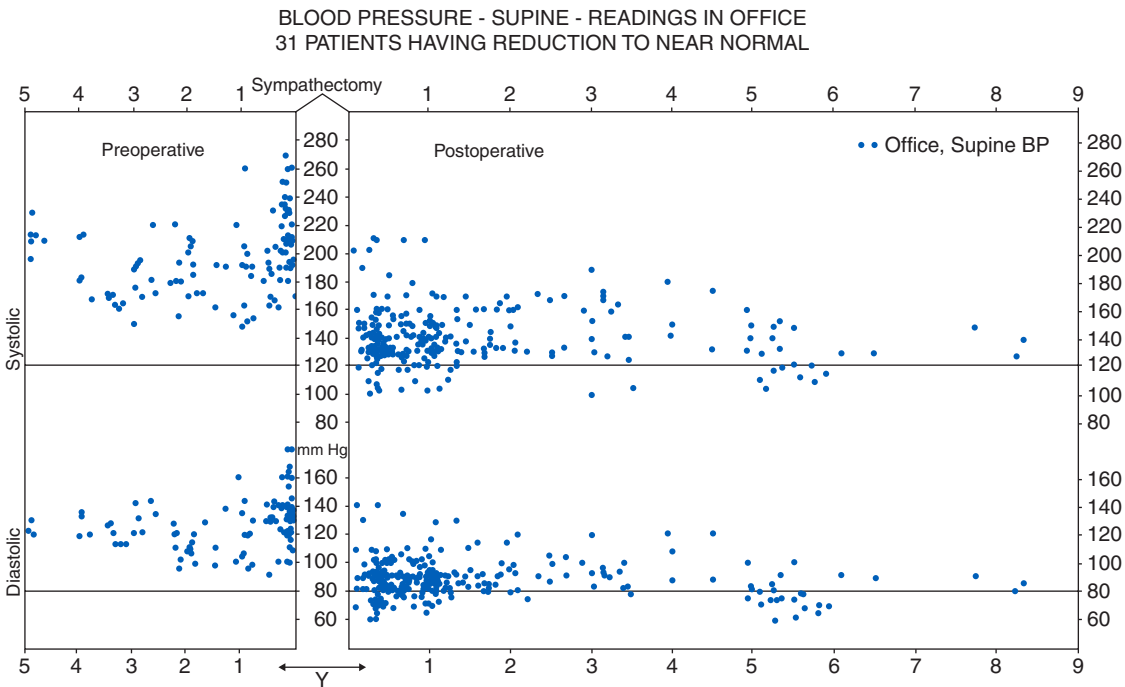
orthostatic hypotension, supine hypertension, and symptomatic postprandial hypotension—the last initiated by splanchnic pooling after carbohydrate-rich meals (Barochiner et al., 2013).

Excitatory Neural Reflexes

The major excitatory reflexes are those arising in carotid body chemoreceptors, the kidneys, and skeletal muscles. Activation of carotid body chemoreceptors by hypoxia evokes reflex sympathetic activation. Repeated activation of this excitatory chemoreflex has



A



B

FIGURE 3-7 • A classical study from the 1940s showing total lumbar sympathectomy (A) and office BPs readings in patients whose BPs improved markedly (B), those in whom BP improved somewhat (C), and those in whom BP did not improve at all (D). (Continued)

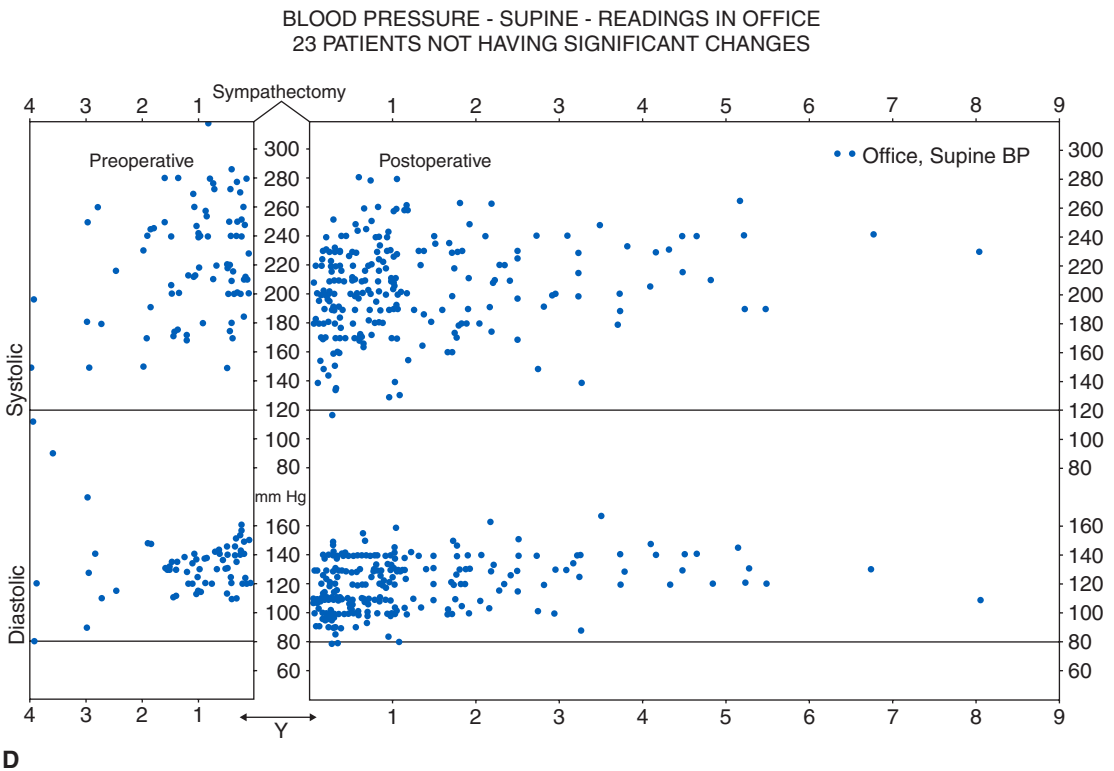
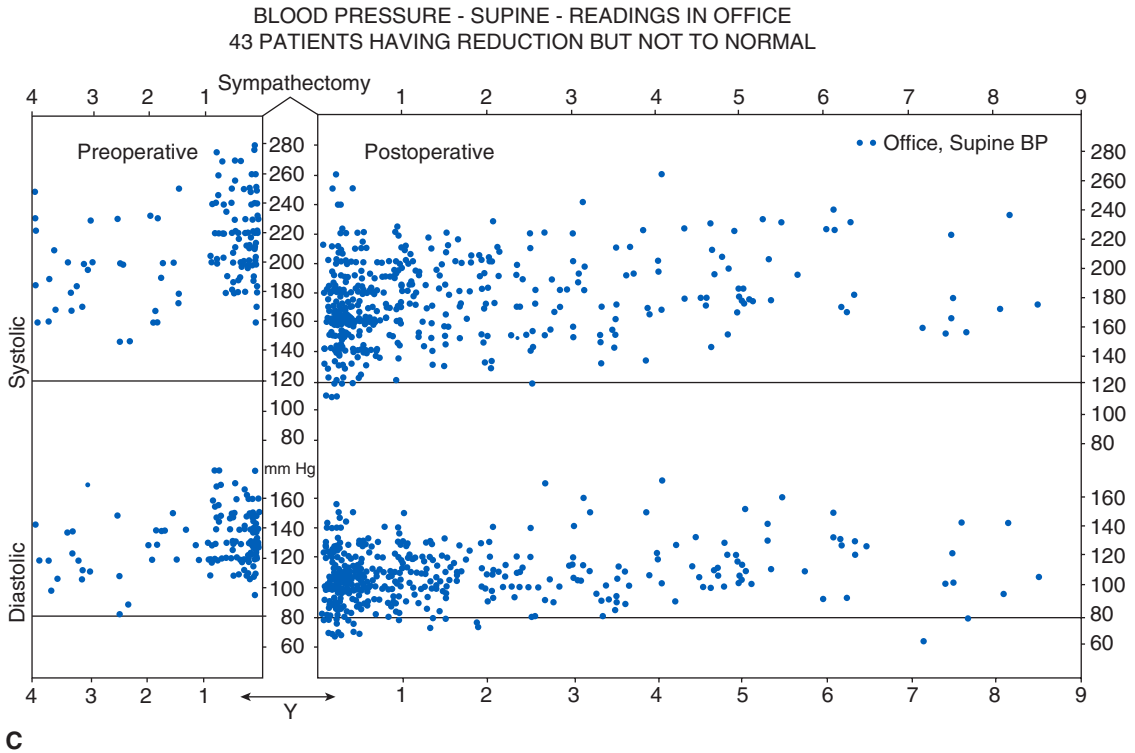


FIGURE 3-7 • (Continued) (From Grimson KS, Orgain ES, Anderson B, et al. Results of treatment of patients with hypertension by total thoracic and partial to total lumbar sympathectomy, splanchnicectomy and celiac ganglionectomy. *Ann Surg* 1949;129:850-871.)

been implicated in the pathogenesis of hypertension with sleep apnea. Thus, carotid body denervation is being explored as another form of percutaneous intervention for hypertension (McBryde et al., 2013). As mentioned earlier, the kidneys are richly innervated with sensory afferents that project centrally to the NTS and can evoke reflex sympathetic excitation. Activation of excitatory renal afferents by ischemic metabolites (e.g., adenosine) has been implicated in the pathogenesis of renovascular hypertension. Activation of these afferents by ischemic or uremic metabolites (e.g., urea) has been implicated in the pathogenesis of hypertension in CKD (Converse et al., 1992); sympathetic overactivity increases with increasing severity of CKD (Grassi et al., 2011). The skeletal muscles also are innervated with sensory afferents that signal the brain of local mechanical and chemical changes occurring during muscle contraction. During exercise, muscle afferents evoke reflex increases in BP and cardiac output that increase muscle perfusion. This reflex mechanism may be augmented in hypertension and lead to an exaggerated rise in BP during exercise (Vongpatanasin et al., 2011).

Central Sympathetic Outflow

Excitatory and inhibitory synaptic inputs from the NTS project centrally to neurons in the rostral ventrolateral medulla (RVLM), the site of origin of sympathetic outflow from the brainstem (Guyenet, 2006). From there, preganglionic sympathetic fibers synapse in the adrenal medulla (to release epinephrine, EPI) and in the paravertebral sympathetic chain ganglia. The postganglionic fibers, which release NE, innervate the heart, blood vessels, and kidney.

Adrenergic Receptors

Catecholamines induce their effects via G-protein-coupled α - and β -adrenergic receptors. The α 1 adrenoceptors are most abundant on resistance vessels and mediate most of the vasoconstriction caused by neurally released NE. There are three subtypes of α 2 adrenoceptors that vary in location and function (Knaus et al., 2007). Studies in genetically engineered mice indicate that α 2A are located in the RVLM and tonically suppress sympathetic outflow. They mediate the hypotensive effect of clonidine and related central sympatholytics. Both α 2A and α 2C subtypes are located on sympathetic nerve terminals and cause feedback inhibition of NE release. In contrast, α 2B

subtypes are located on resistance vessels. But, unlike α 1 receptors, they are not part of the neuroeffector junction but rather mediate vasoconstriction from circulating catecholamines. Their response also explains the paradoxical hypertension seen when patients with autonomic failure are treated with clonidine, which stimulates all three α 2-adrenergic receptor subtypes.

β -Adrenergic stimulation of the heart increases ventricular contractility and heart rate, thereby increasing cardiac output. α -Adrenergic stimulation of the peripheral vasculature causes vasoconstriction and, over time, promotes vascular remodeling and hypertrophy (Bleeke et al., 2004).

Cortical Influences

Cortical influences are particularly evident in the normal nocturnal dip in BP, the morning surge in BP, during physical and emotional stress (especially panic disorder), and with the white-coat reaction (see Chapter 2).

Long-Term Sympathetic Regulation of BP

As noted above, the sympathetic nervous system is well known to regulate short-term changes in BP such as transient pressor responses during physical and emotional stress. In addition, sustained activation of the renal sympathetic nerves may contribute to long-term BP regulation by promoting sodium retention (DiBona, 2005). Moreover, NE's action on α -1 adrenoceptors constitutes a trophic stimulus to cardiac and vascular smooth muscle hypertrophy (Bleeke et al., 2004). In patients with hypertension and LVH, SNA is increased and may predispose to the hypertrophy and sudden cardiac death (Grassi et al., 2009; Schlaich et al., 2003).

Sustained sympathetic overactivity has been demonstrated not only in early primary hypertension but also in several other forms of established human hypertension. These include hypertension associated with obesity, sleep apnea, early type 2 diabetes mellitus and prediabetes, CKD, heart failure, and immunosuppressive therapy with calcineurin inhibitors such as cyclosporine A (Martin & Victor, 2011). In these conditions, central sympathetic outflow can be driven by deactivation of inhibitory neural inputs (e.g., baroreceptors), activation of excitatory neural inputs (e.g., carotid body chemoreceptors, renal afferents), or by circulating angiotensin II (Ang II), which activates

pools of excitatory brainstem neurons that are devoid of a blood–brain barrier (see Fig. 3-2). Apparently, circulating aldosterone also can act centrally to increase SNA, leading to reversibly sympathetic overactivity in patients with primary aldosteronism (Kontak et al., 2010).

With this background in mind, we now review the evidence for a neurogenic component to primary hypertension.

Detection of Sympathetic Overactivity in Primary Hypertension

In its early stages, primary hypertension consistently associates with increased heart rate and cardiac output, plasma and urinary NE, regional NE spillover, decreased NE reuptake, peripheral postganglionic sympathetic nerve firing, and α -adrenergic receptor-mediated vasoconstrictor tone in the peripheral circulation (Martin & Victor, 2011).

These effects are difficult to demonstrate, in part because sympathetic activity is difficult to measure especially in the clinical setting. Plasma NE levels are an insensitive measure. Although easily performed and noninvasive, frequency analysis of heart rate variability simply is not a valid measure of sympathetic activity (Taylor & Studinger, 2006). The two state-of-the-art techniques to quantify sympathetic activity in humans are radiotracer measurements of regional NE spillover (Esler, 2014) and microneurography—microelectrode measurements of SNA (Manolis et al., 2013). The former is invasive and requires arterial cannulation. The latter is minimally invasive but requires specialized training.

Regional NE Spillover

Pioneering work by Esler, Lambert, and coworkers shows that Stage 1 primary hypertension is characterized by sympathetic activation targeted to the kidney, heart, and skeletal muscle vasculature (Esler, 2014).

Direct Measurements of Sympathetic Nerve Activity

As shown in Figure 3-8, microneurography provides direct measurements of postganglionic SNA—the proximate neural stimulus to NE release (Guyenet, 2006). This is a powerful clinical research tool (Guyenet, 2006; Manolis et al., 2013) but too technically demanding for routine diagnostic testing.

Muscle sympathetic nerve activity (*muscle SNA* or *MSNA*) refers to spontaneous bursts of postganglionic sympathetic discharge targeted to the skeletal muscle vasculature. The activity is tightly regulated by carotid sinus and aortic arch baroreceptors, accompanied by parallel changes in regional vasomotor tone, and eliminated by ganglionic blockade (Guyenet, 2006; Wallin & Charkoudian, 2007). These are vasoconstrictor impulses that release NE. Basal levels of MSNA provide a valid measure of resting sympathetic activity—at least to one major vascular bed that contributes to total peripheral resistance and BP.

Figure 3-8 also shows an example of one of many studies showing higher levels of MSNA in hypertensive than normotensive individuals, but with overlap between groups (Guyenet, 2006). The overlap is largely eliminated when the normotensive control group was more carefully defined using 24-hour ambulatory BP monitoring (Grassi et al., 2007). When those with white-coat (office-only) hypertension and masked hypertension (elevated BP only outside the physician's office) were eliminated from the normotensive control group, mean values of MSNA were 70% higher in the persistent hypertensives compared to true normotensives. When measured under experimental circumstances, the MSNA was higher than normal in individuals with either white-coat or masked hypertension.

Potential Mechanisms

Several mechanisms have been implicated in driving the sympathetic nervous system in hypertension.

Emotional and Physical Stress

Sympathoadrenal activation increases BP and heart rate transiently during episodes of physical and emotional stress, but the issue remains: Can it cause chronic hypertension?

Guyton viewed the nervous system as only a short-term controller, adjusting beat-to-beat and minute-to-minute changes in BP but playing a trivial role in chronic hypertension (Guyton, 1991). In contrast, the Swedish physiologist Bjorn Folkow hypothesized that repeated adrenergic spikes in BP eventually will damage the blood vessels producing sustained hypertension (Folkow, 2004).

Despite a vast literature, there still is no conclusive proof for Folkow's hypothesis (Thijssen et al., 2011). Psychological stress is hard to quantify, and

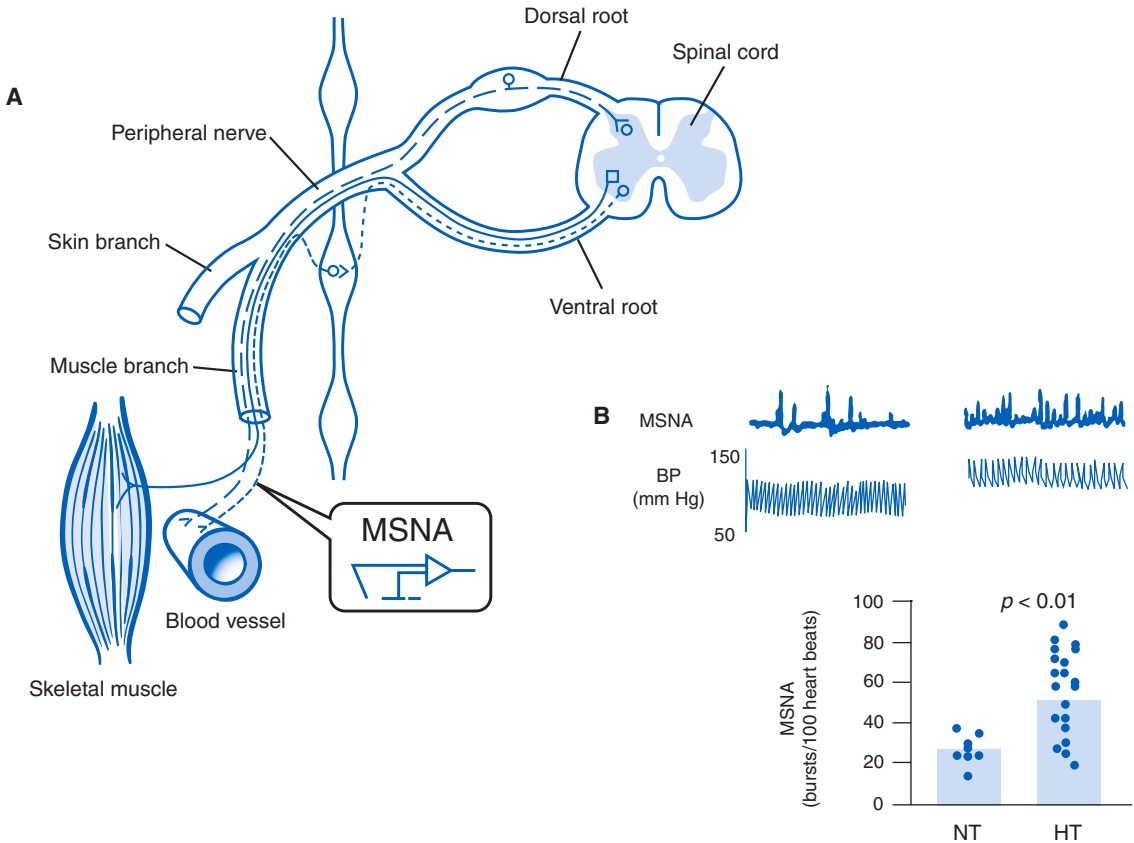


FIGURE 3-8 • Microneurographic measurements of MSNA in normotensive and hypertensive humans. **A:** Schematic diagram showing site of insertion of the recording microelectrode into a peripheral sympathetic nerve bundle innervating blood vessels in human skeletal muscle. **B:** Multiunit recordings of MSNA and BP from two illustrative human subjects (*top panel*) and summary data (*bottom panel*) showing higher mean levels of nerve firing in hypertensive (HT) than normotensive (NT) humans. (**A** modified from Guyenet PG. The sympathetic control of blood pressure. *Nat Rev Neurosci* 2006;7:335–346. **B** adapted from Schlaich MP, Lambert E, Kaye DM, et al. Sympathetic augmentation in hypertension: Role of nerve firing, norepinephrine reuptake, and Angiotensin neuromodulation. *Hypertension* 2004;43:169–175.)

standard semiquantitative laboratory stressors are often weak sympathetic stimuli that do not mirror real-life stress. The acute rise in BP during the cold pressor test (hand in ice water) is an indirect index of increased MSNA and α -adrenergic vasoreactivity (Lambert et al., 2014; Victor et al., 1987).

The pattern of hemodynamic response to more realistic stresses in a laboratory setting may predict real-life BP measured by ambulatory monitoring (Ottaviani et al., 2011). Rumination—preservation about past stressful or anger-provoking events (i.e., anger recall)—may produce repetitive sympathetic activation leading to chronic hypertension (Gerin et al., 2012). In a study of 60 lean normotensive young adults, daytime ambulatory systolic BP averaged 133 mm Hg when they were ruminating versus 114 mm Hg when they were not (Ottaviani et al., 2011). Rumination triggers decreased heart rate variability,

peripheral vasoconstriction, and increased blood levels of inflammatory markers such as soluble intercellular adhesion molecule-1 (Ottaviani et al., 2007; Ottaviani et al., 2013) and is associated with blunted nocturnal dipping of BP (Johnson et al., 2014).

Job stress and sleep deprivation seem to be a cause of hypertension (Magnavita & Fileni, 2013; Pickering, 2006). Among African Americans, perceived racism is associated with nocturnal hypertension (Brondolo et al., 2011). NE spillover is increased in the brains of patients with primary hypertension and in those with panic disorder (Esler, 2014).

Baroreceptor Resetting

Although the baroreceptors are reset to defend a higher BP, this does not explain sympathetic overactivity in human hypertension (Schlaich et al., 2004).

Baroreflex control of heart rate is impaired even in mild hypertension, but baroreflex control of SNA, vascular resistance, and BP is well preserved (Guo et al., 1983). Even baroreflex failure after bilateral carotid body tumor resection does not cause sustained hypertension (Timmers et al., 2004).

Central Effects of Angiotensin II

In rodent models, Ang II can enter the brainstem via unique neuronal pools that are highly vascularized and have a poorly formed blood–brain barrier—the *circum-ventricular organs*—and increase central sympathetic outflow via AT1 receptor–mediated activation of brain NADPH oxidases that produce ROS (Lob et al., 2013). In the spontaneously hypertensive rat—a common model of genetically programmed hypertension—inhibition of the brain renin–angiotensin–aldosterone system (RAAS) in the pregnant mother will eliminate hypertension in her offspring (Wu & Berecek, 1993). If the RAAS blocker is given systemically to the rat pups after delivery, the hypertension will be delayed and attenuated but not entirely eliminated. Chronic renin inhibition with aliskiren lowers upright (but not seated) MSNA in adult patients with uncomplicated primary hypertension (Okada et al., 2013).

Brainstem Compression

Jannetta and coworkers, neurosurgeons at the University of Pittsburgh, hold that pulsatile compression of the left RVLM by a looping posterior inferior cerebellar artery can cause neurogenic hypertension (Levy et al., 2001). After developing an animal model, they have performed microvascular decompression surgery on hundreds of hypertensive patients. However, uncertainty persists due to inconsistent results from uncontrolled observations in small samples with short follow-up (Legrady et al., 2013) and the inability of brain MRI to accurately detect neurovascular compression in prospective studies (Boogaarts et al., 2012).

In an independent study from Germany, 14 patients with primary hypertension were followed sequentially for 24 months after surgery with repeated ABPM and microneurography (Frank et al., 2009). Neurovascular decompression provided only temporary relief from hypertension, as BP and MSNA fell for the first 6 months after surgery but then returned steadily toward preoperative levels thereafter. Larger long-term studies are needed. Hypertension may be the cause rather than the result of vascular tortuosity.

When Does Increased MSNA Cause Hypertension?

Increased MSNA alone does not cause hypertension when it is accompanied by compensatory decreases in cardiac output and α -adrenergic receptor sensitivity to NE (Hart et al., 2014). In young people, the influence of high MSNA on BP is balanced by lower cardiac output and less adrenergic vasoconstrictor responsiveness. Tonic MSNA may restrain vasodilator responses in young men, whereas in older men, a lack of such restraint may be protective against the pressor effects of higher SNA. Presumably, sympathetic overactivity leads to hypertension only when these compensations fail.

Increased MSNA may cause HTN only when accompanied by one or more of the following additional mechanisms:

- ▶ Inappropriately “normal” cardiac output (Charkoudian et al., 2005). This may be less of a factor in women than men (Hart et al., 2009).
- ▶ Increased α -adrenoreceptor sensitivity to NE (Charkoudian et al., 2005)
- ▶ Impaired NE reuptake by sympathetic nerve terminals (Esler, 2014)
- ▶ Corelease of EPI from sympathetic nerve terminals (Berecek & Brody, 1982; Floras et al., 1988; Rumantir et al., 2000)

Summary

Despite abundant documentation of sympathetic overactivity in primary hypertension, we still cannot quantify this neurogenic contribution. More work is needed to define the role of baroreceptor pacing and RDN in hypertension therapeutics and, in so doing, improve our fundamental understanding of neurogenic mechanisms. With that caveat, we now turn to renal mechanisms.

RENAL MECHANISMS

The kidneys are both the culprit and the victim in hypertension. Renal parenchymal hypertension is discussed in Chapter 9 and renovascular hypertension in Chapter 10.

In the mid-19th century, Richard Bright linked hypertensive heart disease with small shrunken kidneys. In the 1930s, seminal work by Harry Goldblatt proved that the kidneys can cause hypertension (Goldblatt et al., 1934). Beginning with the work of

Guyton and his trainees in the 1960s, many believe that renal dysfunction is the sine qua non for hypertension.

According to this view, the fundamental defect in all hypertension is the kidneys’ inability to excrete the excessive sodium load imposed by a high-salt diet (Kotchen et al., 2013).

Excess Sodium Intake as a Major Cause of Hypertension

The basis for the generally accepted—but not in itself sufficient—role of dietary sodium excess is as follows. Because our prehistoric ancestors consumed less than 0.25 g of NaCl (<10 mmol of Na) per day, our kidneys evolved efficient transport mechanisms to retain filtered sodium, which benefits survival during salt and water deprivation but contributes to hypertension when dietary salt is plentiful (He & MacGregor, 2010). For only the past few hundred years—a very short period in human evolution—daily NaCl consumption in developed countries has increased by orders of magnitude to 10 to 12 g/day, which overwhelms the capacity of the human kidney to maintain Na balance (He & MacGregor, 2010; Kotchen et al., 2013). The residual excess total body Na—the main extracellular cation—expands plasma volume, increases cardiac output, and triggers autoregulatory responses that increase systemic vascular resistance. The sodium ion also augments the smooth muscle contraction evoked by multiple endogenous vasoconstrictor substances.

Most of the excess sodium in our diets does not come from the salt shaker but from modern food

processing, which both adds sodium and removes potassium. Table 3-1 shows that our herbivorous ancestors probably consumed less than 10 mmol of sodium per day, whereas our carnivorous ancestors might have eaten 30 mmol/day (Eaton et al., 1996). Human physiology evolved in a low-sodium/high-potassium environment, and we seem ill equipped to handle the current exposure to high sodium and low potassium (He & MacGregor, 2010). Our current preference for salt likely is an acquired taste, developing early in childhood.

Dietary salt is 40% sodium and 60% chloride. Thus,

- 1 g sodium = 2.5 g salt
- 1 mmol sodium = 23 mg sodium
- 1 g salt = 0.4 g sodium = 17 mmol sodium.

The evidence linking dietary salt to hypertension is overwhelming and comes from multiple lines of investigation:

Epidemiologic Studies

- In undeveloped countries, people who eat little sodium have little or no hypertension, and their BP does not rise with age, as it does in all developed and developing countries (Denton et al., 1995; Page et al., 1981). For example, the Yanomamo Indians of northern Brazil, who excrete only 1 mmol of sodium per day, have an average BP of 107/67 mm Hg among men and 98/62 mm Hg among women aged 40 to 49 years (Oliver et al., 1975).

TABLE 3-1
Estimated Diet of Late Paleolithic Humans Versus That of Contemporary Americans

Nutrient	Late Paleolithic Diet (Assuming 35% Meat)	Current American Diet
Total dietary energy, %		
Protein	30	12
Carbohydrate	45–50	46
Fat	20–25	42
Polyunsaturated:saturated fat ratio	1.41	0.44
Fiber, g/day	86	10–20
Sodium, mg	604	3,400
Potassium, mg	6,970	2,400
Potassium:sodium ratio	12:1	0.7:1
Calcium, mg	1,520	740

Data from Eaton SB, Eaton SB III, Konner MJ. An evolutionary perspective enhances understanding of human nutritional requirements. *J Nutr* 1996;126:1732–1740.

- The lack of hypertension may be attributable to other differences in lifestyle, but comparisons made in groups living under similar conditions relate the BP most directly to the level of dietary sodium intake (Page et al., 1981). In developing countries, urbanization—which includes increased salt consumption—brings hypertension (Lawes et al., 2008). Even without urbanization, hypertension occurs in undeveloped tribes who consume a high salt diet (Page et al., 1981).
- Significant correlations between salt intake and hypertension development have been found in most large populations (Chen et al., 2008a; Khaw et al., 2004; Zhou et al., 2003) but not in all (Smith et al., 1988). The seminal data come from the Intersalt study, which measured 24-hour urine electrolytes and BP in 10,079 men and women aged 20 to 59 years in 52 places around the world (Elliott et al., 1996; Intersalt Cooperative Research Group, 1988). For all 52 centers, there was a positive correlation between urine sodium excretion and both systolic and diastolic BP but an even more significant association between sodium excretion and the changes in BP with age (Fig. 3-9). Few populations were found whose levels of sodium intake were in the 50- to 100-mmol/day range (3 g NaCl), wherein the threshold for the sodium effect on BP likely resides (Fig. 3-10) (He et al., 1991; Poulter et al., 1990).

Migration Studies

Migration of people from a low-salt rural environment to a high-salt urban environment is accompanied by increased BP (He et al., 1991; Poulter et al., 1990).

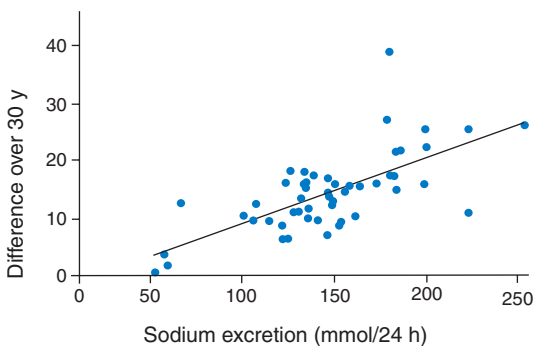


FIGURE 3-9 • Plot of the difference in systolic BP over 30 years (BP at age 55 minus BP at age 25) in relation to median urinary sodium excretion across 52 populations. (Modified from Stamler J, Elliott P, Dyer AR, et al. Commentary: Sodium and blood pressure in the Intersalt study and other studies. *BMJ* 1996;312:1285–1287.)

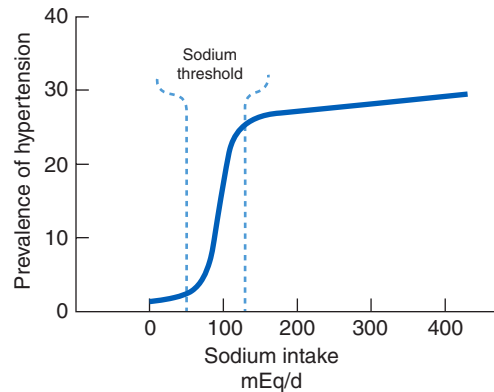


FIGURE 3-10 • Probable association between usual dietary sodium intake and the prevalence of hypertension in large populations. (Modified from Kaplan NM. Dietary salt intake and blood pressure. *JAMA* 1984;251:1429–1430.)

Population-Level Dietary Interventions

It is generally ineffective to try to reduce a person's salt intake with individual dietary counseling alone. Larger effects will require societal and governmental regulation of the food industry, as 75% to 80% of dietary salt comes from food processing. When this has occurred, population-level BPs have fallen.

- Over the past 30 years in Finland, a successful comprehensive nationwide campaign to lower salt intake by one-third has been accompanied by a 10-mm Hg fall in population average systolic and diastolic BP as well as a 75% to 80% fall in stroke and coronary heart disease (CHD) mortality (Karppanen & Mervaala, 2006).
- Canada has followed suit (Campbell & Spence, 2008).
- A 2-year interventional study in two similar Portuguese villages led to a 13/6 reduction in BP in the village with a 50% greater reduction in salt intake (Forte et al., 1989).
- From 2003 to 2011 in England, a reduction in salt intake of 15% (1.4 g/day) was accompanied by a population level reduction in BP of 3/1 mm Hg and a 42% reduction in mortality from stroke (He et al., 2014; Stamler et al., 1989).
- Modest reductions in dietary salt content of processed foods in the U.S. by only 3 g/day are projected to reduce population-level systolic BP by 2 to 3 mm Hg and prevent 54,000 to 99,000 myocardial infarctions (MIs) and 32,000 to 66,000 strokes every year, with the greatest project benefit occurring in African Americans (Bibbins-Domingo et al., 2010).

Feeding Trials

When hypertensives are sodium restricted, their BP falls. Dramatic falls in BP may follow rigid sodium restriction (Kempner, 1948), whereas less rigid restriction to a level of approximately 100 mEq/day (5 to 6 of NaCl) has been found to lower BP modestly—by 5/3 mm Hg on average (He & MacGregor, 2010)—as described further in Chapter 6.

- When prehypertensive individuals moderately restrict their sodium intake, progression to full-blown hypertension is reduced (Stamler et al., 1989; Whelton et al., 1998).
- Long-term intervention studies that start with infants and children to confirm that sodium restriction can prevent hypertension or that sodium excess can cause it are not feasible, but meta-analysis showed short-term benefits (He & MacGregor, 2006; Stamler et al., 1989). In 10 trials involving 966 children and adolescents, BP fell by an average of 1.1/1.2 mm Hg after salt intake had been reduced by 42% for an average of 4 weeks. In 3 trials involving 551 infants, systolic BP fell by 2.5 mm Hg after salt intake had been reduced by 54% for an average of 8 weeks.

Animal Studies

As seen in Figure 3-11, the most impressive evidence for salt-induced hypertension comes from a study on free-living chimpanzees, half of whom were given progressively increasing amounts of sodium in their food, while the other half remained on their usual low-sodium diet (Denton et al., 1995; Stamler et al., 1989). During the 89 weeks in which the chimps received extra sodium, the BP rose an average of 33/10 mm Hg, returning to baseline after 20 weeks without added sodium. In keeping with varying sodium sensitivity, the BP rose in only seven of ten chimpanzees on the added sodium. An important point is that the chimpanzees' salt intake varied from 0.5 g/day (equivalent to that of our predecessors) to 10 to 15 g/day (equivalent to our modern high-salt diet).

Human Genetic Studies

Impaired renal sodium excretion is the final common pathway mediating almost all of the rare monogenic causes of human hypertension (Lifton et al., 2001), as discussed later in this section.

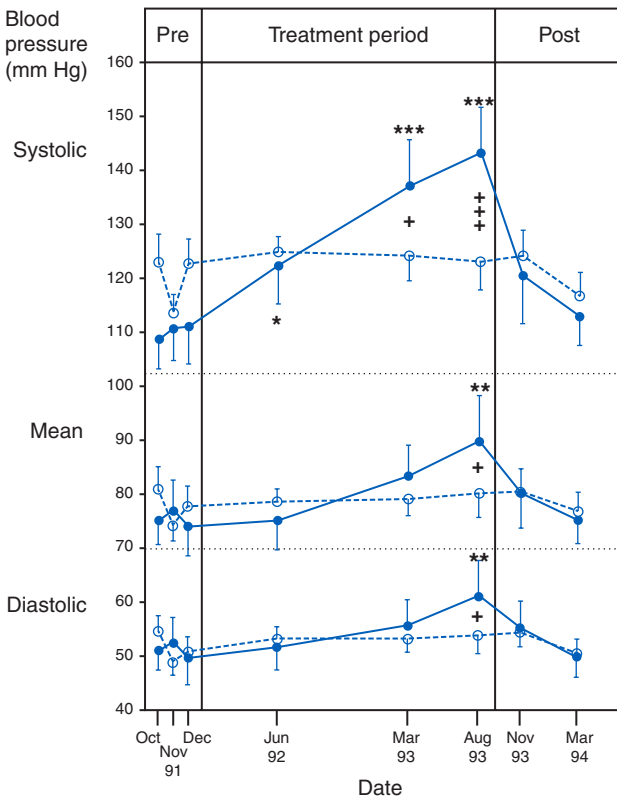


FIGURE 3-11 • A group of 22 chimpanzees maintained in small, long-term, stable social groups and fed a vegetable–fruit diet with the addition of infant formula were studied. The 12 control animals (open circles, dotted line) experienced no change in conditions over 2.4 years and no significant change of systolic, diastolic, or mean BP (mean ± standard error of the mean). For the ten experimental animals (solid circles, solid line), 5 g/day NaCl was added to the infant formula for 19 weeks, 10 g/day for 3 weeks, and 15 g/day for 67 weeks. A 20-week period without salt addition followed. Significance values of the increase in BP relative to the mean of the three baseline determinations were as follows: **p* < 0.05, ***p* < 0.0021; significance values of the difference between the experimental and control groups: **p* < 0.05, ****p* < 0.001. (Modified from Denton D, Weisinger R, Mundy NI, et al. The effect of increased salt intake on blood pressure of chimpanzees. *Nat Med* 1995;1:1009–1016.)

Is There a J-Curve Between Salt Restriction and CV Risk?

Whereas He, MacGregor, and coworkers have argued that dietary salt restriction overwhelmingly reduces the risk of CV events (He & MacGregor, 2010), and a 2011 American Heart Association (AHA) report recommended strict population-wide salt restriction (sodium intake <1,500 mg/24 hours) (Appel et al., 2011), a 2013 Institute of Medicine report (IOM, 2013) concluded that the quality of the evidence was insufficient to support the AHA recommendation while Alderman and coworkers have argued that both very-high- and very-low-salt diets (the latter being recommended by the AHA) increase CV risk—a “sodium J-curve” (Graudal et al., 2014). The latter has been attributed to hypovolemia-induced reflex activation of the sympathetic nervous system and the renin–angiotensin system.

Evidence in favor of the sodium J-curve includes the following:

- In the ONTARGET and TRANSCEND trials, the observed relation between estimated sodium intake and CV events was J-shaped (O'Donnell et al., 2011). The study has been criticized because it was a post hoc observational analysis, and sodium intake was estimated from a single spot urine sodium that is a questionable surrogate (He & MacGregor, 2012).
- In a subset of 3,681 subjects without CVD at baseline in the prospective Flemish and European studies of genes and health outcomes, baseline 24-hour urinary sodium excretion showed a positive association with systolic BP both at baseline and at 6-year follow-up but a weakly inverse association with CV outcomes (Stolarz-Skrzypek et al., 2011).
- In a meta-analysis of 23 cohort studies and 2 follow-up studies of RCTs, both low sodium intakes and high sodium intakes were found to be associated with increased mortality (Graudal et al., 2014). No RCTs in healthy population samples were identified for inclusion in this meta-analysis.

The evidence against a sodium J-curve includes the following:

- The above meta-analysis by Graudal et al. has been criticized for including ultra short-term studies (4 to 5 days) of severe salt restriction (from 20 to 1 g/day) with thus limited public health implications (He et al., 2013). In contrast, a Cochrane systemic review and meta-analysis of 34 randomized trials of modest reduction in 24-hour urinary sodium

excretion ranging from 40 to 120 mmol (equivalent to a reduction of 2.3 to 7 g of salt intake per day) for at least 4 weeks showed significant mean reductions in BP of $-4/-2$ mm Hg with minimal increases in plasma renin activity (PRA), serum aldosterone, and plasma NE and no change in plasma lipids (He et al., 2013). However, in the latter meta-analysis, CV outcomes were not assessed.

- A recent systemic review of observational studies supports a direct relation between sodium intake—starting with values as low as recommended by the AHA—and stroke (Whelton et al., 2012).
- The best evidence against a sodium J-curve comes from new 10–15 year follow-up data from the Trials of Hypertension Prevention (TOHP) showing a continuous decrease in CV events in prehypertensive subjects with decreased sodium intake as low as 1,500 mg/day (Fig. 3-12) (Cook et al., 2014). In contrast to meta-analyses that have included studies using dietary recall, spot urine sodium, or even a single 24-hour urine sodium, each subject in TOHP had three to seven 24-hour urine collections to obtain highly accurate measures of mean dietary salt exposure. This study overcomes other shortcomings of many previous studies on this topic such as short-term follow-up, confounding by potent diuretics, and reverse causality in observational studies with the sickest patients (i.e., with heart failure) receiving the most severely restricted sodium diets.

How Does Salt Raise BP?

There is no one simple explanation of how salt gluttony raises BP. There are multiple possibilities: Salt promotes vasoconstriction, vascular remodeling, and hypertension by both volume-dependent and volume-independent mechanisms (Rodriguez-Iturbe et al., 2007) (Table 3-2).

Volume-Dependent Mechanisms

Sodium, the principal extracellular cation, is the primary determinant of extracellular fluid volume, which in turn drives cardiac preload and cardiac output. Increased cardiac output may initiate hypertension, but either small vessel vasoconstriction or large vessel stiffness seems needed to sustain it.

Two theories—autoregulation and endogenous ouabain-like compounds—have been at the heart of the volume-dependent mechanism.

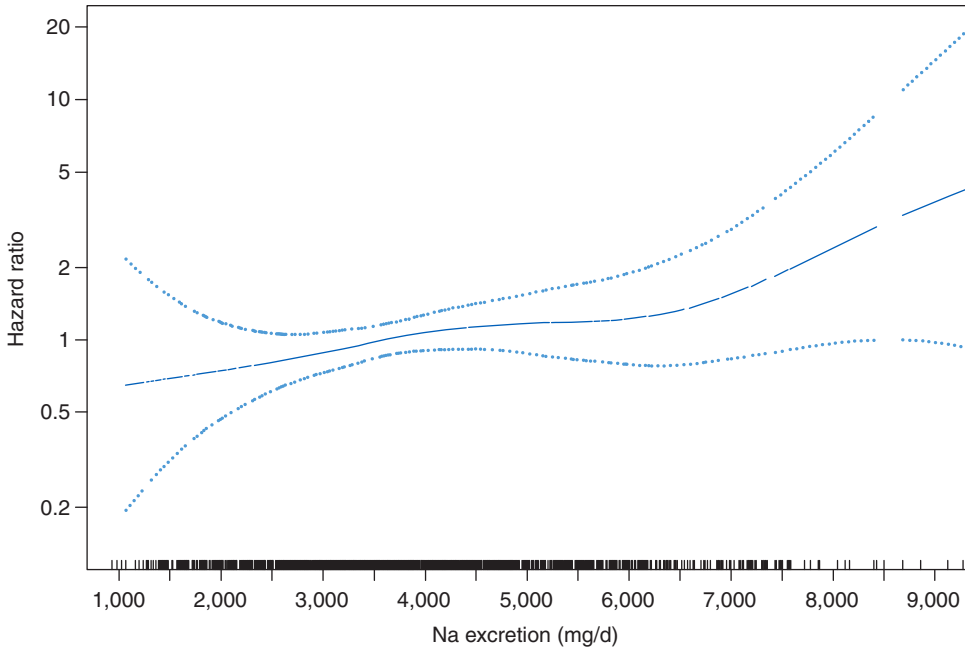


FIGURE 3-12 • Long-term follow-up data from the TOHP. Spline plot of the hazard ratio for CV disease by mean sodium excretion expressed as milligrams per day, adjusted for covariables. These data show no evidence of a sodium J-curve in CV events. *p*-Value for linearity = 0.044; *p* value for nonlinearity = 0.76. Rug plot indicates distribution of sodium excretion. (From Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. *Circulation* 2014;129:981–989.)

Autoregulation

The process of autoregulation was first described by Borst and BorstDe (1963) and demonstrated experimentally by Guyton and Coleman (1969). According

to this view, net renal sodium retention is the inciting event in all hypertensive states. The expanded blood volume increases cardiac preload and thus cardiac output, which increases perfusion of peripheral tissues. As tissue perfusion exceeds metabolic demands, the resistance arteries constrict, thereby stopping overperfusion but at the “expense” of increases in systemic vascular resistance and BP. The resultant increase in cardiac afterload returns cardiac output to normal. The term *autoregulation* implies that the vasoconstrictor response is an intrinsic property of vascular smooth muscle and does not require hormonal or neural inputs.

Guyton first showed conversion from high cardiac output to high systemic vascular resistance with inappropriately normal cardiac output during several days of volume infusion in dogs with reduced renal mass (Guyton, 1992) (Fig. 3-13). His concept has been supported by human studies indicating conversion over one or two decades from an initially high cardiac output to a later increased systemic vascular resistance (Julius et al., 1991).

Autoregulation is a property of small arteries and thus may have little to do with ISH in the elderly, which involves mainly large conduit arteries (Franklin, 2012). It may play a larger role in the volume dependence of diastolic hypertension and of renal parenchymal hypertension, which is discussed in Chapter 9.

TABLE 3-2

How Sodium Retention Can Elevate BP

- Volume-dependent mechanisms
- Autoregulation
 - Production of endogenous ouabain-like steroids^a
- Volume-independent mechanisms
 - Angiotensin-mediated CNS effects
 - Increase in sympathetic nervous system activity
 - Hypertrophy in cardiac myoblasts and contractility of vascular smooth muscle cells
 - Increase in production of NF-κB
 - Increase in expression of AT1r in renal tissue
 - Increase in TGF-β production

^aExtracellular volume expansion induces the production of ouabain-like steroids with impairment of the sodium-potassium adenosine triphosphatase pump and increase in intracellular sodium. Sodium/calcium exchanger activity causes an increment in cytosolic calcium, which results in vasoconstriction and increased peripheral vascular resistance.

AT1r, angiotensin II type 1 receptor.

Adapted from Rodriguez-Iturbe B, Romero F, Johnson RJ. Pathophysiological mechanisms of salt-dependent hypertension. *Am J Kidney Dis* 2007;50:655–672.

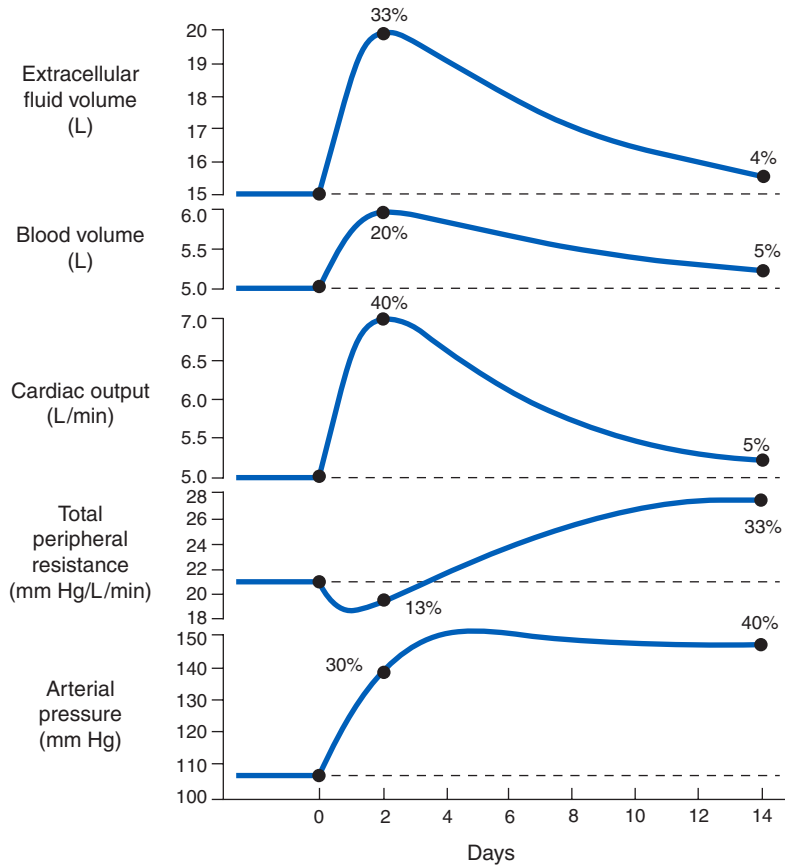


FIGURE 3-13 • Progressive changes in important circulatory system variables during the first weeks in volume-loading hypertension. The initial rise in cardiac output is the basic cause of the hypertension. Subsequently, the autoregulation mechanism returns the cardiac output to almost normal and at the same time causes a secondary increase in total peripheral resistance. (Modified from Guyton AC. *Kidneys and fluids in pressure regulation: Small volume but large pressure changes.* *Hypertension* 1992;19:12–18.)

Endogenous Ouabain-Like Compounds

Haddy and Overbeck (1976) and Blaustein (1977) pioneered the theory that endogenous ouabain-like inhibitors (EOs) of Na-K-ATPase mediate peripheral vasoconstriction in salt hypertension. According to this theory, which has evolved over 40 years (Fig. 3-14), salt retention can stimulate the adrenal glomerulosa cells to release EOs (cardiac glycosides) that inhibit Na/K-ATPase in vascular smooth muscle and cardiac muscle; the resultant increase in Na flux drives the Na–Ca exchanger (NCX) to increase cytosolic Ca^{2+} , enhancing vasoconstriction and cardiac contractility as well as Ca^{2+} -dependent cardiac and vascular hypertrophy (Iwamoto, 2007). Also increased NaCl concentration in the CSF causes hypertension in mice mediated by an ouabain-like substance in the brain, specifically by its binding to an isoform of the Na, K-ATPase (Van Huysse et al., 2011).

Specific NCX inhibitors steeply reduce BP in multiple rat models of salt-sensitive hypertension but have no effect on BP in normotensive rats or those with hypertension that is not salt sensitive (Iwamoto, 2007). Thus, these and ouabain inhibitors may hold

promise as new drugs specifically for salt-sensitive hypertension in patients.

Volume-Independent Mechanisms

Recent work has stressed several of the volume-independent mechanisms of salt-induced hypertension listed in Table 3-2:

- Small increases in serum Na may increase central sympathetic outflow (de Wardener et al., 2004). Small increases in Na in the CSF are sensed by Na channels in the subfornical organs (Orlov & Mongin, 2007).
- Extracellular sodium stimulates renal release of NF- κ B and other proinflammatory cytokines that produce a chronic state of renal inflammation (Rodriguez-Iturbe et al., 2007).
- Extracellular sodium stimulates production of TGF- β , a profibrotic cytokine that promotes vascular remodeling and hypertension. Mice lacking Emilin-1, the endogenous inhibitor of TGF- β , develop salt-sensitive hypertension (Zacchigna et al., 2006).

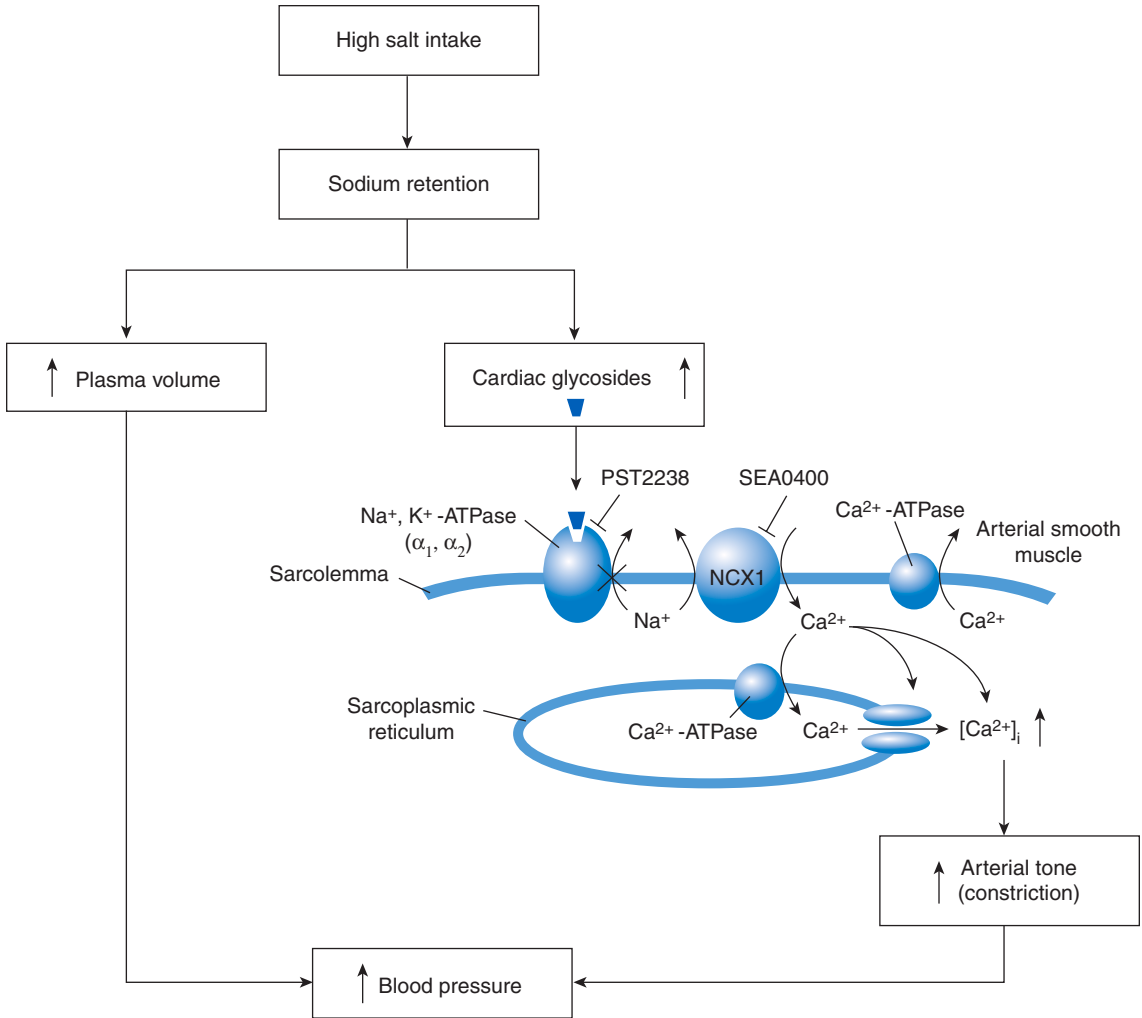


FIGURE 3-14 • Proposed pathway by which Na⁺/Ca²⁺ exchange mediates salt-sensitive hypertension. High salt intake increases plasma levels of endogenous cardiac glycosides that inhibit Na⁺, K⁺-ATPase. This increases subplasma membrane [Na⁺] in arterial smooth muscle, which elevates cytosolic [Ca²⁺] via the Na⁺/Ca²⁺ exchanger (NCX1) and thus enhances arterial tone and contributes to hypertension. SEA0400, an inhibitor of NCX1, and PST2238, a ouabain antagonist, block Ca²⁺ entry and lower BP in experimental models of salt-sensitive hypertension. RyR, ryanodine receptor. (Modified from Iwamoto T. Na⁺/Ca²⁺ exchange as a drug target—insights from molecular pharmacology and genetic engineering. *Ann NY Acad Sci* 2007;1099:516–528.)

- Extracellular sodium increases expression of the angiotensin II type 1 receptors in the kidney (Gu et al., 1998).
- Aldosterone does not cause trouble when dietary sodium is restricted but becomes a cardiac, vascular, and renal toxin—promoting inflammation and fibrosis—when dietary sodium is plentiful (Pimenta & Calhoun, 2006).

Salt Sensitivity and Salt Resistance

Most adults have eaten a high-sodium diet since childhood, but only a portion will have developed

hypertension by age 55, suggesting a variable degree of BP sensitivity to sodium (Rodriguez-Iturbe et al., 2007).

In the rat model developed by Lewis K. Dahl, inbred salt-sensitive rats remain normotensive on a low-salt diet but develop hypertension on a high-salt diet, whereas salt-resistant rats remain normotensive even on high salt (Dahl & Heine, 1975). Thus, salt-sensitive hypertension is often viewed as a classic example of a gene–environment interaction. But, in humans, salt sensitivity also can be acquired—e.g., from weight gain, from low dietary potassium, from nonspecific renal injury, or from progressive renal injury caused by uncontrolled hypertension.

Salt sensitivity—and salt resistance—may be caused by mechanisms that are both intrinsic and extrinsic to the kidney (Table 3-3).

TABLE 3-3

Pathophysiologic Mechanisms Resulting in a Sustained Tendency to Sodium Retention by the Kidneys

Genetic defects
Genetic variants and polymorphisms ^a
Genetic mutations of renal sodium channels/transporters ^b
Systemic mechanisms
Increased sympathetic tone
Insufficient suppression of the renin–angiotensin–aldosterone system
Decreased atrial natriuretic peptide activity
Decreased γ -melanocyte-stimulating hormone
Insulin, metabolic syndrome
Hyperuricemia
Renal mechanisms
Specific defects
Endothelin (A) receptor overactivity
Impairment of endothelin 1 and endothelin (B) action on collecting duct
Decreased dopamine activity (uncoupling)
Nonspecific defects
Decreased number of nephron units
Sodium-driven renal TGF- β overproduction (progression of CKD)
Decreased activity of kallikrein–kinin system
Impaired 20-HETE synthesis and decreased epoxygenase levels
Renal-induced increase in sympathetic nervous system activity
Intrarenal oxidative stress
Increased intrarenal angiotensin II
Tubulointerstitial inflammation

^aGlucocorticoid-remediable aldosteronism, the p.Gly460Trp variant of the α -adducin gene, the p.Gly40Ser variant of the glucagon gene, mutations of glucocorticoid-regulated kinase, gene families involved in the metabolism of arachidonic acid (SS [homozygous for a small number of repeats] genotype of the human prostacyclin synthase gene), angiotensinogen polymorphisms.

^bMutations in the β and γ subunits of amiloride-sensitive ENaC (Liddle syndrome), sodium-chloride cotransport (Gitelman syndrome), sodium-potassium-chloride cotransport, potassium and chloride channels (Bartter syndrome), WNK1 and WNK4 kinases (Gordon syndrome), aldosterone synthase/11 β hydroxylase (glucocorticoid-remediable aldosteronism), 11 β hydroxylase/11 α hydroxylase (adrenal hyperplasia), mineralocorticoid receptor, 11 β hydroxysteroid dehydrogenase (apparent mineralocorticoid excess), MR (progesterone-induced hypertension), pseudoaldosteronism.

TGF- β , transforming growth factor- β ; CKD, chronic kidney disease; 20-HETE, 20-hydroxyarachidonic acid.

Monogenic Human Hypertension and Hypotension

The study of rare Mendelian traits by Richard Lifton's group and others has identified 20 genes in which homozygous mutations cause severe familial forms of hypotension or hypertension (Lifton et al., 2001). Remarkably, every one of these different mutations affects BP mainly by altering the kidney's ability to excrete sodium as illustrated in Figure 3-15.

To maintain salt and water balance, the kidneys normally reabsorb greater than 99% of the filtered sodium load as follows: 60% of the filtered sodium is reabsorbed in the proximal tubule by Na⁺/H⁺ exchange, the target of acetazolamide; 30% in the thick ascending limb of the loop of Henle by the Na–K–2Cl transporter, the target of the “loop” diuretics; 7% in the distal convoluted tubule by the Na–Cl cotransporter, the target of the thiazide diuretics; and 2% in the cortical collecting duct by the epithelial sodium channel (ENaC), which is activated by aldosterone (as part of the effector arm of the RAAS) and the target of the aldosterone antagonists.

In the familial hypotensive disorders, exemplified by Bartter and Gitelman syndromes, the disease-causing mutations impair the diuretic-sensitive transporters, leading to salt wasting and hypovolemic hypotension (Lifton et al., 2001). They typically present in the neonatal period or early childhood.

In the familial hypertensive disorders, the disease-causing mutations all increase ENaC activity either directly as in Liddle syndrome or indirectly due to overproduction of mineralocorticoids as in glucocorticoid-remediable aldosteronism or dysregulation of the MR as pregnancy-exacerbated hypertension (Lifton et al., 2001). The net result is severe salt-sensitive hypertension typically presenting in the first two decades of life. Targeted diuretic therapy is the cornerstone of treatment.

Whether these or other mutations are involved in common primary hypertension in the general population is discussed later in this chapter. Here, suffice it to say that these are extreme *experiments of nature*, proving that altered renal sodium handling can have dramatic effects on human BP.

However, as described next, defining more moderate degrees of sodium resistance and sodium sensitivity in human subjects requires strict clinical research methodology, which is generally too cumbersome for routine clinical use.

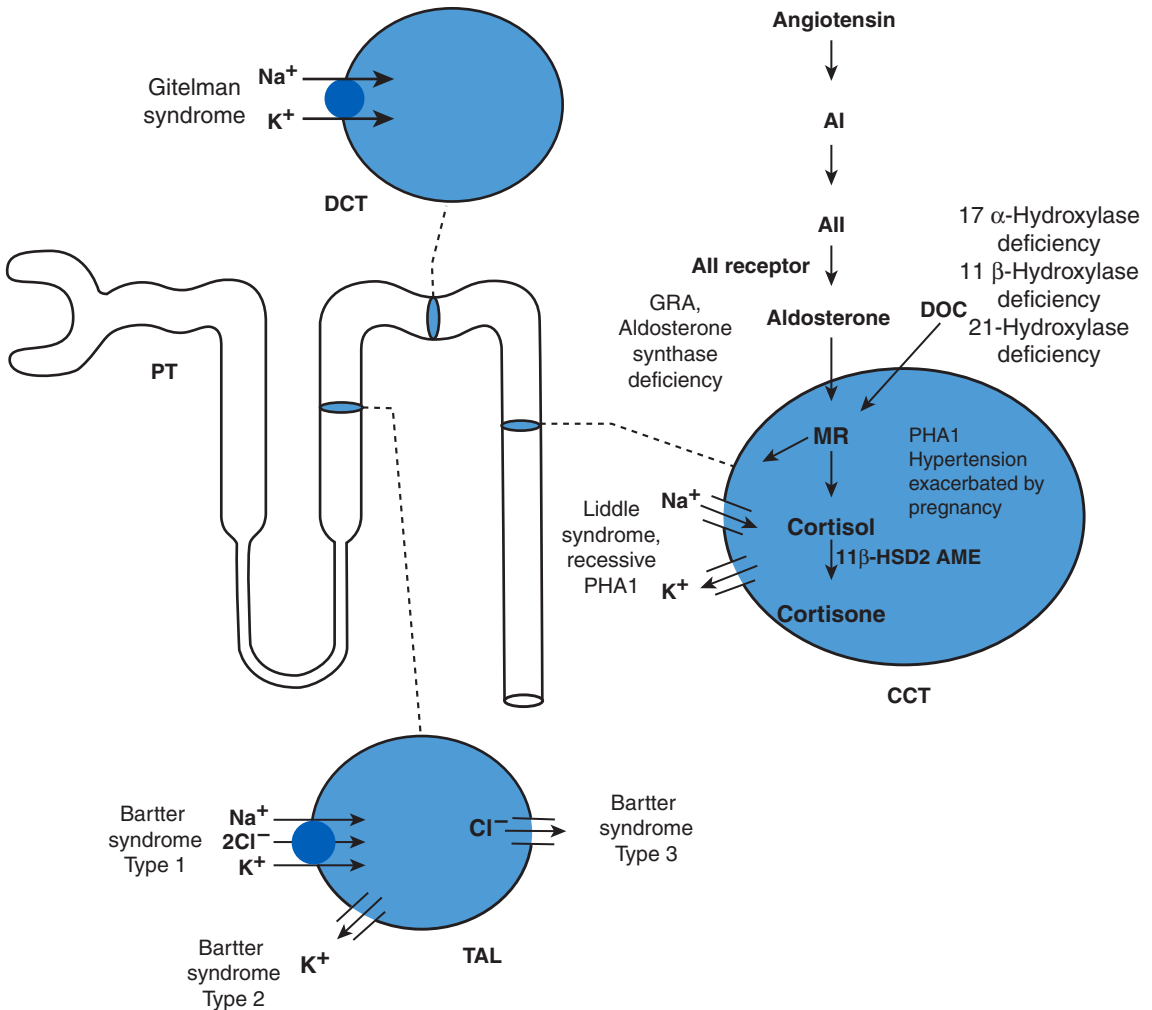


FIGURE 3-15 • Mutations altering BP in humans—a diagram of nephron, the filtering unit of the kidney, is shown. The molecular pathways mediating NaCl reabsorption in individual renal cells in the thick ascending limb of the loop of Henle (TAL), distal convoluted tubule (DCT), and the cortical collecting tubule (CCT) are indicated, along with the pathway of the renin-angiotensin system, the major regulator of renal salt reabsorption. Inherited diseases affecting these pathways are indicated, with hypertensive disorders underlined. AI, angiotensin I; ACE, angiotensin-converting enzyme; A II, angiotensin II; MR, mineralocorticoid receptor; GRA, glucocorticoid-remediable aldosteronism; PHA1, pseudohypoaldosteronism, type-1; AME, apparent mineralocorticoid excess; 11 βHSD2, 11β-hydroxysteroid dehydrogenase-2; DOC, deoxycorticosterone; and PT, proximal tubule. (Adapted from Lifton RP, Gharavi AG, Geller DS. Molecular mechanisms of human hypertension. *Cell* 2001;104:545–556.)

Clinical Research Methodology

Since Luft and Weinberger (1997) and Kawasaki et al. (1978) described varying responses of BP to short periods of low and high sodium intake, numerous protocols have been used to determine sodium sensitivity with variable results (de la Sierra et al., 2002).

Weinberger et al. (1986) defined sodium sensitivity as a 10-mm Hg or greater decrease in mean BP from the level measured after a 4-hour infusion of 2 L normal saline as compared to the level measured the

morning after 1 day of a 10-mmol sodium diet, during which three oral doses of furosemide were given at 10 a.m., 2 p.m., and 6 p.m. Using this criterion, these researchers found that 51% of hypertensives and 26% of normotensives were sodium sensitive. Most studies find BP to be more salt sensitive among persons who are older, overweight, hypertensive, or of African descent (Luft & Weinberger, 1997).

Heightened BP reactivity to cold pressor testing may be an easier way to identify individuals with sodium-sensitive BP (Chen et al., 2008a). A high

dietary intake of sodium (relative to potassium) may act both centrally to augment the sympathetic reactivity to many stimuli such as cold stress and peripherally to augment vascular reactivity to neurally released NE.

^{23}Na MRI holds promise as a powerful new research tool to improve the mechanistic understanding of how sodium is stored in the body and contributes to hypertension (Kopp et al., 2012, 2013). Na^+ is bound to negatively charged proteoglycans that are plentiful in skin and skeletal muscle; when this storage is perturbed, salt-sensitive hypertension may result. This in vivo noninvasive MRI technique has been validated against chemical analysis in tissue extracts and by showing increased tissue deposition of Na^+ in patients with primary aldosteronism that normalized after successful therapy (Kopp et al., 2012). In a cross-sectional study of 57 men and women with primary hypertension and 56 healthy controls, Na^+ concentration in skin and skeletal muscle was found to increase with age and to be higher in patients with refractory hypertension (Fig. 3-16) (Kopp et al., 2013). Further work will be needed to

determine if differences can be detected between patients with salt-sensitive versus salt-resistant hypertension and if tissue Na^+ predicts the BP response to diuretic therapy.

Importance of Pressure–Natriuresis

In normotensive people, when BP rises, renal excretion of sodium and water increases, shrinking fluid volume and returning the BP to normal—the phenomenon of *pressure–natriuresis*. On the basis of animal experiments and computer models, Guyton (1961, 1992) considered the regulation of body fluid volume by the kidneys to be the dominant mechanism for the long-term control of BP—the only one of many regulatory controls to have sustained and infinite power. Therefore, if hypertension develops, he reasoned that something must be amiss with pressure–natriuresis; otherwise, the BP would return to normal.

Experimental Support

The concept has a solid foundation: When BP is raised, the normal kidney excretes more salt and water—i.e., pressure–natriuresis occurs (Selkurt, 1951). The curve relating BP to sodium excretion is steep (Fig. 3-17). A small change in renal perfusion pressure causes a large change in the rate of sodium

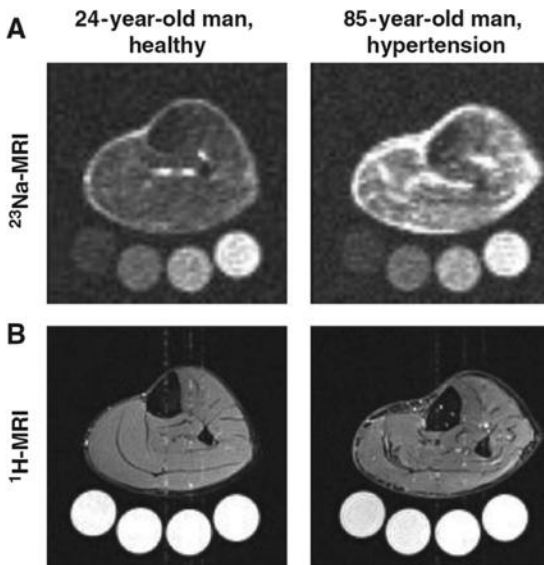


FIGURE 3-16 • ^{23}Na magnetic resonance imaging (^{23}Na -MRI) of tissue Na^+ . **A:** Representative ^{23}Na -MRI image of the lower leg of a young normotensive man and, for comparison, an elderly man with hypertension in whom skin and muscle sodium concentration is clearly increased. Tubes with solutions containing 10, 20, 30, and 40 mmol/L of NaCl are arranged below the extremity for calibration. **B:** Tissue water in the same two subjects detected with conventional ^1H -MRI, which shows no visible difference in muscle water content. (From Kopp C, Linz P, Dahlmann A, et al. ^{23}Na magnetic resonance imaging-determined tissue sodium in healthy subjects and hypertensive patients. *Hypertension* 2013;61:635–640.)

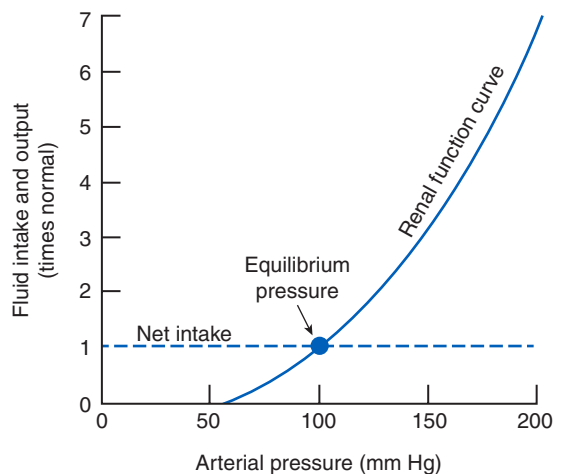


FIGURE 3-17 • Graphic analysis of arterial pressure regulation by the kidney-fluid volume pressure control system. Pressure continually approaches the point at which the renal function curve intersects the net intake line (i.e., equilibrium pressure). (Modified from Guyton AC. *Kidneys and fluids in pressure regulation: Small volume but large pressure changes*. *Hypertension* 1992;19:12–18.)

and water excretion, acting as a powerful negative feedback stabilizer of BP. As BP rises, increased renal perfusion pressure leads to a decrease in sodium reabsorption—particularly in the medulla in the thick ascending limb of the loop of Henle (Cowley, 2008; Dickhout et al., 2002). As a result, body fluid volumes shrink enough to lower BP back to its previous normal level.

Resetting of Pressure–Natriuresis

In patients with primary hypertension—as in every genetic form of experimental hypertension—a resetting of the pressure–sodium excretion curve prevents the return of BP to normal so that fluid balance is maintained but at the expense of high BP (Mayer, 2008). Much work by Guyton, Hall, Brands, and colleagues (Hall et al., 1996b) indicates that the resetting plays a key role in causing hypertension and is not merely an adaptation to increased BP. This resetting explains why sodium retention occurs when BP is lowered by nondiuretic drugs.

As seen in Figure 3-18, either the entire curve can be shifted to the right or the slope can be depressed, depending on the type of renal insult, which is, in turn, reflected by varying sensitivity to sodium (Hall et al., 1996a). Salt-resistant hypertension is characterized by a parallel shift in the pressure–natriuresis curve, whereas salt-sensitive hypertension is accompanied by a change in slope—an exaggerated increase or decrease in BP with increased or decreased sodium intake, respectively.

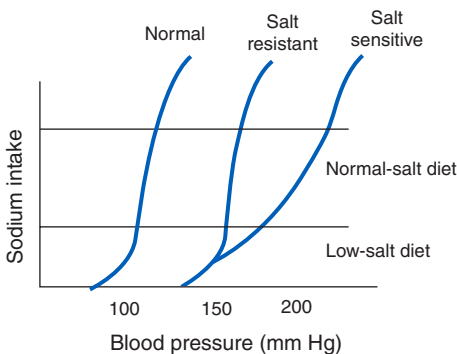


FIGURE 3-18 • Schematic showing resetting of pressure–natriuresis in hypertension. Steady-state relationships between arterial pressures and sodium excretion (equal to intake) are shown for both salt-sensitive and salt-insensitive essential hypertension. (Modified from Hall JE, Brands MW, Henegar JR. Angiotensin II and long-term arterial pressure regulation. *J Am Soc Nephrol* 1999;10:S258–S265.)

Mechanisms of Resetting

Pressure–natriuresis—and the resetting that occurs in hypertension—is mediated first and foremost by changes in tubular sodium transport with unchanged GFR (Cowley, 2008; He & MacGregor, 2010). Extensive rat studies of Cowley and coworkers identify the outer renal medulla as the key site in which pressure–natriuresis occurs (Cowley, 2008).

The renal medulla is uniquely vulnerable to ischemic insult for several reasons. Oxygen extraction is already near maximal under resting conditions to maintain the basal activity of energy-dependent sodium transporters, which are highly concentrated in this part of the kidney. With a sudden increase in BP, medullary blood flow must increase to match the increased energy demands of these transporters. In other words, blood flow to the renal medulla must be poorly autoregulated if pressure–natriuresis is to occur. Impaired medullary blood flow regulation impairs pressure–natriuresis and is evident in virtually all rat models of hypertension.

Table 3-3 is a partial list of the many explanatory mechanisms that underlay a rightward shift in the pressure–natriuresis curve. These include augmented medullary vasoconstrictor mechanisms or impaired medullary vasodilator mechanisms—both autocrine mechanisms that are intrinsic to the kidney and extrarenal neurohormonal mechanisms.

Intrarenal Mechanisms

The best evidence—albeit in rodents—is for an imbalance between an overactive RAAS, which reduces renal medullary blood flow, and a defective nitric oxide (NO) pathway, which normally maintains medullary blood flow and protects against hypertension (Dickhout et al., 2002).

Intrarenal RAAS

The RAAS is a key mechanism regulating renal sodium handling, producing most of its biologic effects via AT1 receptors. In the kidney, AT1 receptors stimulate renal medullary vasoconstriction and increase sodium reabsorption. Renal cross-transplantation experiments between mice with and without targeted disruption of the AT1 receptor gene by Coffman and coworkers emphasize the importance of the renal AT1 receptors in the normal regulation of BP and in the genesis of Ang II–dependent hypertension (Crowley & Coffman, 2008). In addition, AT1 receptors in the brain regulate salt appetite, thirst, and modulate vasopressin release.

Adrenal AT1 receptors enhance secretion of aldosterone, the main mineralocorticoid.

Ang II has been shown repeatedly to cause a rightward shift in the pressure–natriuresis curve (Hall et al., 1996b). The effect is potent because sodium retention is greatly augmented at Ang II concentrations far below those needed to cause vasoconstriction.

As shown in Figure 3-19, in the rat medulla Ang II normally triggers a coordinated calcium signal in the pericytes of the descending vasa recta—promoting vasoconstriction—and the tubular epithelial cells of the thick ascending limb—causing release of NO, a potent vasodilator that diffuses to the adjacent vasa recta and offsets Ang II–dependent vasoconstriction (Dickhout et al., 2002). The balance between vasoconstrictor and vasodilator factors is termed “tubulovascular crosstalk.” Other associated vasoconstrictor factors include ROS (both superoxide and hydrogen peroxide); associated vasodilator factors include cyclooxygenase and prostaglandins (PGE₂) (Cowley, 2008). Any imbalance can cause

medullary ischemia, impaired pressure–natriuresis, and salt-induced hypertension.

One reason the RAAS is so important in renal sodium handling is that Ang II is selectively concentrated in the kidney. Navar and coworkers have shown that intrarenal concentrations of Ang II are several-fold higher than circulating blood levels because the kidney actively produces and sequesters Ang II (Navar, 2014). In multiple experimental forms of hypertension, renal Ang II levels are high even when plasma levels are normal or low. Renal angiotensin-converting enzyme (renal ACE) is required to concentrate Ang II in the kidney because tissue-specific ablation of renal ACE in mice markedly blunts the hypertension induced by Ang II infusion (Gonzalez-Villalobos et al., 2013). Thus, selective overactivity of the intrarenal RAAS may drive hypertension even when extrarenal blood tests (i.e., PRA levels) indicate, as they do in most cases of primary human hypertension, that systemic RAAS activity is either frankly suppressed or “inappropriately normal.”

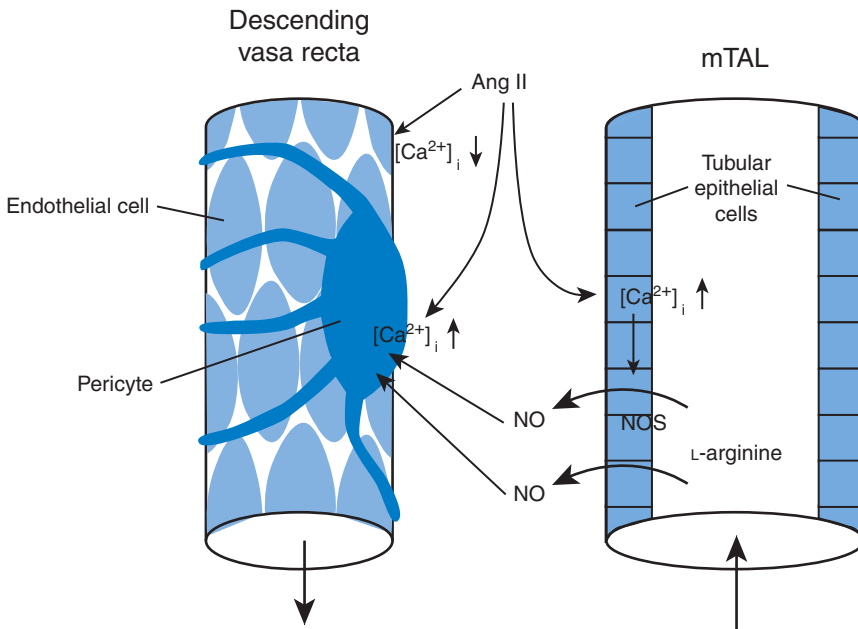


FIGURE 3-19 • Model summarizing the observed actions of Ang II on the medullary thick ascending limb (mTAL) and the adjacent descending vasa recta. Ang II increases $[Ca^{2+}]_i$ in pericytes of the descending vasa recta and reduces it in endothelium of the descending vasa recta. Ang II increases $[NO]_i$ in the pericytes of the descending vasa recta but only when these cells are in proximity to the tubules surrounding the mTAL. Ang II increases $[Ca^{2+}]_i$ and $[NO]_i$ in mTALs even when these tubules were observed in isolation. This indicates that Ang II exerts a constrictor effect on the descending vasa recta by its action on pericytes, and this constrictor action is buffered by NO diffusing from mTALs to the pericytes of the descending vasa recta. (From Dickhout JG, Mori T, Cowley AW Jr. Tubulovascular nitric oxide crosstalk: Buffering of angiotensin II-induced medullary vasoconstriction. *Circ Res* 2002;91:487–493.)

While AT1 receptors promote sodium retention, AT2 receptors promote natriuresis (at least in mice), mediated in part by release of NO (Carey & Padia, 2013). The Angiotensin II Receptor Blockers (ARBs), which cause selective AT1 receptor blockade, induce natriuresis in rodents by unmasking and activating AT2 receptors in the proximal tubule (Carey & Padia, 2013). Despite abundant experimental support, this theory remains untested in patients as selective AT2 receptor antagonists are not available for use in human subjects.

Two more systems that may counter AT1 receptor-mediated sodium retention deserve mention.

Renal Dopaminergic System

Dopamine evokes natriuresis in rodents and humans by stimulation of dopamine (D1) receptors. The renal proximal tubular cells are able to synthesize dopamine locally from L-DOPA and studies in dopamine receptor knockout mice suggest that the intrarenal dopaminergic system can explain half the renal sodium excretion seen with salt loading (Carey, 2013). The normal yin–yang interaction between D1 and AT1 receptors is defective causing sodium retention in common experimental models of hypertension.

Renal Medullary Endothelin System

Endothelin, discovered as a potent endothelium-derived vasoconstrictor, also is plentiful in the renal medulla where it causes vasodilation and natriuresis, thus reducing BP and protecting against salt-induced hypertension (Kohan, 2013). These effects are mediated by the ETB receptor, whereas the vasoconstrictor and prohypertensive actions of endothelin are mediated by the ETA receptor.

A high-salt diet drives endothelin expression in the kidney, increasing renal medullary blood flow via prostaglandins and NO (Schneider et al., 2008) and inhibiting the antinatriuretic effect of vasopressin. Genetically engineered mice and rats that cannot produce endothelin or the ETB receptor in the renal medulla develop salt-dependent hypertension (Garipey et al., 2000; Kohan, 2013). Thus, the ETB receptor is a potential new antihypertensive drug target. *Yet, clinical endothelin receptor antagonists inhibit both ETA and ETB receptors, which likely explains their disappointingly small effect on BP, despite showing much promise for treating pulmonary hypertension* (Garipey et al., 2000; Pulido et al., 2013).

Extrarenal Mechanisms

The following systemic mechanisms also have been shown to reset pressure–natriuresis and have been implicated in causing salt-sensitive hypertension:

- Dysfunction of the natriuretic peptides (Dries et al., 2005)
- Insulin (Rodriguez-Iturbe et al., 2007)
- α -Melanocyte-stimulating hormone, which causes or exacerbates salt-sensitive hypertension in rodent models via the central melanocortin system and activation of SNA (da Silva et al., 2008; Greenfield et al., 2009)
- *Activation of renal sympathetic nerves.* DiBona and coworkers have shown that activation of the renal sympathetic nerves shifts the pressure–natriuresis curve and contributes to salt-sensitive hypertension in rats (DiBona, 2005). Conversely, RDN prevents the development, attenuates the magnitude, or delays the onset of hypertension in multiple animal models (DiBona, 2005). Campese and coworkers showed that even a mild renal parenchymal injury—with a single injection of phenol into the lower pole of one kidney in an otherwise normal rat—will produce sustained salt-sensitive hypertension mediated in part by activation of renal afferents that reflexly increase renal sympathetic nerve activity (RSNA) and in part by reduced NO production (decreased nitric oxide synthase [NOS] expression) by the injured kidney (Bai et al., 2007)—i.e., by both extrarenal and intrarenal mechanisms.
- Activation of the thiazide-sensitive NaCl cotransporter by stimulation of β 1-adrenergic receptors (Terker et al., 2014) or by calcineurin inhibitors (Hoorn et al., 2011) can cause salt-sensitive hypertension in rodent models and possibly in human patients.

Several of these and other putative mechanisms have been implicated in causing salt-sensitive hypertension in non-Hispanic black patients (Richardson et al., 2013).

Importance of Renal Inflammation

Rodent studies point to renal inflammation as both a cause and a consequence of renal medullary ischemia (Franco et al., 2013; Rodriguez-Iturbe et al., 2013). Renal inflammation—whether the chicken or the egg—is a hallmark of both the initiation and progression of experimental salt-sensitive hypertension. Eventually, on-going renal ischemia will kill enough nephrons to decrease GFR.

Nocturia

Nocturia may be a clinical sign of abnormal pressure–natriuresis and a clue to uncontrolled salt-sensitive hypertension related to aging, hypertension, and particularly a blunted or reversed nocturnal dipping pattern in BP (Bankir et al., 2008). In normotensives, nocturnal urine flow accounts for 53% of urine output in 60- to 80-year-olds as compared to 25% in 25- to 35-year-olds (McKeigue & Reynard, 2000). Hypertensives have even more nocturia, presumably reflecting the resetting of the pressure–natriuresis relationship (Fukuda et al., 2006). Fluid retained peripherally during the day leads to central volume expansion at night, with elevated nocturnal BP driving pressure–natriuresis (Bankir et al., 2008).

Salt sensitivity of BP may be inherited or acquired—in utero, during early postnatal life, or during adult life as a result of a low-potassium diet or uncontrolled hypertension.

Inherited Renal Defects in Sodium Excretion

Using rats bred to be either sensitive or resistant to the hypertensive action of dietary sodium, Dahl and Heine (1975) demonstrated the primacy of the kidney in the development of hypertension by a series of transplant experiments. The BP follows the kidney: When a kidney from a normotensive donor was transplanted to a hypertensive host, the BP of the recipient fell to normal. Conversely, when a hypertensive kidney was transplanted into a normotensive host, the BP rose. Moreover, transplantation of a kidney from a hypertensive rat that has been briefly made normotensive with an angiotensin converting enzyme inhibitor (ACEI) causes the BP to normalize in a hypertensive host (Smallegange et al., 2004).

Curtis et al. (1983) observed long-term remission of hypertension after renal transplantation in six black men who likely developed renal failure solely as a consequence of primary hypertension. Because five of these patients had remained hypertensive after removal of their native kidneys, their hypertension was presumably not of renal pressor origin. The most likely explanation for the reversal of hypertension in these patients was the implantation of normal renal tissue, which provided control of body fluid volume, something their original kidneys had been unable to manage. Moreover, hypertension develops more frequently in recipients of renal transplants from hypertensive donors than in recipients from normotensive donors (Guidi et al., 1996).

As noted earlier, impaired renal sodium excretion is the final common pathway for most of the known monogenic forms of human hypertension (Lifton et al., 2001).

Perinatal Origin of Adult Salt-Sensitive Hypertension: Reduced Nephron Number

Low birth weight with reduced nephrogenesis increases the risk of developing adult salt-dependent hypertension. Adult hypertensives have fewer glomeruli per kidney but very few obsolescent glomeruli, suggesting that nephron dropout and decreased total filtration surface area are a cause and not the consequence of hypertension (Keller et al., 2003). This is one of the strongest areas of mechanistic clinical research on primary hypertension.

Brenner and coworkers first proposed that hypertension may arise from a congenital reduction in the number of nephrons or in the filtration surface area per glomerulus, thereby limiting the ability to excrete sodium, raising the BP, and setting off a vicious circle whereby systemic hypertension begets glomerular hypertension, which begets more systemic hypertension (Brenner & Chertow, 1994) (Fig. 3-20).

The first major affirmation of the Brenner hypothesis came from a postmortem analysis of total nephron numbers in kidneys from 10 previously hypertensive patients and 10 previously normotensive people, all of whom having died from accidents (Keller et al., 2003). The two groups were matched for age, gender, height, and weight. The median number of glomeruli in the hypertensives was less than half of the number in the normotensives. Moreover, the glomerular volume in the hypertensives was greater, suggesting that they were hyperfiltering. The likelihood that the lower number of glomeruli in the hypertensives was from birth was supported by the absence of adolescent glomeruli as would be seen if they had been present but dropped out.

Congenital Oligonephropathy

The Brenner hypothesis invokes a reduced number of nephrons from congenital oligonephropathy, i.e., fewer nephrons as a result of intrauterine growth retardation (Mackenzie & Brenner, 1995). As first reported by Dr. David Barker and colleagues on the basis of epidemiologic studies, infants born small for gestational age, i.e., with low birth weight, are at increased risk for

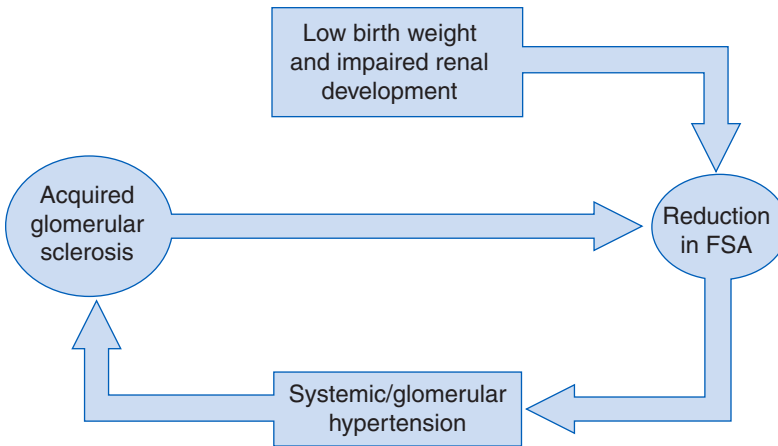


FIGURE 3-20 • A diagram of the hypothesis that the risks of developing primary hypertension and progressive renal injury in adult life are increased as a result of congenital oligonephropathy, or an inborn deficit of filtration surface area (FSA), caused by impaired renal development. (Modified from Brenner BM, Chertow GM. Congenital oligonephropathy and the etiology of adult hypertension and progressive renal injury. *Am J Kidney Dis* 1994;23:171-175.)

development of hypertension, diabetes, and CV diseases later in life (Barker et al., 1989). The concept of “perinatal programming” has focused on maternal protein restriction (Woods et al., 2004) as responsible for the shunting of necessary fuels to the developing brain at the expense of less vital organs including the kidneys and pancreas, a hypothesis described as “thrifty phenotype” (Hales & Barker, 2001).

The presence of congenital oligonephropathy in human babies born with intrauterine growth retardation was first shown by Hinchliffe et al. (1992) and confirmed by several groups (Hughson et al., 2008; Konje et al., 1996; Manalich et al., 2000) with an average of 260,000 fewer nephrons with each kilogram of decrease in birth weight. The reduced number of nephrons at birth in low birth weight babies cannot be replenished later by excellent postnatal nutrition since most nephrons are formed in the first part of the last trimester and no further nephrogenesis occurs after 34 to 36 weeks of gestation (Lucas & Morley, 1994).

The subsequent scenario has been described by Mackenzie and Brenner (Mackenzie & Brenner, 1995):

Deficiencies in the total nephron supply, by limiting total renal excretory capacity and thereby influencing the point at which steady-state conditions between BP and sodium excretion are achieved, could profoundly affect long-term BP regulation. When renal mass is greatly reduced, as in the case of extensive experimental ablation of the kidney in rodents, BP increases in the systemic arterial circulation and in the glomerular capillaries, thus increasing glomerular filtration rate and promoting fluid excretion. However, sustained elevations in glomerular capillary hydraulic pressure are associated with the development of focal and segmental glomerular sclerosis leading to further loss of nephrons and a self-perpetuating

vicious cycle of hypertension and progressive glomerular injury. ... Given the association between low birth weight and fewer nephrons ... it is naturally tempting to speculate that the origins of hypertension in adults who were of low birth weight lie in a deficient endowment of nephrons secondary to intrauterine growth retardation.

Recent evidence supporting the Barker/Brenner hypothesis includes the following:

- A meta-analysis of 20 studies found that low birth weight (<2.5 kg) compared with birth weight greater than 2.5 kg was associated with a 21% increased risk of developing hypertension in adolescence or adulthood while high birth weight (>4 kg) was associated with a 22% lower risk (Mu et al., 2012).
- The largest autopsy study of human nephron number (176 African Americans, 132 white Americans, 19 Aboriginal Australians, and 24 white Australians) showed that the mean is 895,711 nephrons per kidney with an enormous 12-fold range of 210,332 to 2,702,079 (Bertram et al., 2011). However, since the seminal NEJM paper from Brenner's group (Keller et al., 2003), there have not been enough studies to confirm the relation of low nephron number with high BP (Luyckx et al., 2013).
- Using low birth weight as a surrogate for low nephron number, two groups have shown that low birth weight in whites is associated with salt sensitivity of BP in healthy young adults (de Boer et al., 2008) and in pre-adolescents and adolescents (Simonetti et al., 2008).
- However, Flynn et al. (2014) could not show an association of low birth weight/premature birth/small for gestational age with 24-hour ambulatory BP or GFR in a cohort of children with CKD, possibly due to confounding by CKD.

- The National Longitudinal Health Study of over 10,000 young adults found a significant inverse relation between birth weight and SBP in black and white men but not in women (Richardson et al., 2011).
- A population-based sibling comparison study of over 3 million Swedish children—the largest study in this field to date—showed that low birth was associated with a 169% increased risk of CV death and a 79% increased risk of diabetes (Class et al., 2014).

Postnatal Weight Gain

Despite all of the evidence supporting a role of low birth weight with adult hypertension, its contribution may be quantitatively small (Bertram et al., 2011). An even greater contribution has been shown for the rapid postnatal “catch-up” in body weight (Singhal & Lucas, 2004). Singhal et al. (2004) have summarized a great deal of their own and others’ convincing evidence for a critical period—the first 2 weeks after birth—where over-feeding programs the infant for later obesity, insulin resistance, and endothelial dysfunction that, in turn, result in diabetes, hypertension, and coronary disease.

Their evidence includes multiple observations on the benefits of feeding with breast milk (with lower caloric content and lower initial volume) rather than formula milk (with higher caloric content and larger volume) on subsequent adult health (Lawlor et al., 2004; Martin et al., 2006).

Along these lines, additional analyses of 2003 Finnish people in the Helsinki birth cohort led Barker and coworkers to propose two different pathways by which low birth weight predisposes to hypertension (Barker et al., 2007). In the first, low birth weight results from fetal undernutrition and a small placenta, making the child vulnerable to poor postnatal living conditions such as a fast food high-salt diet. Low birth weight during infancy is followed by rapid growth leading to overweight by age 11. As adults, they become obese and develop insulin resistance, severe hypertension, and coronary disease. In the second path, maternal rickets or even a lesser degree of vitamin C deficiency causes the mother to have a small diameter bony pelvis. The low-birth weight infants remain short and thin throughout childhood, possibly due to

protein malnutrition. As adults, they develop mild hypertension, atherogenic lipid profiles, and stroke.

Further support for this theory comes from two recent studies:

- A prospective study of 139 newborns showed that acceleration of early infant weight gain aggravated the effects of low birth weight on SBP, blood glucose and insulin levels, and uric acid at age 5 (Lurbe et al., 2014).
- A population-based prospective cohort study of 9,031 mothers and their children showed that offspring of nulliparous mothers have lower fetal but higher infant growth rates with higher risks of childhood overweight and adverse cardiometabolic profiles (Gaillard et al., 2014).

The public health implications seem obvious. Recent cutbacks in support for teenage contraception, maternal nutrition, and postnatal care in the U.S. suggest that we will continue to pay billions for the eventual care of hypertension-related end-stage renal disease (ESRD), strokes, and heart attacks instead of millions for preventive care of the disadvantaged.

Limitations

These theories have not been shown to explain the excessive hypertension in African Americans (Bertram et al., 2011; Hughson et al., 2008; Luyckx et al., 2013).

Summary

While there may be more evidence for renal mechanisms than for any other in primary hypertension, additional mechanisms are involved.

VASCULAR MECHANISMS

Alterations in the structure and function of both small and large arteries also play a pivotal role in the origin and progression of hypertension (Montezano & Touyz, 2014). In most cases of human hypertension, peripheral vascular resistance is increased while cardiac output is normal. By Poiseuille law, BP is directly related to the first power of cardiac output but inversely related to the fourth power of blood vessel radius. Thus, small changes in blood vessel diameter have enormous effects on BP.

Cellular Mechanisms of Vasoconstriction

As shown in Figure 3-21, an increase in cytosolic calcium is the final common pathway mediating contraction of vascular smooth muscle (Harrison, 2013b). Most potent antihypertensive drugs are vasodilators, as discussed in Chapter 7. BP is elevated in genetically altered mice with increased vascular resistance, showing that blood vessel constriction alone, without renal involvement, can cause hypertension (Harrison, 2013b).

Endothelial Cell Dysfunction and the Nitric Oxide Pathway

The endothelial lining of blood vessels is critical to vascular health and constitutes a major defense against atherosclerosis and hypertension (Harrison et al.,

2012). Dysfunctional endothelium, a hallmark of hypertension and other CV risk factors, is characterized by impaired release of endothelial-derived relaxing factors (NO, endothelial-derived hyperpolarizing factor) and enhanced release of endothelial-derived constricting, proinflammatory, prothrombotic, and growth factors. The latter include endothelin, thromboxane, and transforming growth factor-β (TGF-β) (Montezano & Touyz, 2014). Growing evidence indicates that blood vessels are inflamed in hypertension and that smoldering vascular inflammation plays a central role in the genesis and complications of high BP (Harrison et al., 2012; Montezano & Touyz, 2014).

The endothelium of all blood vessels expresses the enzyme NOS, which can be activated by bradykinin or acetylcholine or by the cyclic laminar shear stress that accompanies hypertension. Once activated, NOS converts L-arginine to citrulline, an inert substance, and NO, a volatile gas that diffuses to the

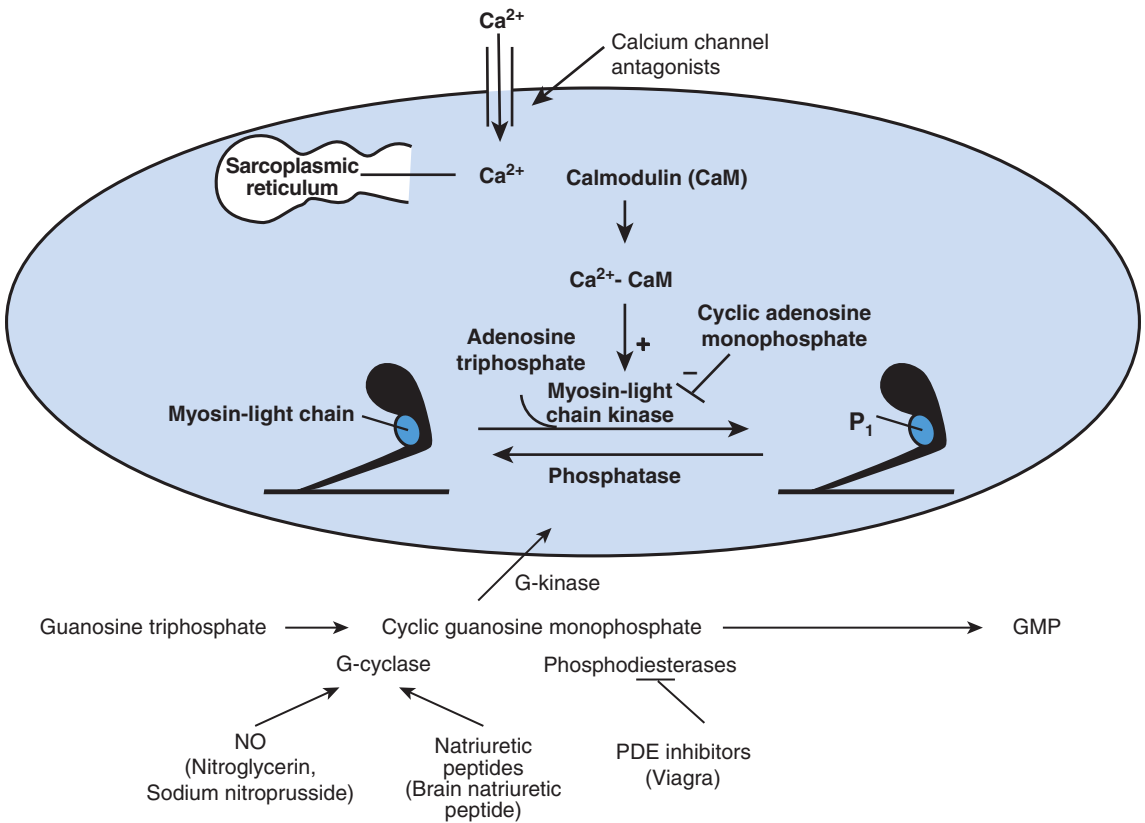


FIGURE 3-21 • Mechanisms of vascular smooth muscle contraction. NTG, nitroglycerin; SNP, sodium nitroprusside. (From Harrison DG. *Vascular Mediators of Hypertension*. New York, NY: American Society of Hypertension, Inc (ASH); 2013b:107–125. Adapted from Griendling K, Harrison D, Alexander R. *Biology of the vessel wall*. In Fuster V, Walsh R, O'Rourke R, Poole-Wilson P (eds). *Hurst's the Heart*, 12th ed. New York, NY: McGraw-Hill; 2008:135–154.)

adjacent vascular smooth muscle and activates a series of G-kinases that culminate in vasodilation (Fig. 3-22). Thus, the NO pathway is thought to be one of the most important regulatory mechanisms that protects against hypertension, and NO deficiency is thought to contribute to hypertension (Montezano & Touyz, 2014).

One of the principal mechanisms of endothelial cell dysfunction in hypertension is the production of superoxide anion and other ROS that quench NO, thereby reducing its bioavailability. The term “oxidative stress” refers to chronic elevations in ROS, which are associated with hypertension, atherosclerosis, and diabetes (Paravicini & Touyz, 2008).

The two main ROS are superoxide radical (O_2^-) and hydrogen peroxide (H_2O_2) (Fig. 3-23). Overproduction of superoxide radical and H_2O_2 can activate signaling molecules that lead to cell growth, fibrosis, inflammation, and eventually vascular remodeling (Fig. 3-24).

Enzymatic Sources of Superoxide

There are four main enzymatic sources of vascular superoxide: (1) NADPH oxidases, which are universally expressed in all vascular cell types and are activated by

circulating Ang II and other factors, (2) NOS, which produces superoxide only when an important cofactor (tetrahydrobiopterin or BH_4) is deficient (a process termed “NOS uncoupling”), (3) xanthine oxidase (XO), which produces uric acid, and (4) mitochondria (Paravicini & Touyz, 2006).

- ▶ NADPH oxidases. Superoxide production by NADPH oxidase is one of the main mechanisms mediating Ang II–induced hypertension. NADPH oxidases also are expressed in the kidney and brain where they play a role in experimental hypertension via renal sodium retention and central sympathetic activation, respectively (Montezano et al., 2014). RAAS blockers should inhibit activation of these NADPH oxidases in patients, but evidence is lacking.
- ▶ Uncoupled endothelial nitric oxide synthase (eNOS). eNOS normally generates NO. However, in the absence of L-arginine or tetrahydrobiopterin (BH_4), NOS stops producing NO and instead starts using oxygen as a substrate for producing superoxide (Mueller et al., 2005) (see Fig. 3-23). In experimental models, ROS generated by NADPH oxidase

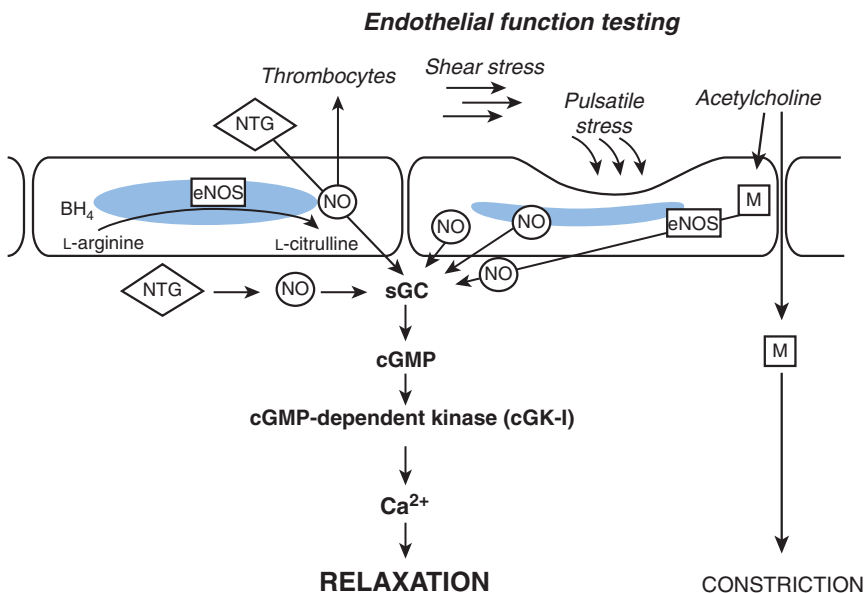


FIGURE 3-22 • Regulation of vascular tone by the endothelium. The eNOS by a two-step oxidation of the amino acid L-arginine thereby leading to the formation of L-citrulline. NO is released into the bloodstream thereby inhibiting platelet aggregation and the release of vasoconstricting factors such as serotonin and thromboxane. NO diffuses also into the media and activates the soluble guanylate cyclase (sGC). The resulting second messenger cGMP in turn activates the cGMP-dependent kinase, which mediates decreases in intracellular Ca^{2+} concentrations thereby causing vasorelaxation. The physiologic stimuli to release NO are shear stress and pulsatile stretch. Muscarinic acetylcholine receptor (M), nitroglycerin (NTG). (From Munzel T, Sinning C, Post F, et al. Pathophysiology, diagnosis and prognostic implications of endothelial dysfunction. *Ann Med* 2008;40:180–196.)

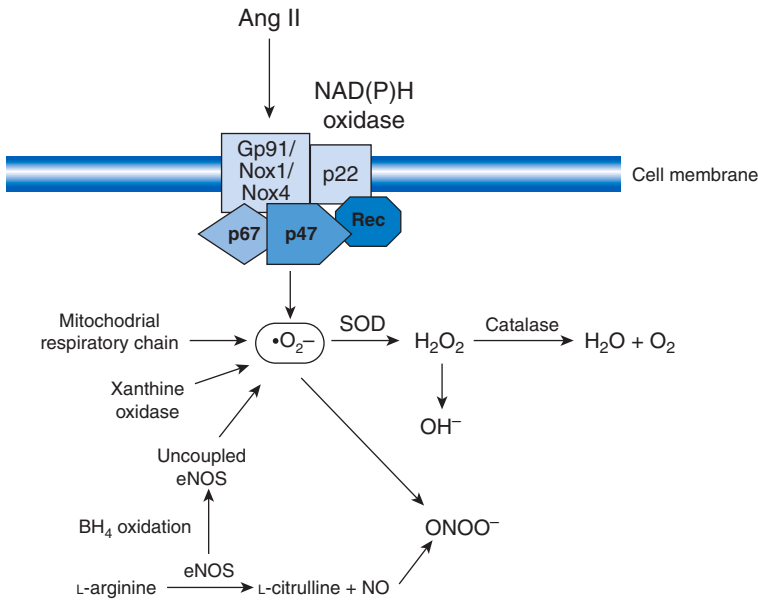


FIGURE 3-23 • Generation of O_2^- and H_2O_2 from O_2 in vascular cells. Many enzyme systems, including NAD(P)H oxidase, XO, and uncoupled NOS among others, have the potential to generate ROS. NAD(P)H oxidase is a multisubunit enzyme, comprising gp91 phox (or its homologues, Nox 1 and Nox4), p22phox, p47phox, p67phox and p40phox, that is regulated by many stimuli, including vasoactive agents, such as Ang II, SOD, superoxide dismutase, BH_4 , tetrahydrobiopterin. (From Paravicini TM, Touyz RM. Redox signaling in hypertension. *Cardiovasc Res* 2006;71:247–258.)

oxidizes BH_4 and uncouples NOS; oxidative stress begets oxidative stress. Oral BH_4 may improve endothelial function and lower BP in patients (Porkert et al., 2008).

- Xanthine oxidase. Generation of ROS by XO may account for the association between elevated serum uric acid levels with endothelial dysfunction and hypertension (Feig et al., 2013). As discussed later in the chapter, elevated uric acid levels are closely associated with new-onset hypertension in children, and pilot studies show that lowering of uric acid with allopurinol or probenecid may lower BP in pediatric and adolescent patients (Feig et al., 2008; Soletsky & Feig, 2012).
- Mitochondrial electron transport. Ang II also can induce mitochondrial dysfunction in vitro by activating the endothelial cell NADPH oxidase and formation of peroxynitrite (Montezano et al., 2014).

NOS Inhibition

Asymmetric dimethyl arginine (ADMA) is an endogenous NOS inhibitor and, as such, is an attractive but unproven mechanism of endothelial dysfunction and hypertension (Rochette et al., 2013). Pharmacologic administration of ADMA or closely related synthetic methylated arginines will sharply elevate BP in normotensive rats (Augustyniak et al., 2006) and normotensive human subjects (Achan et al., 2003; Sander et al., 1999). Plasma ADMA levels are increased in patients with ESRD (Vallance et al., 1992) and are

associated with reduced endothelial function in young overtly healthy adults with or without hypercholesterolemia (Ardigo et al., 2007) and in healthy black Africans compared with healthy white Europeans (Melikian et al., 2007). Plasma ADMA is an independent but weak predictor of all-cause mortality at the population level (Boger et al., 2009). Surprisingly, it is unknown whether plasma ADMA levels are associated with primary hypertension or predict its onset. Moreover, plasma levels of L-arginine (the endogenous substrate for NOS) are greater than two orders of magnitude higher than plasma ADMA levels (Boger et al., 2009), which would seem too low to competitively inhibit NOS in vivo. Also, of surprise, a recent paper from a 7-year follow-up of the Dallas Heart Study found that symmetrical dimethyl arginine (SDMA)—which is generally considered inert—but not ADMA predicted all-cause mortality (Gore et al., 2013).

Measurement of Endothelial Dysfunction in Humans

There are several means of assessing endothelial function in humans (Munzel et al., 2008). They all have limitations.

Flow-Mediated Dilatation

Endothelial-dependent vasodilation can be assessed by measuring increases in the large artery (forearm or coronary) diameter following either intra-arterial

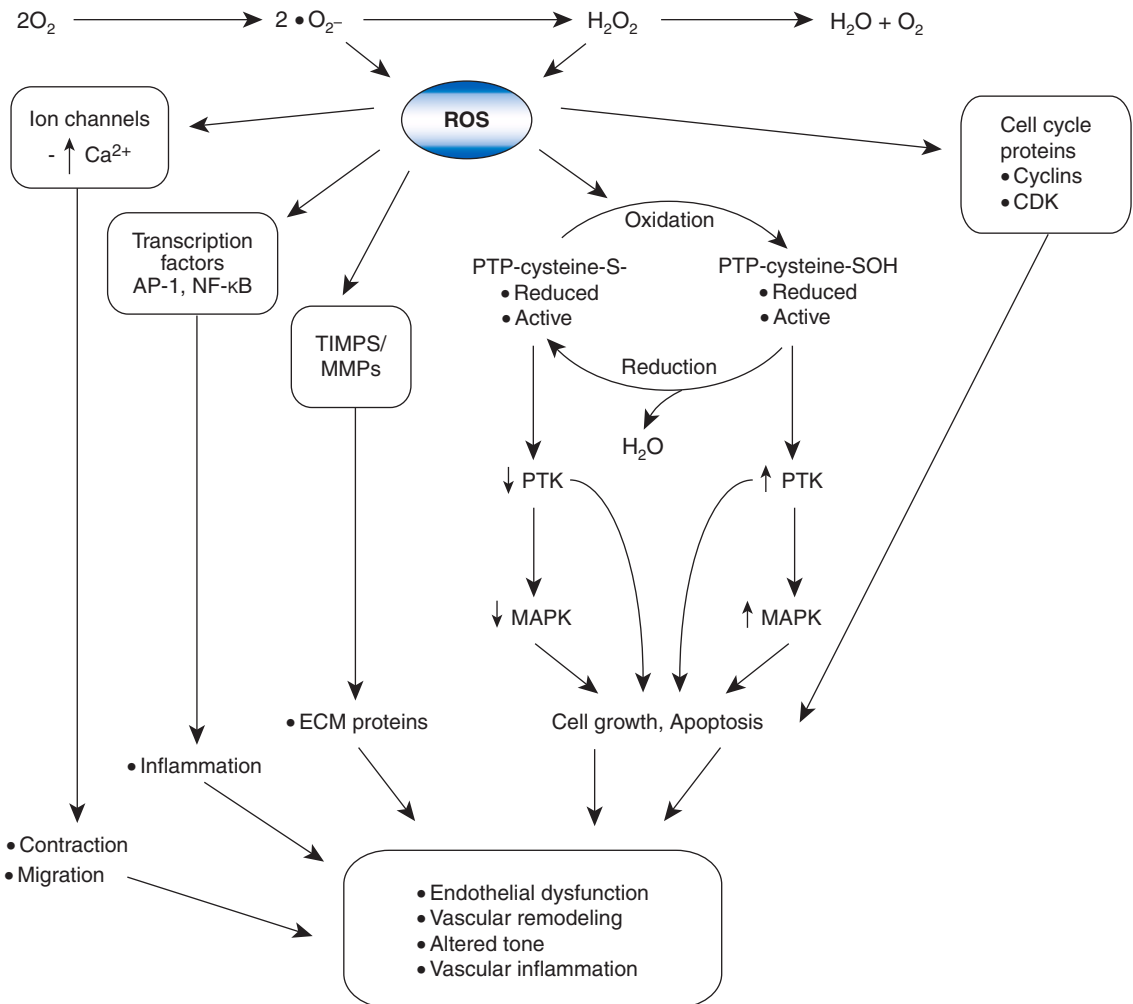


FIGURE 3-24 • Redox-dependent signaling pathways in vascular smooth muscle cells. Intracellular ROS modify the activity of protein tyrosine kinases (PTK), such as Sre, Ras, JAK2, Pyk2, P13K, and EGFR, as well as mitogen-activated protein kinases (MAPK), particularly p38MAPK, JNK, and ERK5. These processes probably occur through oxidation/reduction of protein tyrosine phosphatases (PTP), which are susceptible to oxidation and inactivation by ROS. ROS also influence gene and protein expression by activating transcription factors, such as NF- κ B, activator protein-1 (AP-1), and hypoxia-inducible factor-1. ROS stimulate ion channels, such as plasma membrane Ca^{2+} and K^+ channels, leading to changes in cation concentration. Activation of these redox-sensitive pathways results in numerous cellular responses that, if uncontrolled, could contribute to hypertensive vascular damage. ECM, extracellular matrix; MMPs, matrix metalloproteinases; TIMP, tissue inhibitor of matrix metalloproteinase. (From Paravicini TM, Touyz RM. Redox signaling in hypertension. *Cardiovasc Res* 2006;71:247–258.)

infusion of acetylcholine or release of ischemia (e.g., arrested forearm circulation) or a sudden elevation in BP (cold pressor test). Noninvasive brachial artery ultrasound is the most commonly used technique; peripheral arterial tonometry (EndoPAT) is a new and technically easier but less sensitive technique that requires further validation (Wilk et al., 2013). Competitive inhibitors of NOS specifically block endothelial-dependent dilation, but they do not block the dilation of these arteries produced by exogenous nitrovasodilators such as nitroglycerin and nitroprusside.

C-reactive Protein

C-reactive protein (CRP) is an easily measured serum biomarker for blood vessel inflammation and thus endothelial dysfunction (Savoia & Schiffrin, 2006). CRP could be more than a risk marker for future development of hypertension: Transgenic mice that express human CRP develop hypertension (Vongpatanasin et al., 2007). However, the clinical data regarding an association between CRP and hypertension are mixed. Some cross-sectional studies have shown strong correlations between elevated CRP with arterial stiffness

and elevated pulse pressure (Krishnan, 2014; Lakoski et al., 2005); however, recent analysis of the NHANES 2009–2010 database found that CRP was not associated with hypertension after controlling for uric acid, which was strongly associated (Krishnan, 2014). Some longitudinal studies have implicated elevated CRP as a risk marker/risk factor for new onset of hypertension (Niskanen et al., 2004; Sesso et al., 2003) while others have not (Seven et al., 2014).

There has been controversy over whether the measurement of CRP and other biomarkers improves CV risk stratification beyond the traditional Framingham risk factors, which include hypertension (Wang et al., 2006; Zethelius et al., 2008). Statin therapy reduces the risk of CV events in patients with high CRPs despite an average baseline LDL cholesterol of 108 mg/dL and an average BP in the high normal range (134/80 mm Hg) (Ridker et al., 2008). Analysis of 52 prospective studies of over 246,000 adults without known CVD suggested that assessment of CRP or fibrinogen level in people at intermediate risk for a CV event could help prevent one additional event over a period of 10 years for every 400 to 500 people screened (Kaptoge et al., 2012).

Other Approaches

Oxidative stress also can be assessed indirectly by measuring urinary levels of isoproteins (Ashfaq et al., 2008) or directly by measuring levels of NADPH oxidase in acutely dissociated human endothelial cells (Donato et al., 2007).

Why Don't Antioxidant Vitamins Lower BP in Humans?

As shown in Figure 3-23, the cellular enzyme superoxide dismutase (SOD) converts superoxide to hydrogen

peroxide, which is then converted by catalase to water and oxygen. In rats and mice, hypertension can be eliminated by treating the animals with SOD mimetics such as tempol, which are powerful antioxidants (Paravicini & Touyz, 2008).

Given the wealth of the experimental data, the negative results of antioxidant trials for hypertension and CV disease are disappointing (Paravicini & Touyz, 2008). If oxidative stress is so important in human hypertension, why are antioxidant vitamins not more effective in lowering BP? The best explanation is that vitamins C and E are weak antioxidants—much weaker than tempol and others used in animal studies. Unlike tempol, vitamin E cannot continually renew itself and stops working after an initial interaction with superoxide. With standard oral dosing, these vitamin supplements have limited ability to cross cell membranes where superoxide is produced, and they do not inhibit production of hydrogen peroxide, which itself impairs vascular health. Clearly, stronger antioxidants are needed, as well as better ways to measure oxidative stress in vivo.

In the meantime, reduced oxidative stress is thought to explain part of the beneficial effects of the RAAS blockers (Chapter 7) and statins as well as the DASH diet and regular exercise (Chapter 6).

Vascular Remodeling

Over time, endothelial cell dysfunction, neurohormonal activation, vascular inflammation, and elevated BP cause remodeling of blood vessels, which further perpetuates the hypertension (Fig. 3-25). An increase in the medial thickness relative to lumen diameter (increased *media-to-lumen ratio*) is the hallmark of hypertensive remodeling in both small and large arteries.

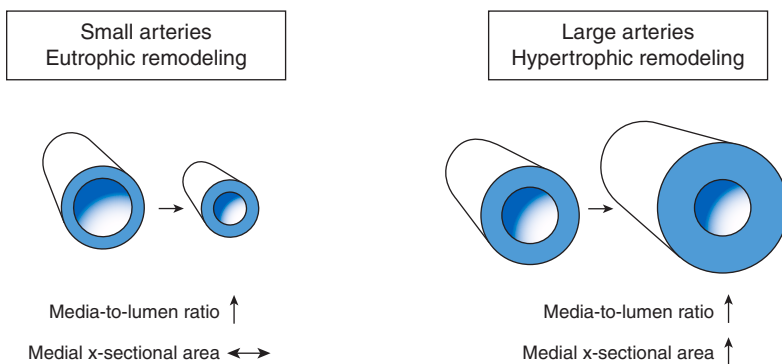


FIGURE 3-25 • Vascular remodeling of small and larger arteries in hypertension. Diagrams represent arteries in cross sections showing the tunica adventitia, tunica media, and tunica intima. (Modified from Duprez DA. Role of the renin-angiotensin-aldosterone system in vascular remodeling and inflammation: A clinical review. *J Hypertens* 2006;24:983–991.)

Mechanisms

Small artery remodeling is initiated by vasoconstriction, which normalizes wall stress and avoids a trophic response (Duprez, 2006). Normal smooth muscle cells rearrange themselves around a smaller lumen, a process termed *inward eutrophic remodeling*. Media-to-lumen ratio increases but medial cross-sectional area is unchanged. In other words, inward eutrophic remodeling describes a decrease in lumen diameter without a change in the composition or amount of vessel wall material. By decreasing lumen diameter in the peripheral circulation, inward eutrophic remodeling increases systemic vascular resistance, the hemodynamic hallmark of diastolic hypertension.

The RAAS seems to be the dominant mechanism in this form of remodeling (Duprez, 2006). Ang II drives this process by generating ROS, activating receptor tyrosine kinases, and negating protective effects of the peroxisome proliferator-activated receptor (PPAR γ).

In contrast, large artery remodeling is characterized by the expression of hypertrophic genes, triggering increases in medial thickness as well as media-to-lumen ratio (Duprez, 2006). Such *hypertrophic remodeling* involves not only an increase in the size of vascular smooth muscle cells but also an accumulation of extracellular matrix proteins such as collagen and fibronectin due to activation of TGF- β . The resultant large artery stiffness is the hemodynamic hallmark of ISH.

Intravascular pressure (i.e., shear stress), sympathetic nerves, and Ang II-induced generation of ROS—especially H₂O₂—seem to be the key mediators of hypertrophic remodeling.

Assessment of Vascular Remodeling in Human Hypertension

Several approaches are being used to study the remodeling of human arteries in hypertension:

Gluteal Biopsy

Resistance arteries can be isolated from subcutaneous tissue obtained by gluteal biopsy. Direct measurements of intra-arterial pressure, vessel wall dimensions, and receptor density show that small artery remodeling in hypertension can be reversed by oral treatment with RAAS blockers but not β -blockers (despite comparable levels of BP reduction), implicating a specific role for Ang II in the remodeling process (Montezano et al., 2014). Arterial smooth muscle from hypertensive

patients generates increased amounts of superoxide when exposed to Ang II (Montezano et al., 2014).

Noninvasive Assessment of Central Aortic Pressure

Vascular remodeling can be monitored noninvasively in patients by derivation of central aortic pressure wave forms via radial artery applanation tonography. Central aortic pressure—though measured indirectly—is superior to brachial artery BP as an index of the hemodynamic stress on the cerebral, coronary, and renal blood vessels (Agabiti-Rosei et al., 2007).

Contours of Central Versus Peripheral Pressure Waves

The arterial pressure waveform changes as it travels from the central aorta to the peripheral arteries. The key concepts are summarized in the consensus document from the American Heart Association (Agabiti-Rosei et al., 2007):

The pressure wave generated by the left ventricle travels down the arterial tree and then is reflected at multiple peripheral sites, mainly at resistance arteries (small muscular arteries and arterioles). Consequently, the pressure waveform recorded at any site of the arterial tree is the sum of the forward traveling waveform generated by left ventricular ejection and the backward traveling wave, the ‘echo’ of the incident wave reflected at peripheral sites. When the large conduit arteries are healthy and compliant, the reflected wave merges with the incident wave during diastole, thereby augmenting the diastolic BP and aiding coronary perfusion. In contrast, when the arteries are stiff, pulse wave velocity increases, accelerating the incident and reflected waves; thus, the reflected wave merges with the incident wave in systole and augments aortic systolic rather than diastolic pressure. As a result, left ventricular afterload increases, and normal ventricular relaxation and coronary filling are compromised... Another important consideration is “pressure wave amplification.” Typically, the diastolic and mean pressures change little across the arterial tree. However, systolic BP is amplified when moving from the aorta to periphery (Fig. 3-26). In general, brachial systolic and pulse pressure tend to overestimate central systolic and pulse pressure, both in younger subjects and in older people.

COMMERCIAL DEVICES

Of the commercially available devices, SphygmoCor (AtCor Medical, Houston, TX) is the one most widely used in clinical studies. It uses standard cuff measurements of brachial artery BP and a validated generalized transfer function (proprietary software) to convert the

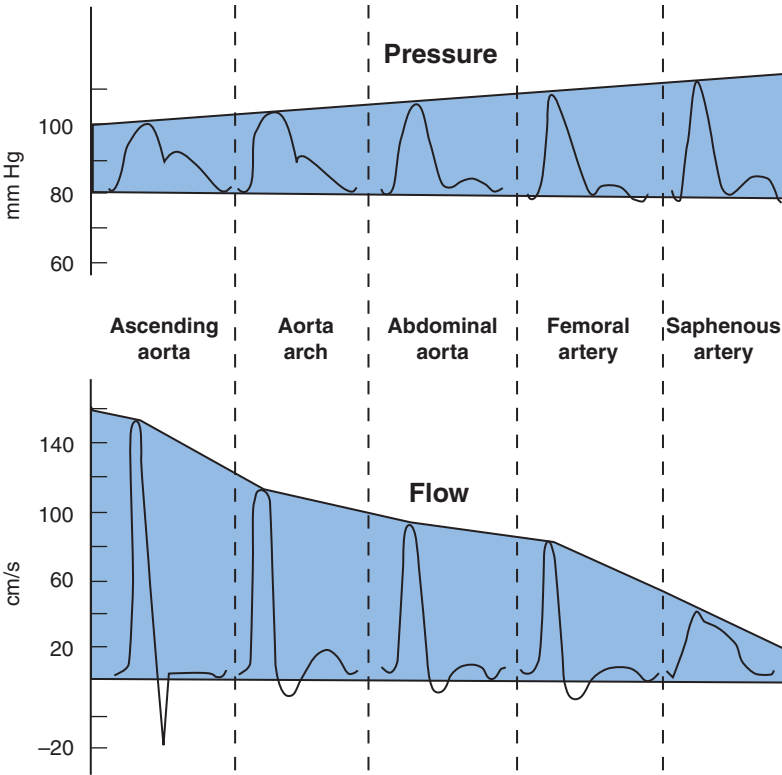


FIGURE 3-26 • Change in contours in pressure wave (**top**) and flow wave (**bottom**) between the ascending aorta and the saphenous artery. (From Agabiti-Rosei E, Mancia G, O'Rourke MF, et al. Central blood pressure measurements and antihypertensive therapy: A consensus document. *Hypertension* 2007;50(1): 154–160.)

radial or carotid artery waveform—measured by applanation tonography—to a derived central aortic BP waveform (Fig. 3-27) (Agabiti-Rosei et al., 2007). The derived values for aortic pulse pressure, the augmentation index, and the pulse wave velocity all are indices of vascular remodeling, in particular aortic stiffness. Typically, in hypertension, pulse pressure is widened, augmentation index is increased, pulse wave velocity is increased, and the dicrotic notch is absent. A simpler brachial arm cuff tonometry system recently has been validated (Hwang et al., 2014).

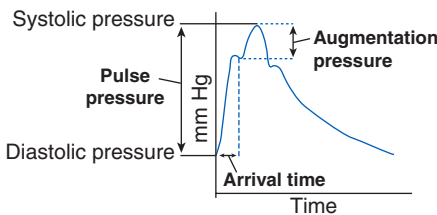


FIGURE 3-27 • Central pressure waveform. The height of the late systolic peak above the inflection defines the augmented pressure, and the ratio of augmented pressure to pulse pressure defines the augmentation index (in percentage). (From Agabiti-Rosei E, Mancia G, O'Rourke MF, et al. Central blood pressure measurements and antihypertensive therapy: A consensus document. *Hypertension* 2007;50(1):154–160.)

AMBULATORY AORTIC STIFFNESS

An index of aortic stiffness from standard ambulatory BP monitoring can also be derived by plotting systolic pressure as a function of diastolic pressure (Dechering et al., 2008). The theory is simple: For a given rise in diastolic BP, systolic BP should rise more if the large arteries are stiff rather than compliant. The ambulatory arterial stiffness index (AASI) is calculated by plotting 1 minus the regression slope for individual values for systolic and diastolic BP downloaded from the ambulatory BP monitor. However, there are conflicting data over the reproducibility of AASI and its correlation with pulse wave velocity and other more established measures of arterial stiffness (Dechering et al., 2008; Gosse et al., 2007; Schillaci & Parati, 2008). The technology for 24-hour ambulatory measurement of pulse wave velocity, aortic augmentation index, and central BP has been developed and is undergoing validation studies (Kuznetsova et al., 2014).

The nagging question is whether any of these expensive measurements will provide important additional information—about hypertensive mechanisms, prognosis, or therapy—beyond that already provided simply by arm cuff BP.

Small Vessel Rarefaction and Impaired Tissue Perfusion

Both experimental and human hypertension are commonly accompanied by *microvascular rarefaction*—reduced number or combined length of small vessels in a given volume of tissue (Levy et al., 2008). ROS can cause both constriction of precapillary vessels with functional rarefaction (decreased capillary recruitment during metabolic demand) and apoptosis with anatomic rarefaction (vascular smooth muscle cell death with vessel dropout).

Microvascular rarefaction involves reduced skin capillary recruitment and reduced reactive hyperemia in forearm and coronary circulations even in the absence of coronary atherosclerosis (Levy et al., 2008). Microvascular rarefaction/ischemia is an attractive mechanism explaining the frequent coexistence of hypertension and diabetes (in particular, impaired insulin-mediated glucose uptake in skeletal muscle) and for the accelerated target organ damage in patients with both conditions. Also, insulin increases muscle perfusion by phosphorylating eNOS, which opens precapillary sphincters to increase capillary surface area for diffusion of oxygen, nutrients, glucose, and insulin into skeletal muscle (Barrett et al., 2009); thus, defective eNOS regulation is another putative microvascular mechanism linking diabetes and hypertension.

Summary

Remodeling of large and small arteries may begin early in the hypertensive process and may be a cause as well as a consequence of high BP. Antihypertensive therapy may not provide optimal CV protection unless vascular remodeling is prevented or reversed by normalizing hemodynamic load, restoring normal endothelial cell function, quenching vascular inflammation, and eliminating adverse neurohormonal activation.

HORMONAL MECHANISMS: THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

As noted, activation of the RAAS is one of the most important mechanisms contributing to renal sodium retention, endothelial cell dysfunction, vascular inflammation and remodeling, and eventual hypertension (Fig. 3-28) (Montezano et al., 2014).

Overview

Beginning with the discovery of renin in 1898 by the Finnish physiologist Robert Tigerstedt and his medical student Bergman, work by multiple research groups has brought us to our current understanding, which continues to evolve (Luft, 2008).

Renin, a protease produced solely by the renal juxtaglomerular cells, cleaves angiotensinogen (renin substrate produced by the liver) to angiotensin I, which is converted by ACE to angiotensin II (Ang II) (see Fig. 3-28). ACE is most abundant in the lungs but also is present in the heart and systemic vasculature (*tissue ACE*). Chymase, a serine protease in the heart and systemic arteries, provides an alternative pathway for conversion of Ang I to Ang II. The interaction of Ang II with G protein-coupled AT1 receptors activates numerous cellular processes that contribute to hypertension and accelerate hypertensive end-organ damage. These include vasoconstriction, generation of ROS, vascular inflammation, vascular and cardiac remodeling, and production of aldosterone. There is increasing evidence that aldosterone, Ang II, and even renin and prorenin activate multiple signaling pathways that can damage vascular health and cause hypertension. Other metabolites of Ang I, including Ang 1–7, may protect against hypertension, but the clinical evidence is less well developed.

Aldosterone and Epithelial Sodium Channel Regulation

RAAS activation constitutes a short-term defense mechanism against hypovolemic hypotension (as with hemorrhage or salt deprivation). Interaction of aldosterone with cytosolic MRs in the renal collecting duct cells recruits sodium channels from the cytosol to the surface of the renal epithelium. The ENaCs so recruited increase sodium reabsorption, thereby re-expanding plasma volume.

Conversely, modern high-salt diets should engender continual feedback inhibition of the RAAS. Suppression of serum aldosterone should cause endocytosis and destruction of ENaC (via dephosphorylation and thus activation of the ubiquitin ligase Nedd4-2) and increased renal sodium excretion, thereby shrinking plasma volume and defending against salt hypertension (Victor, 2007).

In the setting of high dietary sodium and elevated BP, the RAAS should be completely suppressed and any degree of RAAS activity is inappropriate (Victor,

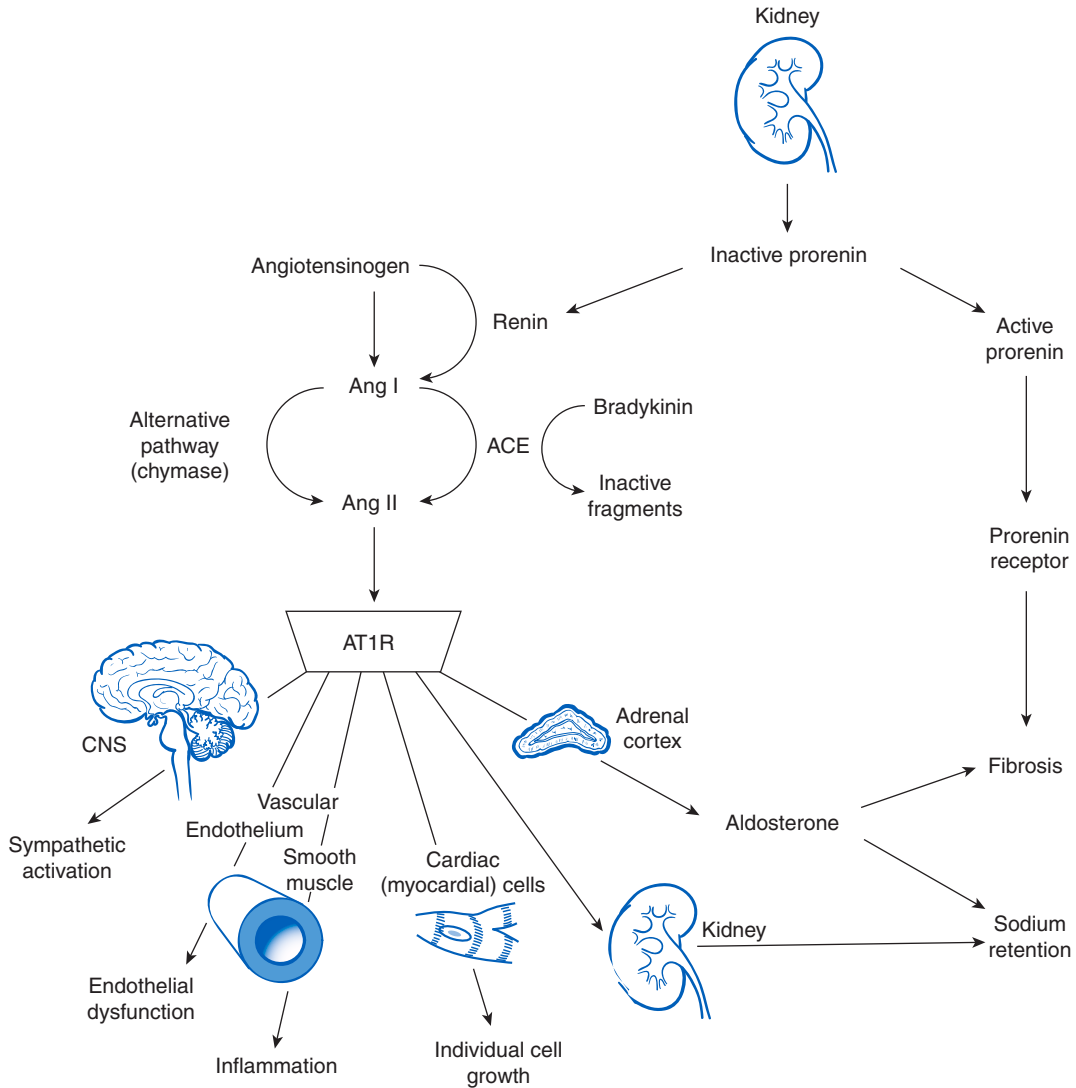


FIGURE 3-28 • The renin–angiotensin–aldosterone system. Ang I, angiotensin I; Ang II, angiotensin II; ACE, angiotensin-converting enzyme; AT1r, type 1 angiotensin receptor.

2007). However, in normotensive individuals, the risk of developing hypertension increases with increasing levels of serum aldosterone within the “normal” range (Vasan et al., 2004). Serum aldosterone levels are lower in black hypertensives than in white hypertensives, but mineralocorticoid receptor sensitivity may be greater (Tu et al., 2014).

MRs are widely expressed outside the kidney so that aldosterone can impair vascular health by multiple extrarenal mechanisms (Briet & Schiffrin, 2012). Aldosterone amplifies Ang II–induced vascular inflammation and remodeling (Kasal et al., 2012). By stimulating MRs in the heart and kidney, circulating aldosterone promotes cardiac and renal fibrosis in

hypertension (Kusche-Vihrog et al., 2014). By stimulating MRs in the brainstem circumventricular organs, aldosterone may contribute to sympathetic overactivity. However, aldosterone only seems to cause trouble in the presence of a high-sodium diet (Korte et al., 2014; Williams et al., 2005a), which is consistent with a newly discovered “feed-forward” activation of ENaC by high sodium (Korte et al., 2014).

Receptor-Mediated Actions of Ang II

Ang II is the main effector peptide of the RAAS. Two main types of G protein–coupled angiotensin receptors are known. AT1 receptors are widely expressed in

the vasculature, kidneys, adrenals, heart, liver, and brain. AT1 receptor activation explains most of the hypertensive actions of Ang II. As noted, stimulation of AT1 receptors by Ang II is the best studied mechanism for the activation of vascular NADPH oxidase and thus ROS in the vasculature, in the kidneys, and in the brain.

Furthermore, enhanced AT1 receptor–mediated signaling provides a common mechanistic explanation for the frequent coexistence of elevated BP with insulin resistance and atherosclerosis and constitutes a major therapeutic target for interrupting every step in CV disease progression from vascular remodeling and formation of atherosclerotic plaque to stroke, MI, and death (Fig. 3-29).

In contrast, AT2 receptors are widely distributed in the fetus but in adults are found only in the adrenal medulla, uterus, ovary, vascular endothelium, and distinct brain regions. In rodents, AT2 receptor activation opposes most (but perhaps not all) of the deleterious effects of AT1 receptors by promoting endothelial-dependent vasodilation by bradykinin

and NO pathways. However, other animal data suggest that AT2 receptors can be profibrotic, and the role of AT2 receptors in human hypertension remains speculative.

The finding of several angiotensin metabolites has added to the complexity of the RAAS (Fig. 3-30).

Receptor-Mediated Actions of Renin and Prorenin

In the traditional view of the RAAS, prorenin has been considered to be the inactive precursor of renin, which functions solely to generate Ang I by enzymatic cleavage of angiotensinogen. New concepts are rapidly evolving as data implicate prorenin and renin as direct cardiac and renal toxins—a notion first advanced and vigorously pursued by Laragh, Sealey, and coworkers (Laragh, 2001).

Prorenin is inactive because a 43-amino acid hinge is closed and prevents it from binding to angiotensinogen. In the kidneys, inactive prorenin is converted to active renin when this inhibitory hinge

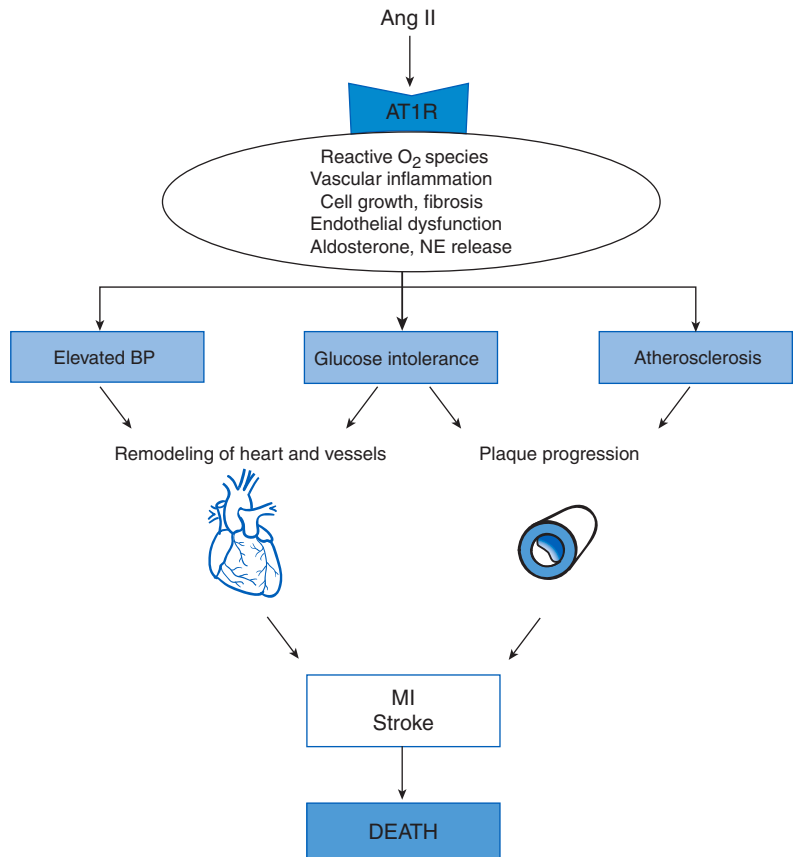


FIGURE 3-29 • Central mechanistic role of angiotensin II type 1 receptor–mediated signaling in hypertension and CV disease progression. Ang II, angiotensin II; NE, norepinephrine; BP, blood pressure; MI, myocardial infarction.

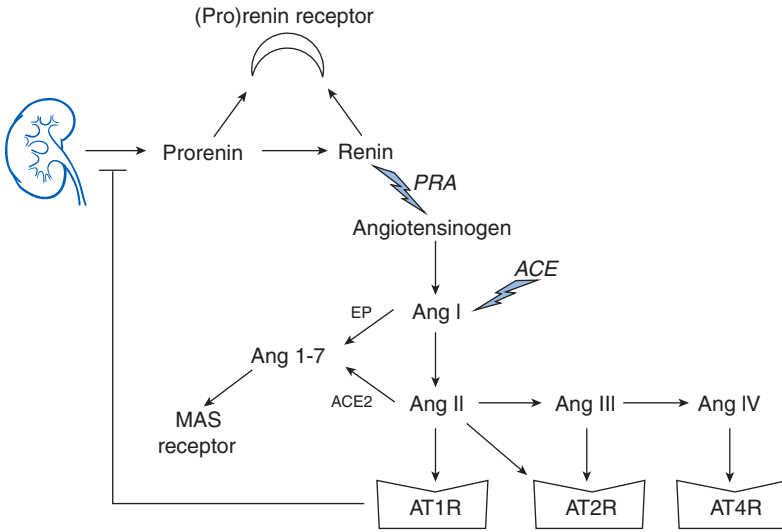


FIGURE 3-30 • Increasing complexity in the understanding of the renin-angiotensin system. Ang 1-7 interacts with a specific G protein-coupled Mas receptor and generally opposes the vasoconstrictor and proliferative actions of Ang II. PRA, plasma renin activity; ACE, angiotensin-converting enzyme; ACE2, type 2 angiotensin-converting enzyme; EP, endopeptidase; Ang I, angiotensin I; Ang II, angiotensin II; Ang III, angiotensin III; Ang IV, angiotensin IV; Ang 1-7, angiotensin one through seven; AT1r, type 1 angiotensin receptor; AT2r, type 2 angiotensin receptor; AT4r, type 4 angiotensin receptor.

region is enzymatically cleaved. When circulating prorenin binds to a newly discovered (pro)renin receptor in the heart and kidneys, the hinge is opened (but not cleaved) and this nonenzymatic process fully activates prorenin (Fig. 3-31) (Danser, 2006; Huang et al., 2006). As a result, TGF-β production is accelerated, leading to collagen deposition and fibrosis.

This receptor-mediated process is independent of Ang II generation and therefore unaffected by ACEIs

and ARBs. While these are excellent antihypertensives (Chapter 7), they trigger large reactive increases in prorenin and renin production that may counter some of the CV protection afforded by reduced AT1 receptor activation. The reactive increases are even greater with the new direct renin inhibitor aliskiren, which reduces renin's ability to cleave angiotensinogen and generate Ang I but nevertheless does not inhibit profibrotic signaling by the pro(renin) receptor (Feldt et al., 2008; Schefe et al., 2008).

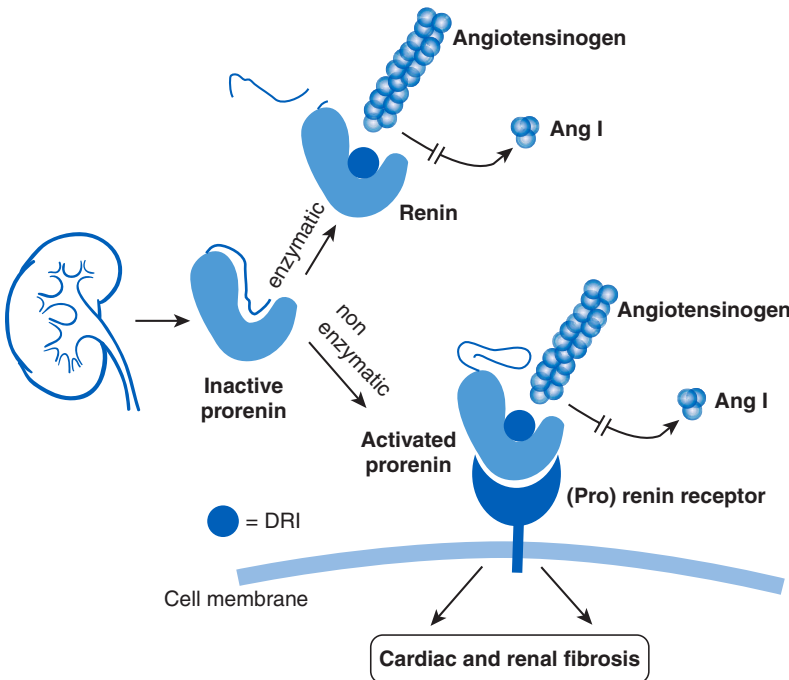


FIGURE 3-31 • Inhibition of both enzymatic and nonenzymatic activation of prorenin. Ang, angiotensin; DRI, direct renin inhibitor. (Modified from Danser AH, Deinum J. Renin, prorenin and the putative (pro) renin receptor. *Hypertension* 2005;46: 1069-1076.)

As prorenin blood levels typically are 100-fold higher than renin levels, pro(renin) receptor activation may turn out to be an important mechanism of human hypertension. Its recent discovery has rekindled interest in older, and largely forgotten, observations. Sealey and Laragh (1975) found prorenin in human plasma. Twenty years later, Wilson and Luetscher (1990) found that children with type 1 diabetes have high levels of prorenin despite their low PRA; moreover, those with high prorenin levels developed diabetic complications of renal failure, blindness, and neuropathy. Thus, prorenin may be a “new” biomarker, particularly for micro- and macrovascular complications of hypertension and diabetes.

Plasma Renin Activity as a Clinical Index of RAAS Activity

Clinical Assays

Both PRA and plasma renin concentration (PRC) can be measured by commercial assays. PRA is measured by incubating a patient’s plasma, which contains both angiotensinogen and renin, to generate Ang 1, which then is measured by radioimmunoassay (Sealey et al., 2005). The amount of Ang 1 generated is proportional to the amount of renin present. Care must be taken to prevent cryoactivation of prorenin, leading to spurious elevations in PRA (Sealey et al., 2005). If plasma is cooled to 4°C, the prosegment hinge unfolds and is subsequently cleaved by plasma proteases (Fig. 3-32). To avoid prorenin cryoactivation, plasma samples should be processed at room temperature.

PRA can be measured by many commercial clinical laboratories. In contrast, PRC and prorenin levels are measured mainly for research purposes. As yet, there is no clear clinical advantage of PRC over PRA,

as both assays require rigorous laboratory standards and avoidance of cryoactivation.

PRA Levels

The multiple factors that can alter renin secretion include those shown in Table 3-4, with changes in pressure within the afferent arterioles (intrarenal baroreceptors), sodium concentration in the macula densa, and RSNA (via β_1 ARs) likely playing the most important roles.

Considering all the factors affecting PRA, the agreement noted in the literature is rather surprising: Almost all patients with primary aldosteronism have suppressed values, most patients with renovascular or accelerated–malignant hypertension have elevated levels, and the prevalence of suppressed values among patients with primary hypertension is surprisingly similar in different series (see Fig. 3-32). Specific information about the use of PRA assays in the evaluation of various identifiable forms of hypertension is provided in subsequent chapters.

The listing in Table 3-4 is not intended to cover every known condition and disease in which a renin assay has been performed, but the more clinically important ones are listed in an attempt to categorize them by mechanism. Some conditions could fit in two or more categories; e.g., upright posture may involve a decreased effective plasma volume and sympathetic activation and decreased renal perfusion.

Role in Primary Hypertension

Elevated BP itself—particularly volume-expanded salt-sensitive hypertension—should cause complete feedback suppression of PRA. In fact, patients with primary hypertension tend to have lower PRA levels than do age- and gender-matched normotensives (Helmer, 1964; Meade et al., 1993). However, most patients with primary hypertension do not have suppressed PRA, stimulating much clinical research to explain the “inappropriately” normal or even elevated PRA levels (see Fig. 3-32).

The following explanations have been proposed: Sealey et al. (1988) proposed the theory of nephron heterogeneity—a subpopulation of ischemic nephrons contributing excess renin. Esler et al. (1977) proposed that high-renin primary hypertension is neurogenic—high-RSNA. Hollenberg, and Williams et al. (1992) proposed the concept of nonmodulation—defective feedback regulation of RAAS within the kidneys and adrenal glands.

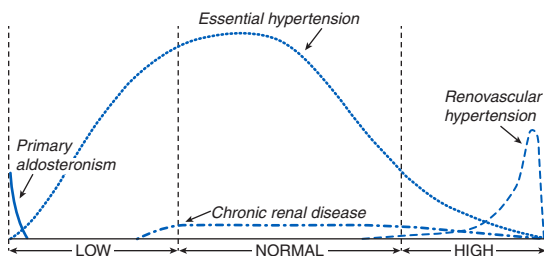


FIGURE 3-32 • Schematic representation of PRA in various hypertensive diseases. The approximate number of patients with each type of hypertension is indicated along with their proportion of low-, normal or high-renin levels. (Modified from Kaplan NM. Renin profiles. *JAMA* 1977;238:611–613.)

TABLE 3-4

Clinical Conditions Affecting PRA

Decreased PRA	Increased PRA
Expanded fluid volume	Shrunk fluid volume
Salt loads, oral or intravenous	Sodium restriction
Primary salt retention	Fluid losses
Liddle syndrome	Diuretic induced
Gordon syndrome	Gastrointestinal losses
Mineralocorticoid excess	Hemorrhage
Primary aldosteronism	Decreased effective plasma volume
Cushing syndrome	Upright posture
Congenital adrenal hyperplasia	Cirrhosis with ascites
DOC, 18-hydroxy-DOC excess	Nephrotic syndrome
11 β -Hydroxysteroid dehydrogenase inhibition (licorice)	Decreased renal perfusion pressure
Sympathetic inhibition	Renovascular hypertension
Autonomic dysfunction	Accelerated–malignant hypertension
Therapy with adrenergic neuronal blockers	Chronic renal disease (renin dependent)
Therapy with β -adrenergic blockers	JG hyperplasia
Hyperkalemia	Sympathetic activation
Decreased renin substrate	Therapy with direct vasodilators
Androgen therapy	Pheochromocytoma
Decrease in renal tissue	Stress: exercise, hypoglycemia
Hyporeninemic hypoaldosteronism	Hyperthyroidism
Chronic renal disease (volume dependent)	Sympathomimetic agents (caffeine)
Anephric	Hypokalemia
Increasing age	Increased renin substrate
Unknown	Pregnancy
Low-renin primary hypertension	Estrogen therapy
Black race	Autonomous renin hypersecretion
	Renin-secreting tumors
	Acute damage to JG cells
	Acute glomerulonephritis
	Decreased feedback inhibition
	Low A II levels (ACEI therapy)
	Unknown
	High-renin primary hypertension

Primary Hypertension with Low Renin

Clearly, there are numerous possible explanations for normal levels of renin in hypertension, which is the usual finding. Although low renin levels are expected in the absence of one or another of the previously described circumstances, a great deal of work has been done to uncover special mechanisms, prognoses, and therapy for hypertensives with low renin, in particular for the twofold greater prevalence of low renin in blacks than in nonblacks (Sagnella, 2001).

MECHANISMS

One of the possible mechanisms for low-renin hypertension is volume expansion with or without

mineralocorticoid excess, but the majority of careful analyses fails to indicate volume expansion (Sagnella, 2001) or increased levels of mineralocorticoids (Pratt et al., 1999). In keeping with normal levels of aldosterone despite the low renin levels, low-renin hypertensives showed a lesser rise in aldosterone secretion on a low-sodium diet (Fisher et al., 1999).

Genetically determined impairment of renal sodium excretion has been associated with low-renin hypertension (Lifton et al., 2001). As described in Chapters 13 and 14, new forms of low-renin hypertension have recently been recognized, one with increased amounts of 18-hydroxylated steroids the other with high levels of cortisol from inhibition of the

11 β -hydroxysteroid dehydrogenase enzyme. Not surprisingly, subtle degrees of these defects have been looked for in low-renin hypertensives, with only equivocal results (Carvajal et al., 2005; Rossi et al., 2001; Soro et al., 1995; Williams et al., 2005b).

Therapy

Laragh (1973), Laragh and Sealey (2003) attached a great deal of significance to the various PRA levels found in patients with primary hypertension. According to their view, the levels of renin can identify the relative contributions of vasoconstriction and body fluid volume expansion to the pathogenesis of hypertension. According to the “bipolar vasoconstriction-volume analysis,” arteriolar vasoconstriction by Ang II is predominantly responsible for the hypertension in patients with high renin, whereas volume expansion is predominantly responsible in those with low renin.

In keeping with their presumed but unproved volume excess, patients with low-renin primary hypertension were found by some investigators (Preston et al., 1998; Vaughan et al., 1973) but not by others (Ferguson et al., 1977; Holland et al., 1979; Hunyor et al., 1975) to experience a greater fall in BP when given diuretics than do normal-renin patients. Age and race were found to be better predictors of response to various drugs (Preston et al., 1998) in some studies, and, in other studies, the renin status simply did not reflect the response at all (Weir & Saunders, 1998).

More recently, short-term studies find that a low PRA generally predicts a larger initial fall in BP with a thiazide diuretic whereas a high PRA generally predicts a larger initial fall in BP with an ACEI or an ARB; however, the effect is small compared with the large degree of inter- and intrasubject variability in these responses. These studies are summarized as follows:

- In a study of 203 African American and 236 white hypertensives, pretreatment PRA was positively associated with the BP response to an ARB, with PRA accounting for 15% of the between-subject variation in the response (Canzanello et al., 2008).
- In a prospective study of 208 Finnish men with moderate hypertension, pretreatment PRA was positively correlated with the BP response to an ARB or a β -blocker and negatively correlated with the BP response to a thiazide diuretic; however, PRA accounted for only 4% of the overall variability in responses between patients (Suonsyrja et al., 2008).

- Similarly, PRA accounted for only 4% of the between-subject variability to one month of HCTZ monotherapy in another study of 197 African Americans and 190 whites with hypertension (Turner et al., 2001); moreover, the responses of individual subjects were not predictable among those who repeated the protocol.

In general clinical practice, most physicians do not find routine renin profiling to be necessary for establishing prognosis or determining therapy. However, as will be noted in subsequent chapters, renin profiling is often used in the diagnosis of low- and high-renin secondary forms of medically refractory hypertension.

T Cells and Hypertension: A Novel Unifying Hypothesis

Mouse studies seem to suggest that Ang II–induced hypertension can be caused by selective activation of NADPH oxidase only in blood vessels (Landmesser et al., 2002), only in the kidney (Dickhout et al., 2002), and only in the brain subfornical organ (Zimmerman et al., 2002). In trying to reconcile these confusing findings, Harrison and coworkers searched for a circulating blood-borne signal as a unifying hypothesis and have provided data that T cells—which also express AT1 receptors and NADPH oxidase—play a central role in the genesis of hypertension—at least in mice and possibly in humans (Trott & Harrison, 2014).

According to this new theory, which is illustrated in Figure 3-33 (Harrison et al., 2012), Ang II, salt, and chronic stress all act on the CNS to increase sympathetic outflow. Circumventricular organs, especially the subfornical organ (SFO), are exposed to circulating Ang II and serum sodium because they are highly vascularized and have a poorly formed blood–brain barrier. Ang II and sodium activate NADPH oxidase and increase ROS in the SFO, triggering SNA to multiple tissues and vascular beds, producing mildly elevated BP (i.e., prehypertension). The molecular mechanism by which Ang II and other signals increase oxidative stress in the SFO involves both endoplasmic reticulum stress (Young et al., 2012) and activation of the brain isoform of the ENaC (Osborn et al., 2014). Importantly, the increased SNA also is targeted to the spleen and lymph nodes causing additional T cells to be released into the circulation and increases renal production of IL-6 and acts on T-cell adrenergic receptors to modify their polarization. T cells infiltrate the kidney and blood vessels. The mechanism by which T cells become activated likely involve interplay with

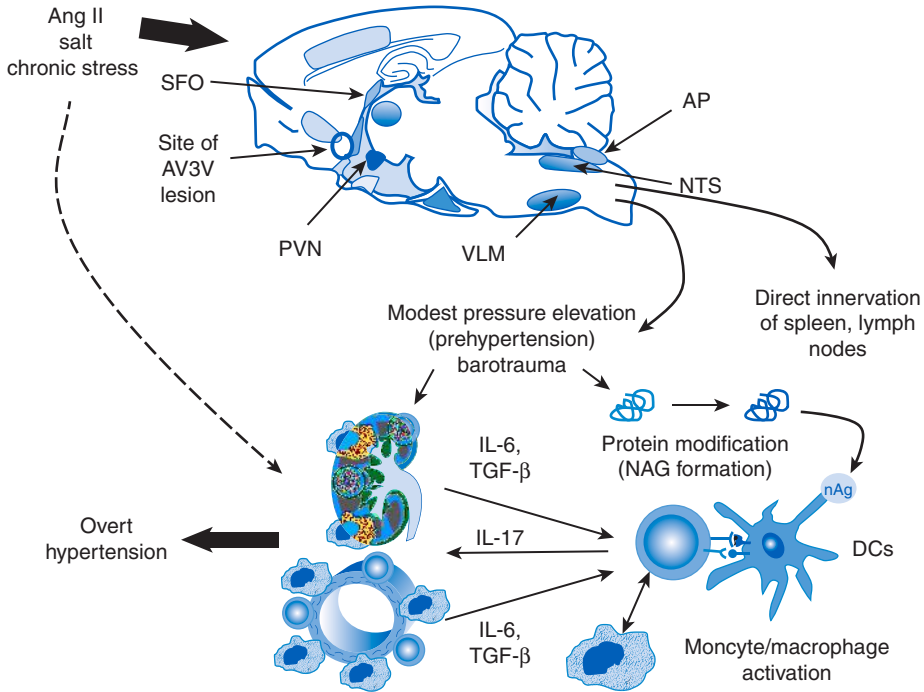


FIGURE 3-33 • Proposed paradigm for inflammation and immune cell activation in hypertension. Stimuli including angiotensin II (Ang II), salt, and chronic stress act on the CNS and increase sympathetic outflow. The circumventricular organs (CVO), including the subfornical organ (SFO), the medium preoptic eminence organum vasculosum lateral terminalis, and the area postrema (AP) have a poorly formed blood–brain barrier and are responsive to circulating A II and sodium. These stimuli increase production of ROS in the CVO, which provide input into hypothalamic centers including the paraventricular nucleus (PVN). Microglial cells are activated in this process and increase input into brainstem centers, including the ventral lateral medulla (VLM) and the NTS. These increase sympathetic outflow, which causes a modest elevation in BP to levels compatible with prehypertension. Sympathetic activation also increases renal production of IL-6 and acts on T-cell adrenergic receptors to modify their polarization. The elevations of pressure, direct actions, and Ang II and catecholamines activate ROS production in the kidney and vasculature, increasing chemokine production and adhesion molecule expression. Neoantigens (NAG) are formed from endogenous proteins in the kidney and vasculature, which are presented by DCs to T cells. Activated T cells interact with monocytes/macrophages, promoting macrophage transformation, and these leukocytes accumulate in the kidney. IL-6 and TGF- β , produced in these organs, help direct T-cell IL-17 production. IL-17 and other cytokines produced by these cells promote ROS production in the vascular smooth muscle and kidney, leading to vasoconstriction, sodium retention, and ultimately severe hypertension. (From Harrison DG, Marvar PJ, Titze JM. Vascular inflammatory cells in hypertension. *Front Physiol* 2012;3:128.)

dendritic cells (DCs), which present novel antigens to T cells resulting in production of cytokines including IL-17 and gamma interferon. The latter promote sodium retention, vasoconstriction, and vascular remodeling that accelerate the hypertensive process.

In other words, CNS activation of sympathetic vasoconstrictor drive is thought to initiate the hypertensive process while T-cell activation in the blood vessels and kidney is thought to gradually convert prehypertension to full-blown hypertension.

Experimental Evidence

The mounting experimental evidence for activated T cells in hypertension includes the following:

- Neonatal thymectomy delays the development of hypertension in rodent models (Khraibi et al., 1987).

- The T-cell–selective immunosuppressant mycophenolate mofetil (CellCept) lowers BP and lessens renal injury in Dahl salt-sensitive rats fed a high-salt diet (Tian et al., 2007) and in rats with salt-sensitive hypertension induced by acute renal ischemia (Pechman et al., 2008).
- Mice lacking the recombinase activating gene (RAG1 $^{-/-}$ mice) lack both T and B cells and have a blunted hypertensive response to challenge with either Ang II or deoxycorticosterone acetate (DOCA) salt (Guzik et al., 2007). Adoptive transfer of T cells—but not B cells—fully restores the hypertension.
- Mutation of the RAG1 gene ameliorates hypertension and renal damage in the Dahl salt-sensitive rat (Mattson et al., 2013).
- The tumor necrosis factor- α (TNF- α) antagonist intercept blocks the generation of vascular

ROS and normalizes BP in mouse models of Ang II–induced hypertension and mineralocorticoid-induced hypertension (Guzik et al., 2007).

- Lesions of the anteroventral third cerebral ventricle, a region that includes the subfornical organ, prevent Ang II–induced T-cell activation, aortic infiltration with T cells, and thus hypertension in mice (Trott & Harrison, 2014). These data indicate that Ang II does not activate T cells directly but rather indirectly via activation of central sympathetic outflow to the spleen.
- Normal (wild-type) mice exposed to 1 week of stress (restraint and cage switching) develop T-cell activation and increased BP, whereas Rag-1 “knock out” (i.e., T-cell deficient) mice do not (until given an adoptive transfer of T cells), indicating the crucial role of the CNS in orchestrating the T-cell response leading to hypertension (Trott & Harrison, 2014).
- The T cells most involved in this experimental hypertension are termed Th 17 cells, a subpopulation that produces IL-17; IL-17-null mice show an abbreviated hypertensive response to Ang II infusion (Trott & Harrison, 2014).
- T cells require two signals for activation: (1) interaction of the T-cell receptor with an antigen and (2) stimulation of costimulatory molecules such as CD28 on the T cells by ligands on the antigen-presenting cell. Ang II– and DOCA/salt-induced hypertension in mice are abrogated when such costimulation is interrupted (Trott & Harrison, 2014).

Translational Evidence in Patients

The translational evidence, though appealing, is as yet circumstantial:

- In patients with AIDS, BP is low before treatment and increases as T cell counts rise with highly effective anti-retroviral therapy (Seaberg et al., 2005). Confounding effects of body weight and general health cannot be excluded in this large study of 5,578 men.
- Patients with rheumatoid arthritis, psoriasis, and other inflammatory collagen-vascular diseases have very high rates of hypertension (Panoulas et al., 2008). Although the risk of hypertension increases with increasing severity of the inflammatory disease (Neimann et al., 2006), steroid therapy also contributes (Panoulas et al., 2007).
- Circulating proinflammatory CD8⁺ T cells recently have been found in patients with primary hypertension (Youn et al., 2013). These cells exhibit loss of CD28 and produce TNF- α and other cytokines.

- Pilot studies suggest that mycophenolate mofetil may benefit hypertension in patients with collagen-vascular disease (Herrera et al., 2006). In this uncontrolled study of eight patients with psoriasis or rheumatoid arthritis and uncomplicated stage 1 hypertension, average clinic BP fell from 152/92 to 137/83 mm Hg after 3 months of mycophenolate mofetil and then returned to pretreatment levels after therapy was stopped. Changes in BP mirrored changes in urinary excretion of TNF- α . A proper trial is needed to draw mechanistic conclusions.

Clearly, the challenge will be to translate this compelling body of preclinical immunology research to benefit human patients by finding new therapies that can interrupt the initiation and progression of hypertension. Implicating T cell activation as a cause of primary hypertension may seem counterintuitive because many other anti-inflammatory agents—including NSAIDs, prednisone, and cyclosporine—often cause hypertension as will be discussed in Chapter 14. In standard pharmacologic doses, these agents cause renal sodium retention and vasoconstriction by multiple other mechanisms.

T cell activation may be particularly important in obesity-related hypertension, which is discussed next, followed by consideration of some clinical conditions that also are associated with a higher incidence of hypertension.

HYPERTENSION RELATED TO OBESITY, THE METABOLIC SYNDROME, AND TYPE 2 DIABETES

The first and foremost of these clinical conditions is the triad of obesity, the metabolic syndrome, and type 2 diabetes. Hypertension is part of the obesity epidemic that is escalating at a phenomenal rate especially in young people (Flynn, 2013) (see Chapter 16). Before discussing mechanisms of obesity-related hypertension, a few introductory comments are in order.

The Obesity Epidemic

The past two decades have seen drastic increase in rates of obesity and type 2 diabetes in both developed and developing countries. Here are some startling statistics:

- Two-thirds of the U.S. adult population is overweight (BMI > 25) with about 32% being obese (BMI > 30); among the latter, 5% are extremely obese (BMI > 40) (Grundy, 2008)

- Among U.S. children, the prevalence of obesity (defined as BMI > 95 percentile) has increased from 5% in 1970 to 17% in 2004 (Barlow, 2007). Currently, 13 million U.S. children are estimated to be obese (DeMarco et al., 2014).
- Obesity is associated with a shortened lifespan both in rodent models and in humans. Among non-smokers, obesity will shorten life expectancy by 5.8 years in men and by 7.1 years in women (Peters et al., 2003).

The Obesity Epidemic as a Gene-Environment Interaction

The recent obesity epidemic is attributed to our modern culture of fast food and sedentary lifestyle. In the words of Esler et al. (2008), the escalation in childhood obesity is due to “potato chips and computer chips.” The introduction of high-fructose corn syrup into processed foods is particularly at blame (Rivard et al., 2013). Thus, lifestyle modification with diet and exercise is considered the cornerstone of treatment (Harsha & Bray, 2008). However, recidivism is nearly universal and, according to Mark (2008), “dietary therapy for obesity is an emperor with no clothes.”

Both genetic and biologic factors contribute to the universal difficulty in maintaining a low-calorie diet (Mark, 2008). On the one hand, weight loss activates powerful compensatory mechanisms that stimulate appetite and slow metabolism. On the other hand, twin and adoptive studies show that BMI is a highly heritable trait and that individuals vary greatly in their genetic propensity or resistance to gain weight in our toxic modern environment.

Association with Hypertension

Across populations, hypertension prevalence tracks with average BMI as illustrated among the African diaspora: Despite common ancestral genes, hypertension is present in only 10% of Africans living in rural Cameroon where average BMI is 22, 25% in Jamaicans with an average BMI 25, but 40% in African Americans in Illinois with an average BMI of 35 (Fig. 3-34) (Cooper et al., 1997). Weight gain, even to levels not considered to be a problem, increases the incidence of hypertension. The Framingham Heart Study investigators estimate that 70% of hypertension in men and 61% in women is directly attributable to excess adiposity; a 4.5-mm Hg average increase in systolic BP was seen with every 10-pound weight gain (Kannel et al., 1993).

Moreover, obesity is accompanied by an increased incidence of hypertensive complications, including stroke (Jood et al., 2004), coronary disease (Widlansky et al., 2004), heart failure (Kenchaiah et al., 2002), and cardiomyopathy (Pilz et al., 2004).

Mechanisms of Obesity-Related Hypertension

The hemodynamic pattern of obesity-related hypertension is volume expansion, increased cardiac output, and systemic vascular resistance that fails to fall enough to balance the higher cardiac output (Esler et al., 2006).

A large number of mechanisms are supported by data from animal and human observations (Fig. 3-35)

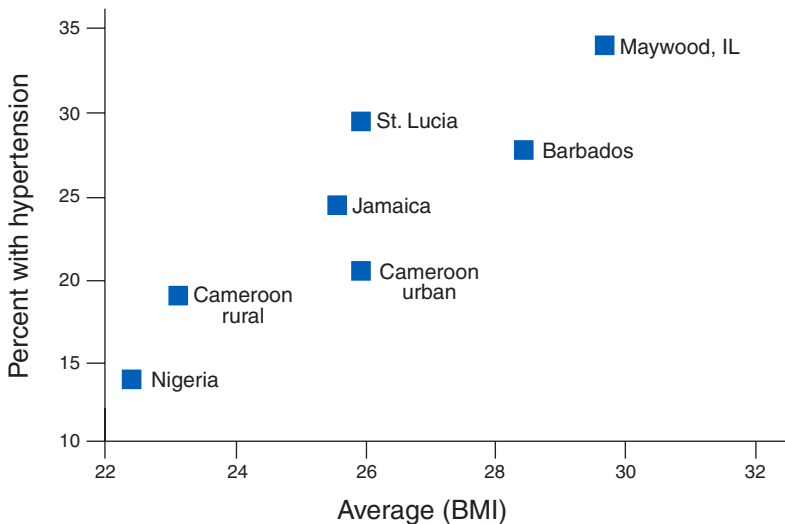


FIGURE 3-34 • Age- and sex-adjusted prevalence of hypertension among seven populations of West African origin. (Modified from Cooper R, Rotimi C, Ataman S, et al. The prevalence of hypertension in seven populations of west African origin *Am J Public Health* 1997;87:160-168.)

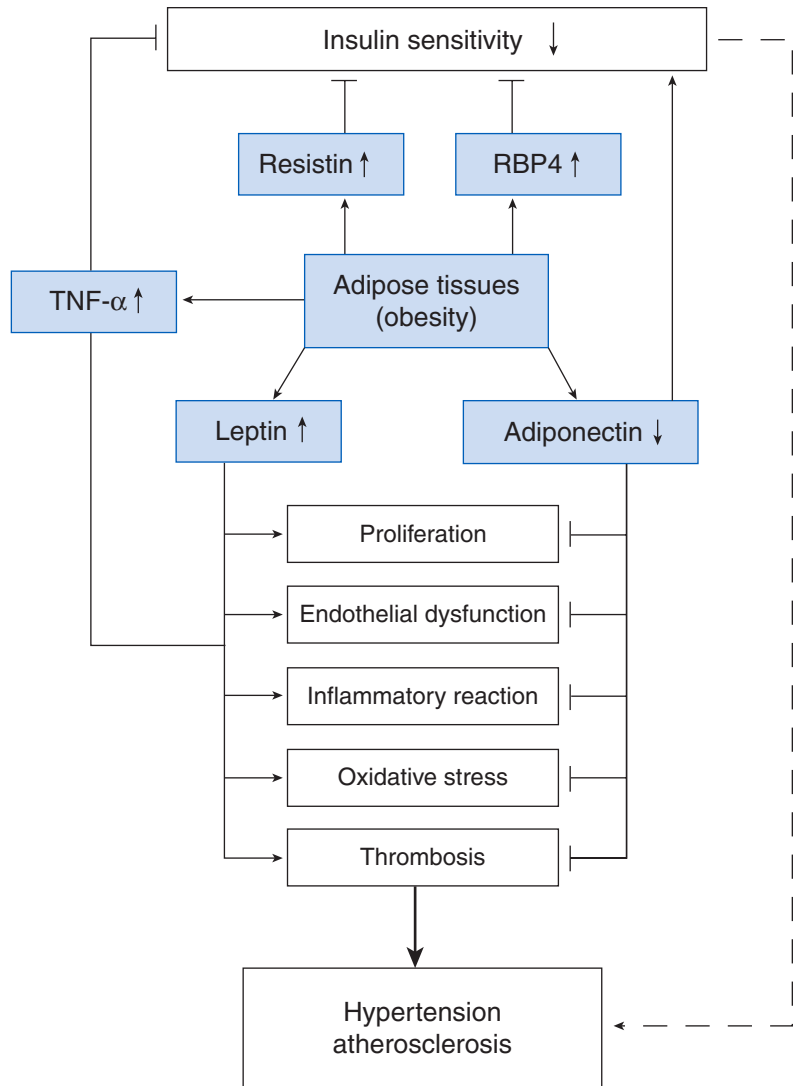


FIGURE 3-35 • Adipocytokines interact in a complex way to regulate vascular function and ultimately the development of CV diseases. (From Katagiri H, Yamada T, Oka Y. Adiposity and cardiovascular disorders: Disturbance of the regulatory system consisting of humoral and neuronal signals. *Circ Res* 2007;101:27–39.)

(DeMarco et al., 2014; Katagiri et al., 2007). A partial list includes the following:

- Sympathetic overactivity (Esler, 2014)
- Selective leptin resistance (Correia & Haynes, 2004; Yang & Barouch, 2007)
- Adipokines including leptin, free fatty acids, Ang II (Katagiri et al., 2007)
- Dipeptidyl peptidase 4, which not only degrades incretins (gut hormones) but also is involved in the regulation of vascular smooth muscle and costimulation of T cells (Zhong et al., 2013)
- RAAS overactivity, ROS, and NO deficiency (Katagiri et al., 2007) with T cell activation (Wu et al., 2007)
- Overactivity of the endocannabinoid pathway (Grassi et al., 2008)

As illustrated in Figure 3-36, visceral adipose tissue seems to link obesity with hypertension and atherosclerosis. Adipose tissue is no longer considered merely a passive energy storage depot. Fat cells produce large numbers of biologically active substances termed *adipokines* (Katagiri et al., 2007). Many of these have been implicated as prohypertensive, including leptin, angiotensinogen, resistin, retinol-binding protein (RBP4), plasminogen activator inhibitor-1, TNF- α , fatty acids, sex steroids, and growth factors. Others such as adiponectin are considered antihypertensive. The prohypertensive/proatherosclerotic adipokines are thought to compromise vascular health by multiple mechanisms including proliferation of vascular smooth muscle, inflammation, oxidative stress, endothelial dysfunction, and thrombosis.

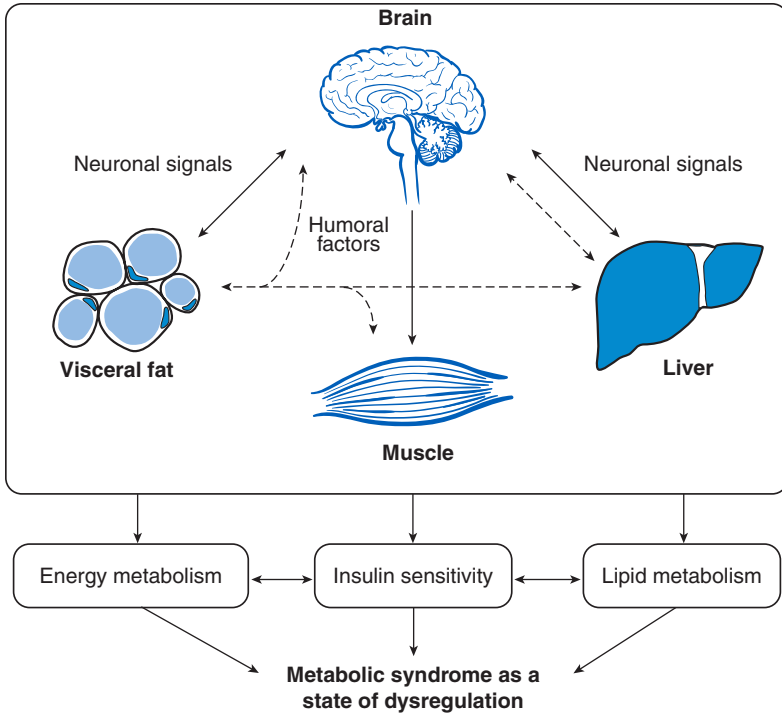


FIGURE 3-36 • Proposed communications among organs/tissues via humoral and neuronal pathways involved in the metabolic syndrome. (From Katagiri H, Yamada T, Oka Y. Adiposity and cardiovascular disorders: Disturbance of the regulatory system consisting of humoral and neuronal signals. *Circ Res* 2007; 101:27–39.)

Neural Mechanisms of Obesity-Related Hypertension

Sympathetic overactivity is one of the most important mechanisms—perhaps the most important mechanism—linking obesity to hypertension and hypertensive target-organ damage (DeMarco et al., 2014). The MSNA is higher in normotensive obese subjects than in normotensive lean subjects and higher still in obese hypertensives (Lambert et al., 2007). With weight gain, increased SNA is thought to be a compensatory mechanism to burn fat—but at the expense of sympathetic activation in tissues regulating BP—kidney and vascular smooth muscle (see Fig. 3-36) (Landsberg, 2006).

However, this appealing teleologic theory, proposed by Landsberg (2006), has been called into question: Ganglionic blockade causes a greater fall in BP in obese than in lean hypertensive patients but surprisingly has a smaller effect on resting energy expenditure (Shibao et al., 2007). Thus, the evidence for a sympathetic contribution to obesity-related hypertension is strong but a complete picture is missing.

Several factors can activate the sympathetic nervous system in obese individuals: (1) Obstructive sleep apnea, which causes recurrent hypoxia and activates the carotid body chemoreceptors that reflexively increase sympathetic activity (Biaggioni, 2007),

(2) accumulation of liver fat, which activates hepatic sensory afferents that reflexively increase SNA (Katagiri et al., 2007), and (3) overfed fat cells, which release adipokines that cross the blood–brain barrier and activate SNA centrally (Katagiri et al., 2007).

Obstructive Sleep Apnea as a Cause of Neurogenic Hypertension

Obstructive sleep apnea, as will be discussed in Chapter 14, is common in obese persons and is considered an important cause of hypertension and hypertensive heart disease (Biaggioni, 2007). In obstructive sleep apnea, repeated episodes of arterial desaturation during sleep trigger large swings in MSNA and BP (Narkiewicz et al., 2005). Furthermore, the chemoreflex seems to reset, causing sustained sympathetic activation even during waking hours.

In patients with obstructive sleep apnea, the elevated levels of plasma and urine catecholamines may mimic those seen with pheochromocytoma, as discussed in Chapter 12.

If obstructive sleep apnea is a common cause of neurogenic hypertension, why does continuous positive airway pressure (CPAP)—the best available treatment for obstructive sleep apnea—produce only a trivial improvement in high BP? A recent meta-analysis (Montesi et al., 2012) including 1,948 patients in

28 trials has confirmed three prior meta-analyses (Alajmi et al., 2007; Bazzano et al., 2007; Haentjens et al., 2007) showing that CPAP only lowers office BP by approximately 3/2 mm Hg. A recent trial in 194 showed similar effects of CPAP on 24-hour ambulatory BP with a somewhat larger benefit on nocturnal BP by converting some patients from the nondipper to the dipper pattern (Martinez-Garcia et al., 2013).

Obstructive sleep apnea is not only a hyperadrenergic state but also a state of hyperaldosteronism (Gonzaga et al., 2010; Pimenta et al., 2013; Sim et al., 2011). Excessive stimulation of MRs in the brainstem has been shown to increase SNA in animals (DeMarco et al., 2014). Pilot studies in patients with uncontrolled hypertension suggest that reduced venous return with lower body positive pressure can reduce upper airway cross sectional area and neck circumference (Friedman et al., 2013) and intensified diuretic therapy can reduce overnight rostral fluid shift and OSA (Kasai et al., 2014). Further work will be needed to see if the reduced OSA normalizes sympathetic overactivity and improves high BP.

Obesity-Related Hypertension as a Neurogenic Hypertension Variant

In the absence of obstructive sleep apnea, obesity-related hypertension is accompanied by a highly characteristic pattern of sympathetic activation—one that differs qualitatively from that in lean hypertensive individuals.

In both obese and nonobese hypertensive patients, sympathetic activation is targeted to the kidneys and skeletal muscle (Esler et al., 2006). In nonobese hypertensive patients, the sympathetic activation also is targeted to the heart, presumably contributing to LVH and ventricular arrhythmias. However, in obese patients with hypertension, the heart somehow is spared this sympathetic activation (Esler et al., 2006). Thus, the work by Esler, Lambert, and coworkers implicates the cardiac sympathetic nerves in pressure-overload cardiac hypertrophy (i.e., hypertension-related LVH) but not in obesity-related cardiac remodeling and hypertrophy.

Moreover, Lambert et al. (2007) find that hypertension in nonobese patients is associated with an increased firing rate of single axons that already were active. In contrast, obesity increases MSNA by recruiting previously silent fibers, with no increase in firing rate. The central neural circuits driving postganglionic MSNA may be frequency modulated in lean hypertensives but amplitude modulated in

obesity-related hypertension—as though their brains were tuned to “FM” or “AM.”

Further evidence for different mechanisms of hypertension in lean and obese persons comes from an unlikely source, namely, post hoc analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial (Weber et al., 2013). In obese hypertensives, CV outcomes were comparable with an ACEI/CCB combination as with an ACEI/thiazide combination, whereas, in lean hypertensives, CV outcomes were far better with the ACEI/CCB. The suggestion is that the diuretic caused greater compensatory neurohormonal activation in the lean hypertensives.

As illustrated in Figure 3-36 (Katagiri et al., 2007), additional neurohormonal mechanisms for obesity-related hypertension include (1) afferent neural signals from the liver and (2) adipokines, i.e., hormonal signals from fat cells.

Afferent Neural Signals from the Liver

In rodent models, raising portal vein levels of glucose or free fatty acids increases the discharge of sensory afferents that project centrally via the vagus nerve and trigger reflex sympathetic activation (Katagiri et al., 2007). In obesity, fat accumulation in the liver may thereby signal the brain of excess energy storage and evoke reflex increases in SNA that increase energy expenditure and lipolysis but contribute to hypertension (Katagiri et al., 2007). This revised version of the Landsberg hypothesis has not been tested directly in humans. In contrast, much recent work has implicated adipokines in linking obesity—especially abdominal obesity—with hypertension, atherosclerosis and type 2 diabetes.

Adipokines

Work has focused most on two adipokines—leptin, which increases with BMI and is thought to contribute to obesity-related hypertension, and adiponectin, which falls with increasing BMI and is thought to be protective.

LEPTIN

Leptin, a 16-kDa protein mainly derived from adipocytes, acts on the hypothalamus and regulates energy metabolism by decreasing appetite and increasing energy expenditure via sympathetic stimulation of numerous tissues. In rodent models of obesity, leptin loses its ability to suppress appetite but retains its

ability to increase SNA (particularly to the kidney), termed “selective leptin resistance” (Mark, 2013; Mark et al., 2004). Recently, acute i.v. leptin infusion has been shown to cause an acute increase, albeit modest, in MSNA in healthy normal-weight human subjects (Machleidt et al., 2013).

Leptin also may contribute to obesity hypertension by inducing smooth muscle cell proliferation, inflammation, and oxidative stress (DeMarco et al., 2014). Leptin can stimulate NO-release and cause endothelial-dependent vasodilation, a protective mechanism that may be lost with obesity—a state of inflammation and oxidative stress.

ADIPONECTIN

Adiponectin is the protein most abundantly produced by adipocytes. Plasma levels are normally high (3 to 30 mg/mL) and correlate inversely with BMI (DeMarco et al., 2014). The inverse correlation is stronger with visceral than with subcutaneous adipose tissue. Adiponectin levels are normal in “healthy” obese subjects who do not have hypertension or diabetes (Aguilar-Salinas et al., 2008). Obese individuals with normal adiponectin levels may be protected against endothelial dysfunction, vascular remodeling, and atherosclerosis. The presence of hypertension is associated with lower plasma adiponectin levels (Shankar et al., 2008).

RAAS Overactivity and T Cell Activation in Adipose Tissue

Despite volume overload, which normally would suppress the RAAS, all components of the RAAS typically are increased in obese patients (Engeli et al., 2005) and more so when obesity is accompanied by hypertension (Dall'Asta et al., 2009). Obesity-related hypertension is high-renin hypertension (Umemura et al., 1997). Logically, RSNA may be driving renin production by the JG cells.

In mouse models of Ang II–induced hypertension, the perivascular fat—but not the vascular smooth muscle per se—becomes infested with activated T cells, demonstrating selective honing to adipocytes (Guzik et al., 2007). Visceral adipose tissue also becomes infested with activated T cells in diet-induced obesity in both mice and humans (Wu et al., 2007). In obese patients, activation of the sympathetics, the RAAS, inflammatory cytokines, and T cells may be a perfect storm for hypertension (Harrison et al., 2008).

The Metabolic Syndrome

Abdominal (upper body) obesity is worse than subcutaneous (lower body) obesity from both a metabolic and CV standpoint. This difference was observed by Jean Vague (1956) (actually in 1947 but in a French paper that received little attention) and has been so well confirmed that an increased waist circumference is a principal component of the metabolic syndrome (Grundy, 2012).

The diagnosis of metabolic syndrome requires three or more of the five components listed in Table 3-5. Associated conditions include fatty liver disease, cholesterol gallstones, gout, depression, obstructive sleep apnea, and polycystic ovarian syndrome (PCOS). The metabolic syndrome carries a twofold risk of atherosclerotic CV disease and a fivefold risk of type 2 diabetes (Grundy, 2012). It increases the risks for coronary disease, stroke, and CV mortality beyond those seen with individual components of the syndrome such as hypertension.

The metabolic syndrome is a worldwide pandemic, affecting 20% to 30% of adults in most Western countries including the U.S. (Grundy, 2008).

Mechanisms

As shown in Figure 3-37, excess body fat is the main driver of the metabolic syndrome, with susceptibility factors—both genetic and environmental—being required for its full expression (Grundy, 2007). The full-blown syndrome is a proinflammatory, prothrombotic state leading to endothelial dysfunction, glucose intolerance, hypertension, and atherosclerosis. It is also a prediabetic state, increasing the risk of progression to full-blown diabetes with its microvascular and

TABLE 3-5

Diagnostic Criteria for the Metabolic Syndrome

Three or more of the following five features

1. Waist circumference, ≥ 102 cm in men or ≥ 88 cm in women
2. Triglycerides ≥ 150 mg/dL
3. HDL-C < 40 mg/dL in men or < 50 mg/dL in women
4. BP $\geq 130/85$ mm Hg
5. Fasting glucose ≥ 100 mg/dL (including diabetes)

Modified from Grundy SM. Metabolic syndrome pandemic. *Arterioscler Thromb Vasc Biol* 2008;28:629–636.

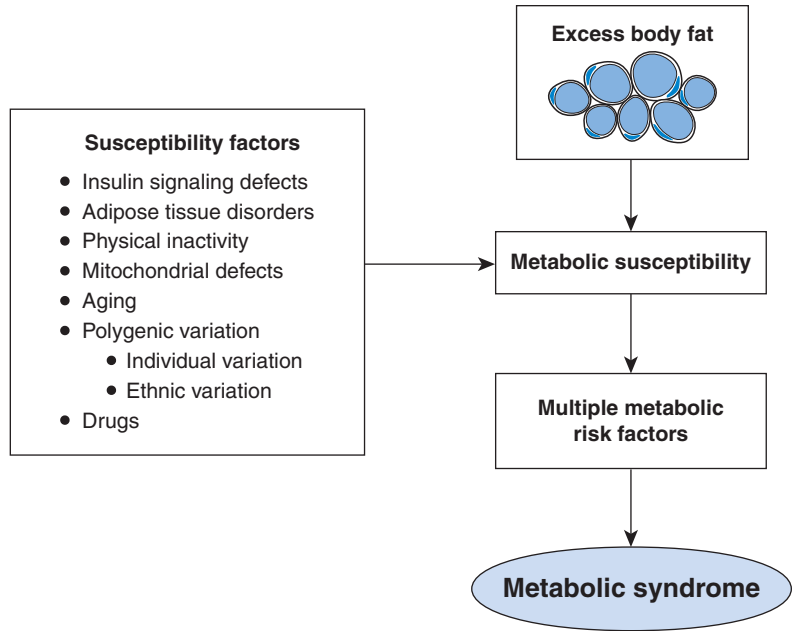


FIGURE 3-37 • Proposed scheme for pathogenesis of the metabolic syndrome. For multiple metabolic risk factors, which compose the MetS that develops, an excess of body fat must be combined with a metabolic susceptibility. This susceptibility is often manifest by insulin resistance. Multiple adverse influences contribute to metabolic susceptibility. (From Grundy SM. Metabolic syndrome: A multiplex cardiovascular risk factor. *J Clin Endocrinol Metab* 2007;92:399–404.)

macrovascular complications (Grundy, 2012). Pathogenetic mechanisms include adipokines, adhesion molecules, inflammatory mediators, overactivity of the RAAS and the sympathetic nervous system, as well as overactivity of the endocannabinoid system.

Diabetes

Prevalence

The obesity epidemic is accompanied by a parallel epidemic of type 2 diabetes mellitus (Selvin et al., 2014). Over 21 million American adults (10% of the adult population) have type 2 diabetes, which is undiagnosed in only one-third of these cases, and another 12% of the adult population has prediabetes (Selvin et al., 2014). Type 2 diabetes is a coronary risk equivalent and has become the number one cause of ESRD (Almdal et al., 2004). The lifetime risk of developing diabetes for people in the U.S. born in 2000 is about 33% for men and 39% for women (Narayan et al., 2003). If diagnosed at age 40, diabetic men will lose 11.6 years of life, women 14.3 years. By the year 2030, it is estimated that 366 million people worldwide will have diabetes (Wild et al., 2004).

Association with Hypertension

Diabetes and hypertension frequently coexist—much more commonly than is predicted by chance. Because

diabetes is so prevalent in the hypertensive population and accelerates target organ damage, all patients with hypertension should be screened for diabetes (Norris et al., 2008).

In the words of the Global Burden of Metabolic Risk Factors for Chronic Diseases Collaborators (The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, 2014):

The salient features of the cardiometabolic disease and risk factor epidemic at the beginning of the 21st century are high blood pressure and an increasing effect of obesity and diabetes. The mortality burden of cardiometabolic risk factors has shifted from high-income to low-income and middle-income countries. Lowering cardiometabolic risks through dietary, behavioral, and pharmacologic interventions should be a part of the global response to noncommunicable diseases.

In 2010, high BP was the leading risk factor for deaths due to cardiovascular diseases, chronic kidney disease, and diabetes in every region, causing more than 40% of worldwide deaths from these diseases; high BMI and glucose were each responsible for about 15% of deaths, and high cholesterol for more than 10%. After accounting for multicausality, 63% (10.8 million deaths) of deaths from these diseases in 2010 were attributable to the combined effect of these four metabolic risk factors. (The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, 2014.)

Mechanisms

The same pathogenetic mechanisms underlying the metabolic syndrome are thought to explain the association of hypertension and diabetes.

The consequences of the coexistence of diabetes and hypertension are covered further in Chapter 4 and the treatment of the diabetic hypertensive in Chapter 7. The special problems of diabetic nephropathy are described in Chapter 9.

Shortcomings of Current Theories and Unexplained Observations

There are some breaks in the chain linking hypertension with obesity and other components of the metabolic syndrome. Current theories do not fully explain some clinically important observations:

- *The metabolic syndrome varies by race/ethnicity.* In African Americans, hypertension predominates but serum triglyceride levels are lower than in nonblacks, and the risk of hepatic steatosis is low (Walker et al., 2012). By contrast, in Mexican-Americans, diabetes predominates; the risk of hepatic steatosis is excessive, but the risk of hypertension is disproportionately low for the high rates of obesity (Walker et al., 2012). Non-Hispanic blacks are prone to insulin resistance whereas white Hispanics are prone to pancreatic steatosis and β -cell failure (Szczepaniak et al., 2012). Similarly, Native Americans have high rates of obesity-related diabetes and gallstones but low rates of hypertension and coronary disease (Saad et al., 1991). Levels of MSNA do not track with BMI in either Pima Indians (Spraul et al., 1993), in whom MSNA levels are low, or in African American men in whom MSNA levels are high (Abate et al., 2001; Spraul et al., 1993) even after substantial weight loss (Abbas et al., 2010; Spraul et al., 1993). These different susceptibilities are related in part to ancestral genes (Romeo et al., 2008), but a complete mechanistic understanding is lacking.
- *Weight loss—whether by diet, drugs, or surgery—often causes proportionally smaller improvements in BP than in glucose tolerance, serum triglycerides, and other components of the metabolic syndrome.* The effects of bariatric surgery are particularly unbalanced (Mark, 2008; Spraul et al., 1993). As the only effective treatment for significant obesity, bariatric surgery produces sustained weight loss but, inexplicably, has a much greater long-term effect on diabetes and

dyslipidemia than hypertension. A seminal prospective study of bariatric surgery followed 1,700 patients, most of whom were 20 kg lighter 10 years later. Despite large and sustained benefits on glucose tolerance, triglycerides, and incident diabetes, the benefits on BP and hypertension risk were small and short lived (Mark, 2008; Sjostrom et al., 2000; Sjostrom et al., 2004) (Fig. 3-38). By 8 to 10 years after bariatric surgery, there were no detectable effects on BP or incident hypertension. Recent major trials substantiate the conclusion that, with all forms of bariatric surgery, the benefits on BP are rather underwhelming given the large amount of weight reduction and when compared to the consistently dramatic benefits on glucose metabolism (Courcoulas et al., 2013; Ikramuddin et al., 2013; Schauer et al., 2012). A pilot study indicated that bariatric surgery causes a sustained reduction in MSNA (Seravalle et al., 2014); but again, the magnitude of the reduction was smaller than has been reported with much smaller diet-induced weight loss (Mark et al., 2014). Perhaps body weight is overestimated as a driver of BP or sustained surgically induced weight loss activates offsetting pressor mechanisms.

Prevention of Obesity Hypertension

The lifestyle changes and drug therapy of obesity-related hypertension are covered in Chapters 6 and 7, respectively. However, in view of its importance, a few comments about the need and the possible methods for prevention of obesity seem appropriate.

Obesity and obesity-related hypertension, as noted earlier in this chapter, start in early childhood (Flynn, 2013). Particular demographic groups are disproportionately affected: 24% of African American girls and 22% of Mexican American boys are obese (Barlow, 2007). Obesity also is increasing rapidly among Native American and Asian American children. In general, obesity is more common among low-income inner city minorities who lack sufficient access to healthy food choices and safe playgrounds. Obese children are more likely than normal weight children to become obese adults and to develop hypertension, diabetes, and coronary disease. Prevention needs to begin in infancy and childhood.

Given the low success of individual behavior therapy, global societal changes will be needed (Table 3-6). The same aggressive, multifaceted strategies used against tobacco will likely be needed to

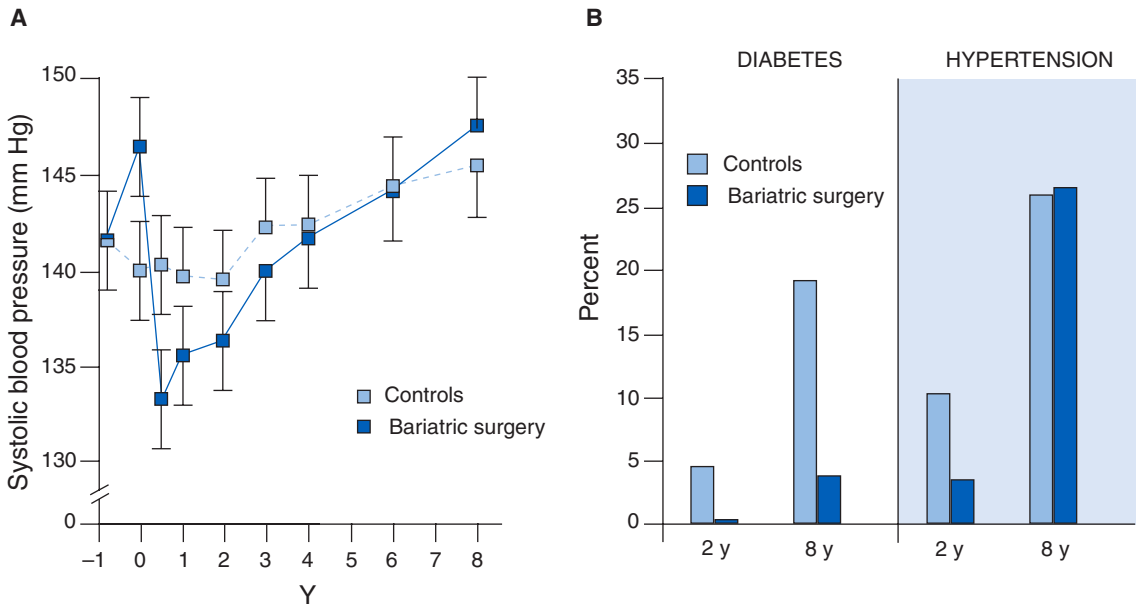


FIGURE 3-38 • Data from the Swedish Obesity Study showing a differential long-term effect of bariatric surgery on diabetes and hypertension. BP decreased initially after bariatric surgery but returned to control levels after 6 to 8 years despite persistent substantial decreases in body weight (A). In addition, although bariatric surgery was accompanied by a persistent decrease in the incidence and severity of diabetes and dyslipidemia, the 8- to 10-year incidence of hypertension did not differ between the surgical and control groups (B). (From Mark AL. Dietary therapy for obesity: An emperor with no clothes. *Hypertension* 2008;51:1426–1434. Adapted from Sjostrom L, Lindroos AK, Peltonen M, et al. Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. *N Engl J Med* 2004;351:2683–2693; and Sjostrom CD, Peltonen M, Wedel H, et al. Differentiated long-term effects of intentional weight loss on diabetes and hypertension. *Hypertension* 2000;36:20–25.)

TABLE 3-6

A Commonsense Approach to Prevention and Treatment of Childhood Obesity

Home	Set aside time for Healthy meals Physical activity
School	Limit television viewing and computer gaming Fund mandatory physical education Establish stricter standards for school lunch programs Eliminate unhealthy foods—e.g., soft drinks and candy—from vending machines Provide healthy snacks through concession stands and vending machines
Urban design	Protect open spaces Build pavements (sidewalks), bike paths, parks, playgrounds, and pedestrian zones
Health care	Improve insurance coverage for effective obesity treatment
Marketing and media	Consider a tax on fast food and soft drinks Subsidies nutritious foods—e.g., fruits and vegetables Require nutrition labels on fast food packaging Prohibit food advertisement and marketing directed at children Increase funding for public health campaigns for obesity prevention
Politics	Regulate political contributions from the food industry

Modified from Ebbeling et al. (2002).

force the large multinational companies that are responsible for pushing energy dense foods on a willing public, particularly children. Until or if that campaign works, just increasing peoples' daily level of physical activity can make a major impact on the prevention of obesity and its adverse metabolic consequences (Blair & Church, 2004). Perhaps we can walk up that flight of stairs—or better follow the 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk (Eckel et al., 2014)—just as an example to our patients.

URIC ACID AND HYPERTENSION

The steadily growing evidence for a causal role of uric acid in primary hypertension is impressive. Yet it falls short of being conclusive or supporting the use of the XO inhibitor allopurinol or the uricosuric agent probenecid to reduce the risk of developing adult hypertension in young people with asymptomatic hyperuricemia (Gois & Souza, 2013).

Evidence

The growing appreciation of uric acid's potential role in causing hypertension is largely due to the ongoing work of Richard Johnson, Daniel Feig, and coworkers (Feig et al., 2013). Their evidence includes the following:

- The initial description of an association between uric acid and hypertension by Mahomed in 1,879 was followed by many similar observations over the next 100+ years (Feig et al., 2013).
- The induction of hypertension in rats made hyperuricemic (Feig et al., 2013).
- The continued publication of studies (well over a dozen in all) and a recent meta-analysis (Grayson et al., 2011) showing that an increased uric acid level predicts the development of hypertension. These include data from the Bogalusa Heart Study wherein childhood uric acid levels predicted hypertension over an average 12-year follow-up (Alper et al., 2005), from the Framingham Study wherein uric acid level was an independent—albeit modest—predictor of hypertension (Sundstrom et al., 2005), and more recently from NHANES 3 showing that normotensive adolescents with a serum uric acid greater than 5.5 mg/dL had a twofold greater risk of developing hypertension, with the risk increasing

by 38% for every 0.1 mg/dL increase in the uric acid level (Loeffler et al., 2012).

- Demonstration of impaired endothelial function with hyperuricemia that was improved when uric acid levels were reduced (Kanbay et al., 2011b; Kato et al., 2005).
- Recognition of an elevated uric acid level as a strong predictor of CV mortality and CKD independent of BP and other traditional risk factors (Kanbay et al., 2011a; Ofori & Odia, 2014).
- Evidence that an elevated serum uric acid level is an independent predictor of preeclampsia in women with gestational hypertension (Bellomo et al., 2011).
- Publication of the first carefully controlled, though small Phase 2B, clinical trial showing that allopurinol lowers BP in primary hypertension (Feig et al., 2008). In a randomized double-blind placebo-controlled cross-over trial of 30 adolescents with hyperuricemia and recently diagnosed hypertension, 1-month treatment with allopurinol lowered 24-hour ambulatory BP by $-7/-5$ mm Hg, achieving normotension in 2/3 of subjects. This is a short-term study, and it is unknown whether the encouraging results are due to decreased uric acid or some other property of allopurinol—in particular reduced XO activity and thus reduced production of superoxide.
- Subsequent publication of a larger Phase 2B trial of 60 obese adolescents with prehypertension randomized equally to allopurinol, probenecid, or placebo. After 8 weeks, 24-hour BP was unchanged with placebo, but it decreased by $-10/-8$ mm Hg with allopurinol and by $-9/-7$ mm Hg with probenecid indicating that the reduction in BP was related to reduction in serum uric acid per se (Soletsky & Feig, 2012). While these data certainly advance the hypothesis that uric acid plays an important and potentially reversible causal role in the initiation of clinical hypertension, conclusive proof awaits a longer-term Phase 3 multicenter trial.

Potential Mechanisms

The new pilot clinical trials data are consistent with animal model data suggesting a 2-phase mechanism for uric acid-mediated hypertension: The first phase is caused by peripheral vasoconstriction and can be reversed by urate-lowering therapy while the second phase is caused by impaired renal sodium excretion and cannot be so reversed (Feig et al., 2013). While

extracellular uric acid crystals cause gout, intracellular uric acid may stimulate oxidative stress in vascular smooth muscle and kidney both directly by stimulation of NADPH oxidase or indirectly as a by-product of increased XO overactivity; the increased oxidative stress may contribute to both the initiation and progression of hypertension by causing alteration in mitochondrial respiration, destruction of NO, activation of the RAAS, and increased endothelin (Johnson et al., 2013).

Mean uric acid levels have doubled in the past century, as Americans consume more meat, fructose, and total calories (Feig et al., 2013). Hyperuricemia can be caused by overproduction (as in the metabolic syndrome) or decreased renal transport (as with excessive alcohol consumption or diuretic therapy).

Uric acid levels are higher in humans and monkeys than other mammals due to a missense mutation in the gene encoding hepatic uricase, which converts uric acid, an insoluble organic anion, to allantoin, which is more soluble and thus more easily excreted in the urine. From an evolutionary standpoint, this mutation may have allowed ancient apes to convert fructose to fat and raise BP thereby providing a survival advantage in the Miocene ice age but contributing to diabetes and hypertension in the modern era (Kratzer et al., 2014).

GENDER DIFFERENCES AND SEX HORMONES

Before age 50, women have less hypertension than men but quickly catch up after menopause and have more hypertension thereafter (Ong et al., 2007). However, we know little about the mechanisms mediating these gender differences in hypertension. Are they linked to protective effects of estrogen, prohypertensive effects of androgens, both, or neither?

Androgens

The role of androgens in the genesis of primary hypertension is controversial but evidence is mounting (Qiao et al., 2008). In almost all rodent models of hypertension, males have much higher BPs than females before but not after castration (Kienitz & Quinkler, 2008). Testosterone measurements may not tell the whole story because testosterone production can fall acutely with stress and androgens other than testosterone may be involved.

Hyperandrogenemia is implicated in the hypertension and other metabolic abnormalities in women with PCOS (Kienitz and Quinkler, 2008; Sung et al., 2014). Long-term administration of testosterone to female-to-male transsexuals increases BP—sometimes markedly (Kienitz & Quinkler, 2008; Mueller et al., 2007). Androgens may contribute to vasoconstriction and hypertension by upregulation of thromboxane A2 expression, NE, Ang II expression, and endothelial action (Kienitz & Quinkler, 2008).

Estrogen

In physiologic concentrations, estrogen's effects on BP are less clear than testosterone's (Qiao et al., 2008). Exogenous estrogen—as the contraceptive pill in premenopausal women or as hormone replacement therapy in postmenopausal women—can raise BP and contribute to hypertension, as will be discussed in Chapter 15.

Factors Associated with Hypertension in Women

There are no major gender differences in the factors predisposing to hypertension. In the Women's Health Initiative—a well-characterized cohort of 98,705 women aged 50 to 79 years—hypertension was more common in those who were overweight than lean (48% vs. 29%), physical inactive versus physically fit (45% vs. 31%), and nondrinkers and heavy drinkers than moderate drinkers (46% vs. 36% vs. 32%) (Oparil, 2006).

Other Associations

Lee (2002) has summarized the association of various hemorheologic factors associated with hypertension. These factors may be associated with vascular inflammation and include the following: Increased circulating inflammatory endothelial cells, which detach from the vessel wall in sites of vascular injury (Eirin et al., 2013), increased hematocrit (Eirin et al., 2013; Smith et al., 1994), elevated plasma fibrinogen levels (Landin et al., 1990), decreased fibrinolytic activity reflected by increased levels of plasminogen activator inhibitor and tissue plasminogen activator antigen (Poli et al., 2000), and increased whole-blood viscosity (Devereux et al., 2000). Increased blood viscosity along with increased hematocrits and thrombogenic factors may be involved in the greater threats of thrombotic rather than hemorrhagic complications in hypertensive patients.

A number of other diseases in which accompanying hypertension frequently is noted are described in Chapter 14.

GENES AND ENVIRONMENT

Family History

Hypertension runs in families. A parental history of hypertension increases the lifetime risk of developing hypertension, especially if both parents were hypertensive (Wang et al., 2008b). Large studies of biologic and adopted siblings that used ambulatory BP monitoring estimate that approximately 60% of the familial association of BP is caused by shared genes and approximately 40% by shared environment (Kupper et al., 2005). We know much more about the environmental factors than the genetic ones.

Genetic Determinants of Primary Hypertension

General Comments

The complex regulation of BP has thwarted the genetic dissection of human hypertension either with candidate genes, genome-wide scans, intermediate phenotypes, gene expression studies, and comparative genomics in rodent models. The enthusiasm released by the elucidation of the human genome has been quickly dampened by the reality, as Sir George Pickering warned 50 years ago (Pickering, 1964) that “elevated blood pressure is not a function of one gene, but rather a host of genes, each contributing a small effect.” The seemingly weak genetic “signals,” the strong environmental determinants of BP, the large amount of unrelated genetic information, and the large “noise” in BP measurement all increase the risk of both false-positive and false-negative studies.

In the words of Dr. Joseph Loscalzo (2007), editor-in-chief of *Circulation*:

Whereas I and many others believe that understanding the genome in precise molecular detail will ultimately give us truly unique insight into disease risk and pathogenesis, my review of the growing body of genome-wide association studies does not convince me that this goal is likely to be realized soon... Because of the extraordinary number of comparisons made between two often large populations (e.g., 500,000 SNPs [single nucleotide polymorphisms] in the human genome of 17,000 subjects in a

recent genome-wide association study, modest differences in prevalence can achieve startling high statistical significance, even after adjustment for multiple comparisons... Remember that although 500,000 SNPs may seem like a large number, there are 3.2 billion base pairs in the human genome, indicating that less than 0.02% of the genome is specifically assessed with this marker panel... Genetic epidemiologists address this issue by noting the statistical association among groups of SNPs (i.e., haplotypes).

Genome-Wide SNP Association Studies

The Wellcome Trust Case Control Consortium (2007) conducted a landmark genome-wide association study of 14,000 cases of 7 common diseases (including 2,000 cases of primary hypertension) and 3,000 controls in the United Kingdom (U.K.); analysis of 500,000 SNPs in each subject confirmed several previously defined SNPs and identified new SNPs associated with coronary disease and diabetes but failed to identify any associated with hypertension at the pre-defined statistical significance level. However, six SNPs showed an association with a less stringent corrected *p* value, thus meriting future study.

Subsequently, only 1 of these 6 SNPs showed a potential association with hypertension in a study of 11,433 subjects in the U.S. conducted by the Family Blood Pressure Program (Ehret et al., 2008). Strangely, the association was positive for Americans of European origin, negative for those of Hispanic origin, with no association being found among African Americans. This SNP (rs1937506) is located in a gene “desert” on chromosome 13q21 where the two closest flanking genes have never been associated with hypertension.

Given these negative findings, positive reports from smaller SNP association studies should be taken with a “grain of salt.”

The results of recent genome-wide association studies in hypertension include the following:

- A genome-wide association study in 1,017 African Americans identified several SNPs that reached genome-wide statistical significance for systolic BP (Adeyemo et al., 2009). However, none of the associations could be replicated in a subsequent independent sample of 2,474 African Americans (Kidambi et al., 2012). Independent replication is now required to publish genetic association studies in most journals.
- Two very large genome-wide association studies have confirmed associations with previously discovered variants and several novel variants but with

meager effects on BP (Ehret et al., 2011; Nguyen et al., 2013). These worldwide research consortia of genome-wide association studies confirmed multiple loci for BP, but the individual effect size for each is so small that together these loci explain less than 1% of BP variance. The large gap between estimated and observed variance—termed “missing heritability”—could be due in part to “epigenetics,” which refers to the inheritance of gene expression patterns not strictly dependent on differences in DNA sequence (Cowley et al., 2012).

- An encouraging finding is that 88% of the 30 gene variants associated with higher BP in the above studies were also positively associated with coronary artery disease (CAD), one of the major complications of hypertension (Lieb et al., 2013). On average, each allele increased the risk of CAD by 3%; however, quartile of subjects carrying the largest number of alleles for increased systolic BP had a 70% higher odds of having CAD than those in the lowest quartile.

Other Gene Association Studies: Candidate and Newly Discovered SNPs

We should note a few examples of recent positive findings from gene association studies, including some that have been replicated in independent study samples.

- *Corin gene minor allele, hypertension, and LVH in Blacks.* Corin is a serine protease that enzymatically converts pro-ANP and pro-BNP, which are inactive prohormones, into smaller biologically active natriuretic peptides. In the Dallas Heart Study—a large multiethnic population-based sample—a minor (less common) allele defined by two missense mutations in the corin gene is carried by 12% of blacks but by almost no whites and is associated with a greater prevalence of hypertension and higher systolic BP (4 mm Hg at the population level); these findings are confirmed in two more large independent population samples (Dries et al., 2005). When coexpressed in various cells, these SNPs reduce corin’s enzymatic activity in vitro although neither one alone had any effect (Wang et al., 2008d). We still do not know if they reduce corin function in patients. If so, this would indicate that natriuretic peptides normally defend against hypertension, and genetic impairments in this defense mechanism could explain $\geq 10\%$ of hypertension and hypertensive heart disease in U.S. blacks.

- *Adrenergic receptor polymorphisms.* In the same Dallas Heart Study, there is no association between candidate $\alpha 2A$ or $\alpha 2C$ alleles, alone or in combination, with hypertension, untreated BP, or LV mass (Li et al., 2006) and no association between several candidate β -adrenergic receptor alleles alone or in combination with $\alpha 2C$ alleles and LVH (Canham et al., 2007). On the other hand, O’Connor and coworkers in San Diego find several associations between hypertension and indices (albeit indirect) of sympathetic reactivity to laboratory stressors with novel variants in genes regulating the synthesis and exocytotic release of catecholamines (Fung et al., 2008; O’Connor et al., 2008; Rao et al., 2007a,b; Shih & O’Connor, 2008; Zhang et al., 2007). A concise picture is yet to emerge from this work, as some associations are specific for only diastolic BP; some are seen only in men, but others only in women. The implication is that individual variability in BP reactivity to environmental stressors is in part genetically predetermined.
- *A novel thiamine transporter.* O’Connor and coworkers recently discovered a new hypertension susceptibility locus uncovering a previously unsuspected thiamine transporter whose genetic variants were accompanied by increased cardiac output and decreased peripheral vascular resistance reminiscent of the high-output state caused by thiamine deficiency (Zhang et al., 2014). The initial association of the risk allele with BP was made by studying the extremes of BP in a large primary care population and then confirmed in an independent population sample. The further association with high cardiac output/low vascular resistance (and augmented cold pressor response) was discovered in twin-pair studies. The generalizability of this rigorously determined and unexpected association remains to be determined, as peripheral vasoconstriction is, with rare exception, the *sine qua non* for most human hypertension.
- *Common noncoding uromodulin (UMOD) gene variants and salt-sensitive hypertension.* One of the group of common variants identified by genome-wide hypertension association studies involves the promoter of the *UMOD* gene that encodes uromodulin (Tamm-Horsfall protein), the major protein excreted in urine. Uromodulin overexpression in transgenic mice engendered salt-sensitive hypertension mediated by activation of the furosemide-sensitive renal sodium cotransporter NKCC2 (Trudu et al., 2013). Impressively, the authors

went on to show that pharmacologic inhibition of NKCC2 by furosemide was more effective in lowering BP in hypertensive patients who were homozygous for *UMOD* promoter risk alleles than in other hypertensive patients. This powerful combination of functional mouse transgenetics and translational human pharmacogenetics is an important benchmark for future studies in the molecular genetics of human hypertension.

- *eNOS variants as hypertension susceptibility genes.* The international GWAS studies also identified an *eNOS* gene variant (rs3918226) as having a small effect on BP. In a cohort of 2,722 Europeans followed for a mean of 7.6 years, BP increased by 10/7 mm Hg on average in 28 TT homozygotes versus 4/2 mm Hg in 2,694 C allele carriers (Salvi et al., 2013). Moreover, *eNOS* promoter activity was found to 20% to 40% lower in the T- versus C-transfected cells. It makes sense that a genetic defect in *eNOS* activity could predispose to high BP. It would seem important to test whether hypertensive patients who are T-allele homozygotes are particularly sensitive to antihypertensive therapy with inorganic NO donors, which generally produce modest decreases in BP (Siervo et al., 2013).
- *K⁺ channel mutations in aldosterone-producing adenomas.* Lifton's group recently discovered that over one-third of patients with aldosterone-producing adenomas (Conn syndrome, Chapter 11) have somatic mutations in the *KCNJ5* potassium channel gene (Choi et al., 2011). The mutant channels display abnormally increased Na⁺ conductance and cell depolarization and thus Ca²⁺ entry that in adrenal glomerulosa cells signals aldosterone production and cell proliferation, thus providing a mechanistic explanation for a disease that is perhaps the most common secondary forms of hypertension. Subsequently, additional mutations that result in excessive Ca²⁺ entry have been identified (Moraitis et al., 2013).
- *Common variants (SNPs) in genes underlying monogenic hypertension and hypotension in the general population.* In a study of 2,037 adults from 520 families in the U.K. (Tobin et al., 2008), 298 candidate SNPs were identified in regions of genes where deletions, copies, or substitutions of comparatively large chromosomal regions cause the rare monogenic forms of hypertension or hypotension described earlier in this chapter. Five polymorphisms in the gene encoding the ROMK potassium channel (involved in a form of Bartter syndrome) show negative

associations with BP by 24-h monitoring. The strongest effect is with one allele on chromosome 11, present in 16% of the population, which is associated with a lower systolic BP of 1.5 mm Hg and lower EKG voltage (Tobin et al., 2008), a finding that awaits independent confirmation.

Carriers of Barter and Gitelman Syndrome Mutations in the General Population

As stated earlier in the chapter, major mutations (not SNPs) in 20 salt handling genes cause the ultrarare monogenic forms of severe early-onset hypotension and hypertension. But the applicability of this work to primary hypertension previously was unknown. New data from the Framingham Heart Study now show that gene mutations underlying the pediatric salt-wasting syndromes (Barter's and Gitelman's) in the homozygous state are present in 1% to 2% of the general adult population in the heterozygous state and may confer resistance against primary hypertension (Ji et al., 2008). As many as 1 in 64 of these subjects carry 1 of 3 functional mutations of genes encoding the NCCT, the NKCC2, or ROMK. Among those between ages 51 and 60 years, hypertension is present in only 19% of the carriers compared with 42% of the noncarriers (Fig. 3-39).

Thus, normotensive young adults lacking these (and other) protective mutations may be at increased

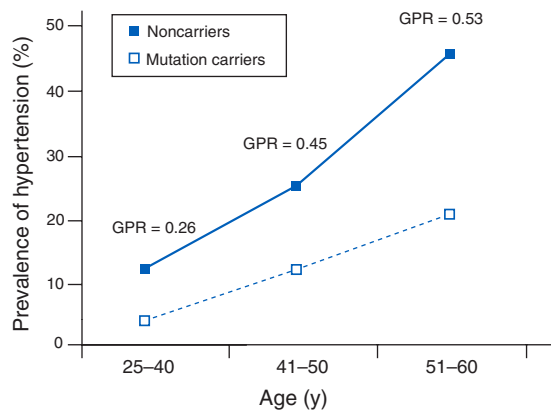


FIGURE 3-39 • Reduced prevalence of hypertension among mutation carriers. Prevalence of hypertension at the last exam within ages 25 to 40, 41 to 50, and 51 to 60 for mutation carriers and noncarriers of genes causing Bartter and Gitelman syndromes. The genotype relative risk (GRR) for mutation carriers is shown. (From Ji W, Foo JN, O'Roak BJ, et al. Rare independent mutations in renal salt handling genes contribute to blood pressure variation. *Nat Genet* 2008;40:592-599.)

risk for developing salt-sensitive hypertension in middle age and may benefit from preemptive therapy with a low-dose diuretic or at least a low-sodium diet. The carriers presumably have salt-resistant BP and need not worry about eating too much salt.

Racial and Ethnic Aspects of Hypertension

Among U.S. adults, 44% of non-Hispanic blacks have hypertension compared with 33% of non-Hispanic whites and 29% of Hispanic whites (Go et al., 2014). It is surprising that hypertension is not more common among Hispanics given the high rates of obesity and type 2 diabetes. Even more surprising is that hypertension is more common in Mexico than among Mexican immigrants to the U.S., suggesting the importance of environmental factors other than obesity (Barquera et al., 2008).

In U.S. blacks, hypertension is not only more prevalent than in other U.S. racial and ethnic groups but also starts at a younger age, is more severe, and causes more target organ damage, premature disability, and death (Go et al., 2014). The high prevalence of hypertension in U.S. blacks has been attributed to selection pressure of sub-Saharan African origin populations to develop augmented renal sodium absorption (Chun et al., 2008). Blunted daytime urine sodium excretion is associated with blunted nocturnal dipping in BP, which is more often seen in black than white individuals (Bankir et al., 2008). PRA is lower in blacks than other groups but higher in Hispanics suggesting different mechanisms of hypertension (Rifkin et al., 2014).

Recent clinical research suggests the following about the pathogenesis of hypertension in non-Hispanic blacks:

- Compared with normotensive white young adults, normotensive black young adults had greater constriction of hand veins to infusion of phenylephrine suggesting enhanced sensitivity of vascular alpha-1 adrenergic receptors (Adefurin et al., 2013).
- However, in the Symplicity HTN-3 trial of patients with difficult hypertension, RDN lowered BP in whites but not in blacks (Bhatt et al., 2014), supporting the long-held notion that neurogenic mechanisms are less important in the pathogenesis and progression of hypertension in blacks than whites.
- Despite having lower PRA and a generally smaller BP response to ACEI monotherapy (Peck et al.,

2013), blacks have greater 24-hour urinary excretion of angiotensinogen, suggesting overactivity of the intrarenal RAS that thus may contribute to the hypertension (Michel et al., 2014).

- In a cohort of black and white subjects studied at age 11 and again at age 31, black children had lower levels of PRA and serum aldosterone and this effect persisted into adulthood (Tu et al., 2014).
- In the above cohort (Tu et al., 2014), a 2-week oral challenge with fludrocortisone, a MR agonist, raised clinic and ambulatory BP and increased body weight in the black adults but not in the white adults, implicating enhanced BP sensitivity to endogenous MR agonists (i.e., aldosterone as well as DOC and cortisol). This provocative finding should be confirmed in a larger separate cohort.

Clinical research center studies should be interpreted cautiously since they generally are not designed to consider effects of socioeconomic disadvantage and other factors related to racial prejudice (Victor et al., 2004). Observed black–white differences in BP regulation in rather small convenience samples may have as much—or more—to do with a lifetime of an unhealthy high-salt/low-potassium diet than with ancestral genes (Bartley et al., 2014; Stamler et al., 2003, 2013). Metabolomic analysis of normotensive middle-aged black participants of the Atherosclerosis Risk in Communities (ARIC) cohort identified a product of the gut microbiome as one novel risk factor for incident hypertension (Zheng et al., 2013).

Although U.S. blacks are often assumed to have the highest rates hypertension in the world, this is not so (Cooper et al., 2005). Hypertension is more prevalent in several predominately white European countries than in U.S. blacks and is relatively uncommon among blacks living in Africa (Fig. 3-40). These international data underscore the importance of environment in human BP variation.

Ancestral gene analysis (as discussed further in Chapter 9) has produced a major breakthrough in understanding the genetic underpinning of CKD, which disproportionately affects African-origin populations. Two common variants in the apolipoprotein L1 (*APOL1*) gene that confer resistance to lethal *Trypanosoma brucei* infection are associated with an increased risk of ESRD from common forms of renal disease including that related to hypertension (Parsa et al., 2013). However, the same type of ancestral gene analysis has not as yet produced a breakthrough for hypertension per se.

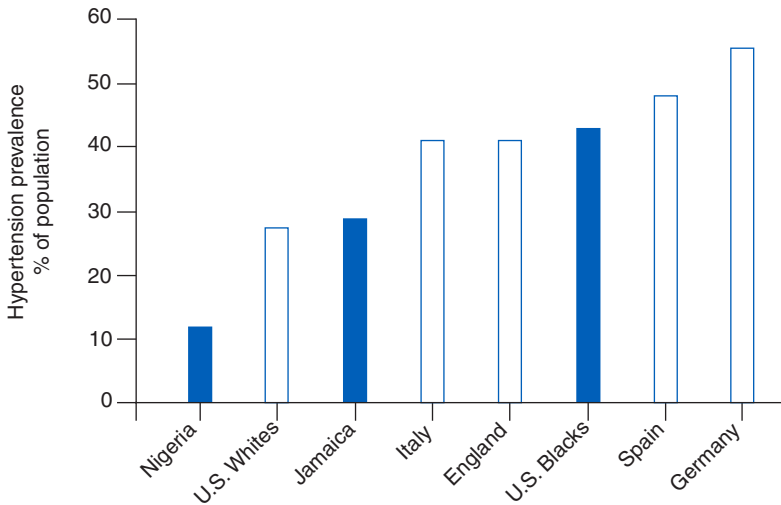


FIGURE 3-40 • Age-adjusted hypertension prevalence in populations of African and European descent. (Modified from Cooper RS, Wolf-Maier K, Luke A, et al. An international comparative study of blood pressure in populations of European vs African descent. *BMC Med* 2005;3:2.)

ENVIRONMENTAL DETERMINANTS

For primary hypertension, the most important and best studied exposures—fetal environment, postnatal weight gain, adult obesity—were covered earlier in this chapter. Many other exposures may work to initiate hypertension, aggravate it, or counteract antihypertensive therapy.

Tobacco

The nicotine in cigarette smoke acutely raises BP mainly by stimulating release of NE from sympathetic nerve terminals (Fitzgerald, 2013)—an effect that is augmented when baroreceptor reflexes are impaired as often the case in older patients with coronary disease (Shinozaki et al., 2008). No tolerance develops, so BP rises with each cigarette—by 7/4 mm Hg on average but twice as much in many patients with hypertension (Verdecchia et al., 1995). Cigars and smokeless tobacco also raise BP (Bolinder & de Faire, 1998) but nicotine replacement therapy (even high dose) does not (Hatsukami et al., 2007).

However, the pressor effect of each cigarette is transient and is over by 30 minutes; if the BP is taken in a smoke-free environment, as in physicians' offices and medical research clinics, the pressor effect may be missed (Verberk et al., 2008). Thus, casual clinic BP measurements used in large epidemiologic studies (Bowman et al., 2007; Halperin et al., 2008) may have underestimated the risk of cigarette smoking on incident

hypertension. In addition to raising plasma NE levels, cigarette smoke also may contribute to hypertension by impairing NO-dependent vasodilation both by increasing oxidative stress and increasing plasma ADMA levels (Zhang et al., 2007).

Water pipe (Hookah) smoking is an emerging public health crisis affecting high school and college age young adults, who are too young to go to bars but can enjoy the “bar scene” in Hookah cafés (which escaped the Clean Air Act) (Cobb et al., 2010, 2012a). In a typical 90-minute session of Hookah smoking, young adults will inhale as much nicotine as in 50 to 100 cigarettes leading to acute increases in BP and heart rate; even smoking nicotine-free Hookah decrease heart rate variability likely due to inhalation of fine particulate matter emitted from the burning charcoal that is the heat source (Cobb et al., 2012b). The effect of e-cigarettes and e-Hookah is under investigation.

Coffee, Colas, and Caffeine

Caffeine—the most widely consumed stimulant in the world—acutely raises BP by blocking vasodilatory adenosine receptors and by increasing plasma NE (Cano-Marquina et al., 2013). In a controlled laboratory setting, ingestion of caffeine, equivalent to that in two to three cups of coffee, will raise BP acutely; however, the size of the pressor response varies widely between studies and individuals from 3/4 to 15/13 mm Hg and tends to be larger in hypertensives (Cano-Marquina et al., 2013). Typically, BP peaks 1 hour after caffeine

ingestion and returns to baseline after 4 hours. However, as stated by Myers (2004): “despite numerous studies..., it is still uncertain if caffeine increases BP only under ideal laboratory conditions or if it causes a clinically important pressor response with regular use during usual daily activities.” In particular, do frequent coffee drinks show habituation to the acute pressor effect of caffeine throughout the day and are they at increased risk of developing chronic hypertension?

In the Nurses’ Health Study, a woman’s risk of developing hypertension did not vary with coffee consumption but increased steeply when caffeine was consumed in soft drinks (even with sugar-free diet colas) (Winkelmayer et al., 2005), presumably because coffee contains protective antioxidants (polyphenols) not present in colas (Cano-Marquina et al., 2013). The polyphenols in coffee also may confer some protection against developing diabetes (Beaudoin & Graham, 2011; O’Keefe et al., 2013), whereas soft drinks increase the risk of developing all components of the metabolic syndrome including hypertension (Cohen et al., 2012).

Alcohol

A drink of alcohol sometimes raises BP due to increased SNA and sometimes lowers BP due to vasodilation (Chen et al., 2008b; Randin et al., 1995). Ethically, there can be no prospective RCTs of chronic ethanol consumption on BP levels.

Most large epidemiologic studies find that the relation between alcohol consumption and many health outcomes—including BP levels, hypertension risk, stroke risk, and total mortality—is *J-shaped* (Fig. 3-41) (Kloner & Rezkalla, 2007; O’Keefe et al., 2007). The risk is higher in teetotalers than moderate drinkers—those who have one or two drinks per day—but then increases progressively with heavy drinking. However, it has been argued that the J-limb is an artifact of including previous heavy drinkers—who have a high prevalence of hypertension—among nondrinkers (Okubo et al., 2014). When previous heavy drinkers were excluded in selecting a middle-aged and older cohort of over 37,000 Japanese men and over 78,000 Japanese women who were normotensive at baseline, the 10-year risk of developing hypertension increased linearly in a dose-dependent fashion with alcohol consumption without any evidence of a J-limb (Okubo et al., 2014).

Moreover, oriental persons with a loss-of-function mutation in the gene encoding alcohol dehydrogenase

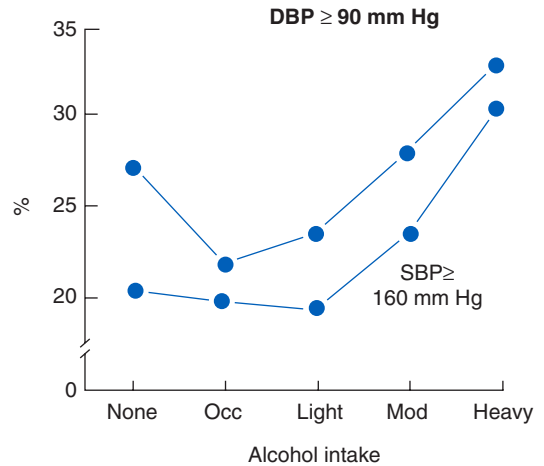


FIGURE 3-41 • Age-adjusted prevalence rates (%) of measured systolic and diastolic hypertension by levels of alcohol intake in drinks. DBP, diastolic blood pressure; Occ, occasional drinking; Light, one or two drinks daily; Mod, moderate (three to six drinks daily); Heavy, more than six drinks daily; SBP, systolic blood pressure. (Modified from Shaper AG, Wannamethee G, Whincup P. Alcohol and blood pressure in middle-aged British men. *J Hum Hypertens* 1988;2:71S–78S.)

(*ALDH2*) become flushed and nauseated after drinking and thus drink little or no alcohol. A meta-analysis of 10 published studies of mainly Japanese men found a linear gene dose effect, with no evidence of an initial *J-limb* (Chen et al., 2008b). Men with the *1*1 genotype (highest alcohol tolerance/intake) and those with the *1*2 genotype (intermediate alcohol tolerance/intake) were 2.4 and 1.7 times more likely to have hypertension than men with the *2*2 genotype (least alcohol tolerance/intake). Systolic BP was 7 mm Hg higher in men with the *1*1 genotype and 4 mm Hg higher in those with the *1*2 genotype than in those with the *2*2 genotype. In contrast, no association was found between *ALDH2* genotype and hypertension or BP levels in Japanese women who drink very little alcohol for cultural reasons regardless of genotype.

The risk of developing hypertension seems to be highest in binge drinkers due to sympathetic activation with each intervening mini-period of alcohol withdrawal (Kloner & Rezkalla, 2007). The potent central sympatholytic drug dexmedetomidine effectively reduces BP and benzodiazepine requirements during alcohol withdrawal syndrome (Frazee et al., 2014).

Temperature and Altitude

BP tends to be higher in colder weather (Modesti et al., 2006), which may play a role in the increase in MI and sudden cardiac death during the winter months

(Gerber et al., 2006). Similarly, ascent to higher altitude may raise the BP (Wolfel et al., 1994)—sometimes dramatically—and more hypertension may be seen among those who live at higher altitudes (Khalid et al., 1994).

Sympathetic activation likely underlies these effects. Cold exposure increases MSNA and BP (Victor et al., 1987). Lower partial pressures of oxygen activate the carotid body chemoreceptors (McBryde et al., 2013) with increased SNA lasting for at least 4 weeks after ascent to altitude (Hansen & Sander, 2003).

On the other hand, the largest study of ambient temperature and BP—based on ABPM in 6,404 patients—found that hot weather was associated not only with lower clinic and daytime ambulatory BPs but surprisingly with higher nighttime BPs especially in the elderly (Modesti et al., 2006). The lower daytime BP is likely due to vasodilation. The higher sleeping BP could be due to lower thermostats and more air-conditioning at night.

Vitamin D

In brief, observational studies continue to make a case for mild vitamin D deficiency as a cause of hypertension, but multiple vitamin D treatment trials have shown no improvement in BP.

The positive observational studies are summarized as follows:

- ▶ In the Intersalt study, hypertension was increasingly prevalent in populations that are further from the equator (Rostand, 1997).
- ▶ BP tends to be higher in winter than summer (Richart et al., 2007). This and the relation to latitude noted above may be related both to cold temperature and less sun exposure.
- ▶ Reduced absorption of vitamin D by dark skin has been suggested as one potential explanation for higher BP in blacks, who have lower vitamin D blood levels (Scragg et al., 2007).
- ▶ In prospective cohort studies, low blood levels of 25-hydroxyvitamin D₂ have been independently associated with an increased risk of hypertension (Forman et al., 2007, 2008; Wang et al., 2008a), CV events (Giovannucci et al., 2008; Wang et al., 2008c), and death (Melamed et al., 2008). In the Nurses' Health Study, normotensive women who took vitamin D supplements were less likely to develop hypertension two decades later (Forman et al., 2007).

About 80% of vitamin D comes from sunlight, specifically UVB light, absorbed through the skin and 20% from the dietary sources absorbed through the gut (Richart et al., 2007). Vitamin D₃ is converted to 25-hydroxyvitamin D₂, an inactive metabolite that is converted by a hydroxylase enzyme to 1,25-hydroxy D₂ that is the active form. The enzyme is abundantly expressed not only in the kidney but also in vascular smooth muscle and other tissues involved in BP regulation (Richart et al., 2007). Because human blood tests assay only for the inactive 25-hydroxyvitamin D₂, the epidemiologic data—though positive—may underestimate the strength of association. Vitamin D receptor knockout mice develop high-renin hypertension, because vitamin D regulates the calcium signal that normally suppresses renin release from the JG cells (Bouillon et al., 2008).

However, enthusiasm for this hypothesis is dampened considerably by negative results of now several RCTs, which are summarized as follows:

- ▶ In the Women's Health Initiative Calcium/Vitamin D Randomized Trial of over 36,000 postmenopausal women in whom calcium and vitamin D supplements had no effect on BP or on the risk of developing hypertension over 7 years (Margolis et al., 2008).
- ▶ In the Vitamin D Isolated Systolic Hypertension (VitDISH) randomized trial of 159 older patients with Stage 2 ISH and low levels of vitamin D, oral vitamin D was no different than placebo on office BP, ambulatory BP, central BP, endothelial function, arterial stiffness, or walking ability (Witham et al., 2013).
- ▶ In an RCT of 68 patients with resistant hypertension, 6 months of treatment with high-dose oral vitamin D₃ (100,000 units vs. placebo every 2 months) had no effect on ambulatory BP, office BP, or LV mass (Witham et al., 2014).
- ▶ In an RCT of 283 normotensive black subjects who have lower blood levels of vitamin D, 3 months of vitamin D therapy had a marginal effect on systolic BP but no effect on diastolic BP (Forman et al., 2013).

Nutrients

INTERMAP (Stamler et al., 2003)—a major epidemiologic study of 4,680 men and women ages 40 to 59 from 17 populations around the world—is providing new data about associations of macro- and micronutrients with BP, which was measured carefully (rather

than by subjective recall as in other large studies such as the Nurses' Health Study).

INTERMAP and other databases provide updated information about nutrient deficiencies as potential causes of hypertension:

- BP is 7/7 mm Hg higher in INTERMAP participants from northern versus southern China, which is related to higher intake of calories and salt and lower intake of potassium, magnesium, and phosphorus (Zhao et al., 2004).
- BP is 5/3 mm Hg higher in African American men than white men in the U.S. and 9/5 mm Hg higher in African American women than white women in the U.S., with one-fourth to one-half of the higher BPs in African Americans being attributed to less favorable dietary intake of multiple nutrients (Stamler et al., 2013).

Analysis of individual nutrients may underestimate the full impact of diet on BP due to interactions, as between dietary sodium excess and dietary potassium deficiency (Adrogué & Madias, 2007).

Potassium

Potassium is the most abundant intracellular cation in the body, and potassium channels play a key role in the relaxation of vascular smooth muscle, which lowers BP (Stolarz-Skrzypek et al., 2013). Whereas our prehistoric ancestors consumed 200 mmol/day of potassium, processed foods are low in potassium causing average potassium consumption in most Western countries to be less than 70 mmol/day (see Table 3-1), which is far below the World Health Organization (WHO) recommended lower limit of 120 mmol/day (Aburto et al., 2013).

As noted in Chapter 6, potassium depletion will raise BP, whereas potassium supplementation may lower the BP. The overall potassium intake of modern people has certainly been reduced below that of our ancestors, so there are logical reasons to advocate a return to a more “natural” higher-potassium/lower-sodium diet.

Recent analyses of the third NHANES cohort show the following:

- Among adults taking neither antihypertensive drugs nor a low-sodium diet, the risk of incident hypertension is 40% higher in those consuming the highest versus lowest quartile of dietary potassium intake (Zhang et al., 2013).

- Among normotensive and hypertensive adults not taking a low-sodium diet, the risk of overall 15-year mortality was 20% lower in those consuming a higher potassium diet (Yang et al., 2011).

The most recent and most comprehensive meta-analysis to date of RCTs on dietary potassium supplementation found that this is associated with a placebo-corrected reduction in BP of $-3/-2$ mm Hg (Aburto et al., 2013). Moreover, high potassium intake was associated with a 24% reduction in stroke risk (Aburto et al., 2013). An independent systemic review came to the same conclusions (Aaron & Sanders, 2013).

Magnesium, Calcium, Phosphorus

Magnesium is the second most common intracellular cation next to calcium. As most cations enter cells through voltage-gated calcium channels, magnesium can be viewed as an endogenous CCB. In INTERMAP, dietary calcium and phosphorus vary with magnesium, showing an inverse but weak association with increased BP (Elliott et al., 2008). More recently, the Prevention of Renal and Vascular End-Stage Disease (PREVEND) 7.5-year prospective cohort study of 5,511 initially normotensive subjects found that low levels of 24-hour urinary magnesium are a strong predictor of incident hypertension (Joosten et al., 2013). In hypertensive women treated with a thiazide, low red blood cell magnesium levels are associated with higher office BPs and greater central pressure augmentation (Cunha et al., 2013; Joosten et al., 2013). Low serum magnesium levels are associated with higher ambulatory pulse pressure and augmentation index (Afsar & Elsurur, 2014). Yet, whether magnesium supplements lower BP is uncertain, with three meta-analyses showing disparate results depending on which studies were included (Kass et al., 2012; Rosanoff, 2010; Rosanoff & Plesset, 2013).

Citrate

A low level of 24-hour urine excretion of citrate is associated with self-reported hypertension in the Nurses' Health Study and the Health Professionals Follow-up Study (Mandel et al., 2013). The hypocitruria could be due to dietary deficiency in citrus fruits or to acidic urine (from high meat consumption) that alters renal citrate transport. Low urinary citrate constitutes a putative common mechanism of a

modestly increased risk of renal stones in patients with hypertension (Taylor et al., 2006).

Toxic Exposures

Lead

Heavy occupational lead exposure has been shown to cause renal damage and thus hypertension (Ghiasvand et al., 2013; Vaziri, 2008). Low-level chronic lead exposure increases aortic stiffness and thus systolic BP in rats (Silveira et al., 2014) and has been associated with ISH in the elderly, perhaps due to greater lead exposure in the past and to deposition of lead in the arterial wall contributing to arterial stiffness (Perlstein et al., 2007).

Most population studies indicate a positive but modest association between blood lead levels with BP and incident hypertension (Navas-Acien et al., 2007). However, blood levels reflect acute lead exposure and the association with chronic hypertension may be somewhat stronger on the basis of x-ray measurements of tibial bone lead, which better reflect cumulative exposure (Navas-Acien et al., 2007; Perlstein et al., 2007).

Air Pollution

Under experimental conditions, short-term exposure to air pollution rapidly increases BP (mainly diastolic BP) in normotensive subjects (Urch et al., 2005). In a cohort of 3,236 initially normotensive black women (mean age 38) living in Los Angeles between 1995 and 2005, the 10-year risk of developing hypertension increased by 48% with each 10- $\mu\text{g}/\text{m}^3$ increase in exposure to fine particulate matter with an aerodynamic diameter of $\leq 2.5 \mu\text{m}$ ($\text{PM}_{2.5}$) (Coogan et al., 2012). Inhalation of such fine particulate matter stimulates lung afferents that reflexively increase SNA, while the smallest particles can enter the systemic circulation causing oxidative stress and vascular inflammation (Brook et al., 2010).

In a retrospective study of 1,705 Boston area patients hospitalized with acute ischemic stroke, the odds of having a stroke were found to be 34% higher after a moderate air quality day than after a good one (Wellenius et al., 2012). The greatest risk occurred within 12 hours of exposure to increased levels of $\text{PM}_{2.5}$ and was most strongly associated with markers of traffic-related pollution. Thus, urban air pollution may be a culprit in the pathogenesis of both hypertension and its most feared acute complication.

CONCLUSION

The preceding coverage does not exhaust the possible mechanisms for primary hypertension, but it at least touches on all that have received serious attention to date. It should be reemphasized that multiple defects likely are involved, and some of the initiating factors may no longer be discernible, having been dampened as hypertension develops. Without specific genetic markers, it is impossible to know whether a normotensive person, even with a strongly positive family history, will definitely develop hypertension, so that long-term prospective studies are difficult to design and perform.

In the absence of certainty about the pathogenesis of hypertension, it will be difficult to convince many patients that preventive measures should be undertaken. However, there seems no possible harm and a great deal of potential good to be gained from moderation in intake of sodium, calories, and alcohol; maintenance of good physical condition; and avoidance of unnecessary stress. As is described in Chapter 6, the value of these preventive measures has been demonstrated.

Now that the possible causes of primary hypertension have been examined, we turn to the natural history and clinical consequences of the disease. Regardless of cause, its consequences must be addressed.

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Primary Hypertension: Natural History and Evaluation

Now that the probable causes of primary hypertension have been considered, we turn to its clinical course and complications. We will first view the natural history of the disease if left untreated, examining the specific manner by which hypertension leads to premature cardiovascular damage and how such damage is clinically expressed. Additional coverage is provided for special populations—the elderly, women, blacks and other ethnic groups, diabetics, and the obese—who may follow somewhat different courses. Based on this background, guidelines for evaluating the newly diagnosed hypertensive patient are presented.

As noted in previous chapters, hypertension seems logically divided into three main categories: isolated diastolic hypertension in the young, diastolic with systolic hypertension, and isolated systolic hypertension (ISH) in the elderly. Table 4-1 delineates some of the main differences between the two types seen in those over age 50. They may overlap. For example, about one-third of ISH patients started with combined systolic and diastolic hypertension (Franklin et al., 2005). Most of the following relates to both forms, but the majority of studies on the natural history of hypertension involved younger patients with combined disease. Only recently has ISH received its deserved recognition (Franklin et al., 2001; McEniery et al., 2005; Wallace et al., 2007).

NATURAL HISTORY OF PRIMARY HYPERTENSION

The natural history of hypertension, simplistically depicted in Figure 4-1, starts when some combination of hereditary and environmental factors sets into

motion transient but repetitive perturbations of cardiovascular homeostasis (*prehypertension*), not enough to raise the blood pressure (BP) to levels defined as abnormal but enough to begin the cascade that, over many years, leads to BPs that usually are elevated (*early hypertension*). Some people, abetted by lifestyle changes, may abort the process and return to normotension. The majority, however, progress into *established hypertension*, which, as it persists, may induce a variety of complications identifiable as target organ damage and disease.

As was noted in Chapter 1, the higher the BP and the longer it remains elevated, the greater the morbidity and mortality. Although some patients with markedly elevated, untreated BP never have trouble, we have no way of accurately identifying in advance those who will have an uncomplicated course, the few who will enter a rapidly progressing, accelerated-malignant phase, and the many who will more slowly but progressively develop cardiovascular complications. Even without such foreknowledge, as BP and other risk factors are increasingly being treated, rates of morbidity and mortality related to hypertension have fallen (Go et al., 2013). Evidence for these changes is provided in Chapter 5 and the methods to achieve them in Chapters 6 and 7.

It should be noted that the role of hypertension probably is underestimated from morbidity and mortality statistics, which are largely based on death certificates. When a patient dies from a stroke, a heart attack, or renal failure—all directly attributable to uncontrolled hypertension—the stroke, the heart attack, or the renal failure, but *not* the hypertension, usually is listed as the cause of death.

TABLE 4-1

Differences Between Combined Systolic and Diastolic Versus ISH

Age of Onset	Combined	ISH
	30-50	>55
Mechanisms	Multiple	Atherosclerotic stiffness
Progression	Slow variable	More rapid continuous
Consequences	Coronary artery disease, nephrosclerosis	Stroke, CHF
Response to therapy	Renin-angiotensin blockers	Diuretics, calcium channel blockers

PREHYPERTENSION

The natural history of hypertension starts with normal BP, i.e., below 120/80 mm Hg, that typically slowly rises until middle age when hypertension, i.e., 140/90 mm Hg or higher, appears. In many people, only the systolic rises with further aging, inducing ISH, which is the most common form of hypertension in people over age 50 (Cheng et al., 2012).

As perhaps best seen in data from the Framingham cohort shown in Figure 4-2, the BP tends to track over many years, remaining in the same relative position over time (Franklin et al., 1997). Subjects in each BP segment tend to remain in that segment, with a slow, gradual rise over the 30 years of follow-up. In a later survey of the Framingham population, hypertension developed over a 4-year interval in only 5% of

men and women with BP less than 120/80 mm Hg, in 18% with a BP less than 130/85 mm Hg, and in 37% with a BP 130 to 139/85 to 89 mm Hg (Vasan et al., 2001).

Naturally, the progressive rise in pressure proceeds from 120/80 to 140/90 mm Hg through levels that were traditionally labeled “high-normal.” However, more and more evidence shows the appearance of cardiovascular risk factors and even target organ damage among these people (Shen et al., 2013). Therefore, the 2003 Joint National Committee (JNC-7) report introduced the term “prehypertension” to cover those with sustained BP levels from 120/80 to 139/89 mm Hg (Chobanian et al., 2003). Although “prehypertension” was not accepted in the 2013 European guidelines (Mancia et al., 2013), the term should be recognized for the rationale stated in JNC-7:

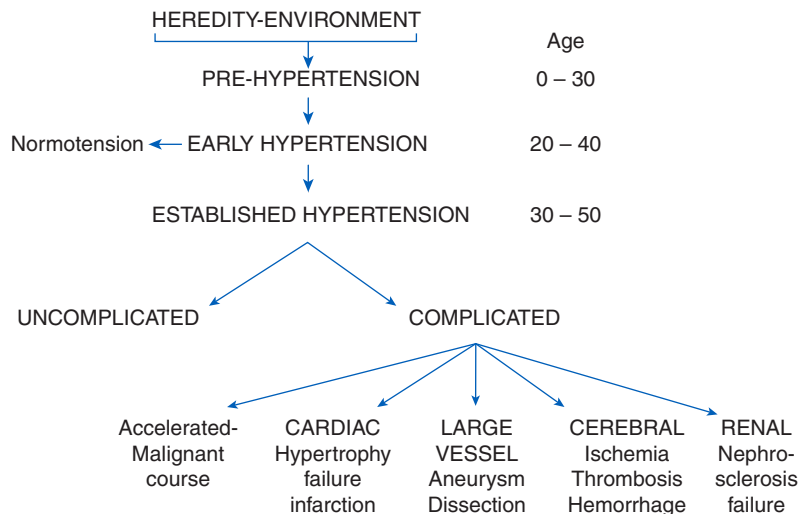


FIGURE 4-1 • Representation of the natural history of untreated essential hypertension.

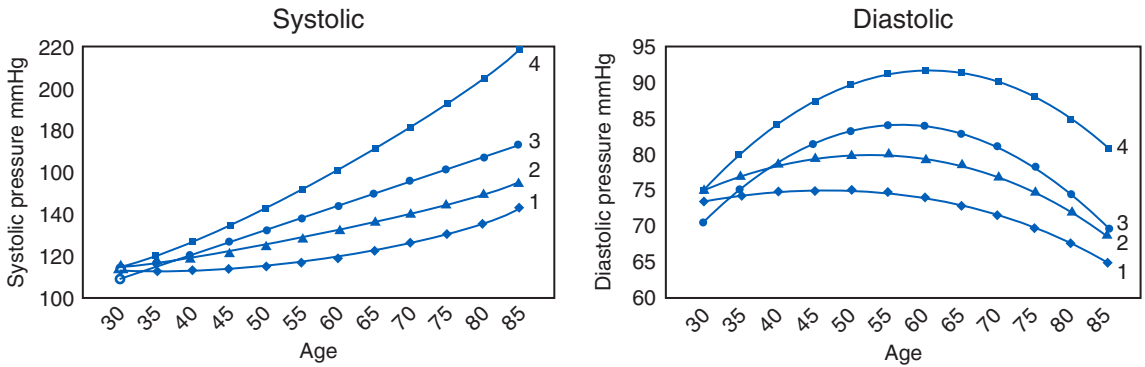


FIGURE 4-2 • Tracking systolic and diastolic BPs by age for up to 30 years in the Framingham Heart Study. Subjects who were stratified by their systolic BP in middle age: less than 120, 120 to 139, 140 to 159, and less than 160 mm Hg. The curves are derived from averaged individual regression analysis. (Modified from Franklin SS, Gustin W IV, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure: The Framingham Heart Study. *Circulation* 1997;96:308–315.)

Prehypertension is not a disease category. Rather it is a designation chosen to identify individuals at high risk of developing hypertension, so that both patients and clinicians are alerted to this risk and encouraged to intervene and prevent or delay the disease from developing. The goal for individuals with prehypertension and no compelling indications is to lower BP to normal with lifestyle changes and prevent the progressive rise in BP.

Prevalence

As many or more people are prehypertensive as are hypertensive, with an average number in surveys of the United States (U.S.) population of 60 million (Elliott & Black, 2007).

Predictors

Since prehypertension is one step toward hypertension, the same factors are involved in the development of both. Obesity is foremost, with male gender and black race also involved (Franklin et al., 2005; Toprak et al., 2009). In addition, these factors are associated with more prehypertension: diabetes, impaired glucose tolerance, the metabolic syndrome, dyslipidemia, and smoking (Elliott & Black, 2007; Parikh et al., 2008).

Associations

As best portrayed in the Prospective Studies Collaboration (Lewington et al., 2002), an increase in

BP from 115/75 to 135/85 mm Hg doubles the mortality rate for both ischemic heart disease and stroke (see Fig. 1-1 in Chapter 1). The evidences for target organ damage in prehypertension include these:

- Left ventricular hypertrophy (LVH) (Kokkinos et al., 2007)
- Coronary calcification (Pletcher et al., 2008)
- Reduced coronary flow reserve (Erdogan et al., 2007)
- Progression of coronary atherosclerosis (Sipahi et al., 2006)
- Increases in ischemic coronary disease and stroke (Lee et al., 2011)
- Poor cognitive function (Knecht et al., 2008)
- Retinal vascular changes (Nguyen et al., 2007)
- Proteinuria (Konno et al., 2013)
- Renal arteriosclerosis (Ninomiya et al., 2007)
- Elevated serum uric acid (Cicero et al., 2014)
- Increased levels of various markers of cardiovascular risk, including C-reactive protein (Bo et al., 2009)

With all of these indices of impending or existing target organ damage, attempts have been made to prevent prehypertension or at least to slow its progression into hypertension. As described more fully in Chapters 6 and 7, these have focused on lifestyle changes (Bavikati et al., 2008), but the difficulties in achieving lasting effects from lifestyle changes have led to trials of antihypertensive drugs (Julius et al., 2006; Luders et al., 2008; Skov et al., 2007).

EARLY HYPERTENSION: COURSE OF THE BLOOD PRESSURE

In most people who become hypertensive, the hypertension persists, but in some, the BP returns to normal, perhaps not to rise again. As emphasized in Chapter 2, hypertension should be confirmed by multiple readings, preferably taken out of the office, before the diagnosis is made and therapy is begun. If subsequent readings are considerably lower and the patient is free of obvious vascular complications, the patient should be advised to adhere to a healthy lifestyle and either to return every few months for repeat BP measurement or to self-monitor the BP at home.

The wisdom of this course is shown by data from an Australian therapeutic trial (Management Committee, 1982); 12.8% of the patients whose diastolic BPs averaged more than 95 mm Hg on two sets of initial readings obtained 2 weeks apart had a subsequent fall to less than 95 mm Hg that persisted over the next year, such that the patients could not be entered into the trial. An even larger portion (47.5%) of those who entered the trial with a diastolic BP above 95 mm Hg and who received only placebo tablets for the next 3 years maintained their average diastolic BP at less than 95 mm Hg. A significant portion remained below 90 mm Hg while on placebo, including 11% of those whose initial diastolic BP was as high as 105 to 109 mm Hg. On the other hand, 12.2% of the placebo-treated patients experienced a progressive rise in diastolic BP to more than 110 mm Hg.

From these data and others that will be described, a number of implications can be made:

- Multiple BP readings, preferably out of the office, over at least 6 weeks may be needed to establish the diagnosis of hypertension.
- Many patients who are not given antihypertensive drugs will have a significant decline in their BP, often to levels considered safe and not requiring therapy.
- Patients who are at low overall cardiovascular risk and free of target organ damage and whose diastolic BPs are lower than 90 mm Hg can safely be left off active drug therapy.
- If not treated, patients must be kept under close observation since a significant number will have a rise in pressure to levels requiring active therapy.

ESTABLISHED HYPERTENSION

As delineated in Chapter 1 and shown in Figure 1-1, the long-term effects of progressively higher levels of BP on the incidence of stroke and coronary heart disease (CHD) are clear: In 61 prospective observational studies involving almost 1 million people with BP starting as low as 115/75 mm Hg who were followed for up to 25 years, the associations were “positive, continuous, and apparently independent” (Lewington et al., 2002).

Untreated Patients in Clinical Trials

The best data on the course of untreated hypertension are derived from those patients who served as the control populations in the trials of the therapy of hypertension up to the mid-1990s, at which time placebo-controlled trials were no longer considered ethical, with the exception of one in the very elderly wherein no data were available, the HYVET trial (Beckett et al., 2008). Although these trials were not designed to observe the natural history of hypertension, their data can help to define further the course of untreated disease (Table 4-2). The trials involving elderly patients are considered separately.

The types of patients included in these randomized, controlled trials (RCTs) and the manner in which they were followed up differ considerably, so comparisons between them are largely inappropriate. Moreover, the patients enrolled in these RCTs were, in general, much healthier than the general population. In most, they had to be free of major debilities and, often, any coexisting diseases, such as diabetes. For example, only 1.1% of those screened were eligible for enrollment in the Systolic Hypertension in the Elderly Program (SHEP) trial (SHEP Cooperative Research Group, 1991). Therefore, the rate of complications seen during the few years of follow-up on no therapy can be considered the minimum. In the overall population, much higher rates of cardiovascular diseases (CVDs) would be expected, and the dangers of untreated hypertension would obviously expand over a longer time. More about these trials is covered in Chapter 5.

Untreated Elderly Patients in Trials

Table 4-3 summarizes data from eight RCTs of elderly hypertensives, two of them (SHEP Cooperative Research Group [1991] and the Systolic Hypertension

TABLE 4-2

Complications Among Control Groups in Trials of Nonelderly Hypertensives

Factor	Veterans Administration Cooperative ^a					Medical Research Council ^e
	1967	1970	USPHS ^b	Australia ^c	Oslo ^d	
Mean age (year)	51	52	44	50	45	52
Range of diastolic BP (mm Hg)	115–129	90–114	90–115	95–109	90–110	95–109
Number of subjects on placebo	70	194	196	1,617	379	8,654
Average follow-up (year)	1.3	3.3	7.0	3.0	5.5	5.5
Coronary disease ^f						
Fatal	1.0	6.0	2.0	0.4	0.5	1.1
Nonfatal	3.0	1.0	26.0	4.9	2.9	1.6
Congestive heart failure ^f	3.0	6.0	1.0	0.1	0.2	—
Cerebrovascular disease ^f	16.0	11.0	3.0	1.5	1.8	1.3
Renal insufficiency ^f	4.0	2.0	1.0	0.1	—	—
Progression of hypertension ^f	4.0	10.0	12.0	12.1	17.2	11.7
Total mortality ^f	6.0	10.0	2.0	1.2	2.4	2.9

USPHS, U.S. Public Health Service.

^aData from Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of treatment on morbidity in hypertension. *JAMA* 1967;202:116–122;1970;213:1143–1152.

^bData from Smith WM. Treatment of mild hypertension. *Circ Res* 1977;40(Suppl 1):98–115.

^cData from Management Committee. The Australian therapeutic trial in mild hypertension. *Lancet* 1980;1:1261–1267.

^dData from Helgeland A. Treatment of mild hypertension. *Am J Med* 1980;69:725–732.

^eData from Medical Research Council Working Party. Medical Research Council trial of treatment of mild hypertension. *Br Med J* 1985;291:97–104.

^fData reported as rate per 100 patients for the entire trial.

in Europe Trial [Staessen et al., 1997]) including only patients with ISH, the others including a portion with ISH. The control patients in these trials had much higher rates of the various end points than were seen in the trials of younger hypertensives listed in Table 4-2.

Systolic Versus Diastolic Pressure

A meta-analysis of all published trials of elderly patients until 2000 (Staessen et al., 2000) reconfirmed what has been repeatedly shown in multiple observational studies: Rises in systolic levels and falls in diastolic levels, with the resultant widening of pulse pressure, are typical changes that occur with aging and all predict risk (Gu et al., 2014). As shown in Figure 4-3, risk of death rises steeply for every increment of systolic BP, but, at every level of systolic BP, the risk increases further the lower the diastolic BP.

From these multiple sources, the picture of the natural history of hypertension shown in Figure 4-1 is derived. We now will examine the various complications shown at the bottom of that figure.

COMPLICATIONS OF HYPERTENSION

The end of the natural history of untreated hypertension is an increased likelihood of premature disability or death from CVD. Before considering the specific types of organ damage and the causes of death related to hypertension, the underlying basis for the arterial pathology caused by hypertension and the manner in which this pathology is expressed clinically will be examined.

Types of Vascular Lesions

As described in Chapter 3, the pathogenesis of combined systolic and diastolic hypertension involves structural changes in the resistance arterioles subsumed under the terms *remodeling* and *hypertrophy*. As people age, large artery atherosclerosis becomes an increasing factor, aggravated by the high shear stress of hypertension (Lakatta & Levy, 2003). Small-vessel arterial and arteriolar sclerosis may be considered

TABLE 4-3

Complications Among Control Groups in Trials of Elderly Hypertensives

Complication	Australian ^a	EWPHE ^b	Coope and Warrender ^c	SHEP ^d	STOP-HT ^e	MRC-2 ^f	Syst-Eur ^g	HYVET ^h
Mean age (year)	64	72	69	72	76	70	70	84
BP at entry (mm Hg)								
Systolic	<200	160–239	190–230	160–219	<180–230	160–209	160–219	160–199
Diastolic	95–109	90–119	105–120	<90	90–120	<115	<95	<110
Mean	165/101	182/101	197/110	170/77	195/102	185/91	174/85	173/91
Number of subjects on placebo	289	424	465	2,371	815	2,113	2,297	1,912
Average follow-up (years)	3.0	4.6	4.4	4.5	2.1	5.7	2.0	1.8
Coronary disease ⁱ								
Fatal	1.3	11.8	6.0	3.4	2.5	5.2	1.8	
Nonfatal	8.3	2.8	2.2	3.4	2.7	2.3	1.4	
Congestive heart failure ⁱ	—	5.4	7.7	4.5	4.8	—	2.1	–6.4 [†]
Cerebrovascular disease ⁱ	4.2	13.7	9.4	6.8	6.6	6.4	3.4	–8.0 [†]
Progression of hypertension ⁱ	—	6.8	—	15.0	9.3	8.3	5.5	
Total mortality ^j	3.1	35.1	14.8	10.2	7.9	15.0	6.0	–22.0 [†]

EWPHE, European Working Party on Hypertension in the Elderly; MRC, Medical Research Council; SHEP, Systolic Hypertension in the Elderly Program; STOP-HT, Swedish Trial in Old Patients with Hypertension; Syst-Eur, Systolic Hypertension in Europe Trial.

^aData from Management Committee. Treatment of mild hypertension in the elderly. *Med J Aust* 1981;2:398–402.

^bData from Amery A, Birkenäger W, Brixko P, et al. Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly Trial. *Lancet* 1985;1:1349–1354.

^cData from Coope J, Warrender TS. Randomized trial of treatment of hypertension in elderly patients in primary care. *Br Med J* 1986;293:1145–1151.

^dData from SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. *JAMA* 1991;266:3255–3264.

^eData from Dahlöf B, Lindholm LH, Hansson L, et al. Morbidity and mortality in the Swedish Trial in older patients with hypertension. *Lancet* 1991;338:1281–1285.

^fData from Medical Research Council Working Party. Medical Research Council trial of treatment in older adults. *Br Med J* 1992;304:405–412.

^gData from Staessen JA, Fagard R, Thijs L, et al. Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. *Lancet* 1997;350:757–764.

^hData from Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008;358:1887–1898.

ⁱData reported as rate per 100 patients for the entire trial.

^jData in HYVET are rates per 100 patient-years.

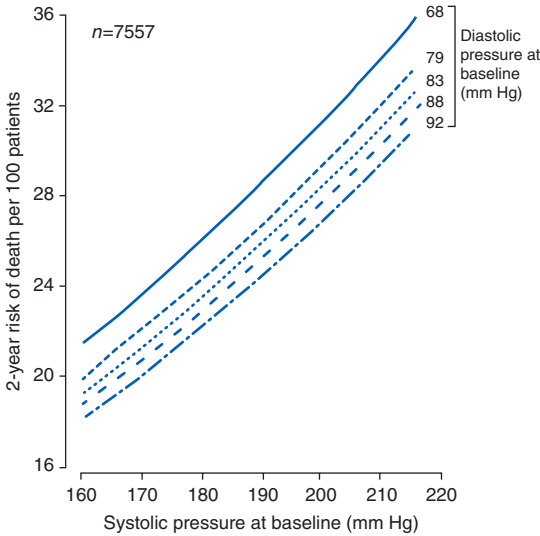


FIGURE 4-3 • The 2-year probability of death associated with systolic BP at different levels of diastolic pressure at baseline in untreated elderly women with ISH but no prior cardiovascular complications enrolled in eight RCTs. (Modified from Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly. *Lancet* 2000;355:865–872.)

secondary consequences of combined systolic–diastolic hypertension, whereas large-vessel atherosclerosis is primarily responsible for the predominantly systolic hypertension so common among the elderly.

Most of the premature morbidity and mortality associated with hypertension is related to atherosclerosis. Although usually only one of the multiple risk factors involved, hypertension has an independent role (Vernooij et al., 2013). There are variable rates of atherosclerotic stiffness between genders (Waddell et al., 2001) and ethnic groups (Chaturvedi et al.,

2004), which may explain the variability in vascular damage between them (Daugherty et al., 2013).

Causes of Death

Death may result when these arterial lesions either rupture or become occluded enough to cause ischemia or infarction of the tissues they supply. The causes of death in hypertensives, mostly from series published before the availability of effective therapy, can be summarized thusly:

- CVDs are responsible for a higher proportion of deaths as the severity of the hypertension worsens.
- Heart disease remains the leading cause of death overall, but strokes become increasingly more common in populations over age 65 (Kjeldsen et al., 2001).
- Heart failure becomes increasingly common in the elderly (Rodeheffer, 2011).

TARGET ORGAN INVOLVEMENT

We will now examine in more detail the pathophysiology and consequences of these various complications. Thereafter, the clinical and laboratory manifestations of the target organ damage will be incorporated into guidelines for evaluating the hypertensive patient.

Hypertensive Heart Disease

Hypertension more than doubles the risk for symptomatic coronary disease, including acute myocardial infarction (MI) and sudden death, and more than triples the risk for congestive heart failure (CHF) (Kannel, 1996). As shown in Figure 4-4, hypertension, usually

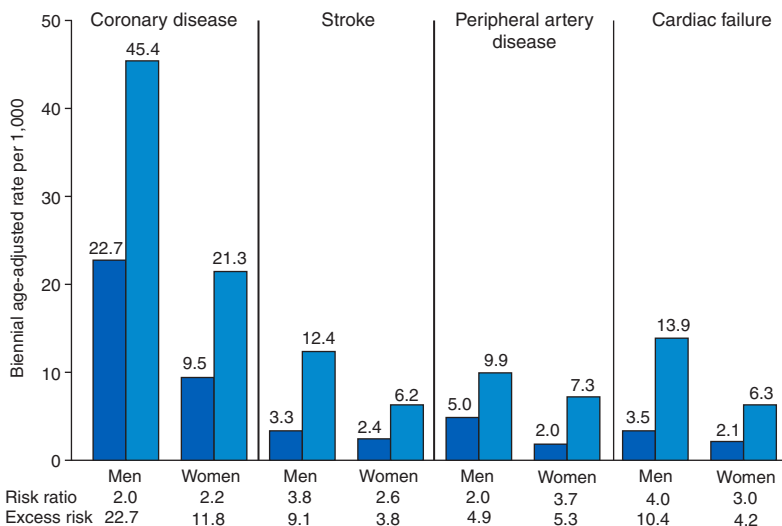


FIGURE 4-4 • Risk of cardiovascular events by hypertensive status in subjects aged 35 to 64 years from the Framingham study at 36-year follow-up. Coronary disease includes clinical manifestations such as MI, angina pectoris, sudden death, other coronary deaths, and coronary insufficiency syndrome; peripheral artery disease is manifested as intermittent claudication. **Left bars** in each set of columns represent normotensives; **right bars** represent hypertensives. (Modified from Kannel WB. Blood pressure as a cardiovascular risk factor. *JAMA* 1996;275:1571–1576.)

in concert with a number of other risk factors, often leads to LVH and/or myocardial ischemia and/or infarction. These processes, in turn, precipitate systolic and diastolic dysfunction, which often progresses to overt CHF (Drazner, 2011).

Left Ventricular Hypertrophy

Prevalence

Whereas LVH is identified by electrocardiography in only 5% to 18% of hypertensives, dependent on the criteria used (Ang & Lang, 2008), when present by ECG, LVH predicts strokes (Ishikawa et al., 2009) and accompanies renal damage (Peterson et al., 2013). LVH is found by echocardiography in many more hypertensive adults, in as many as 30% of unselected hypertensives, and in up to 90% of persons with severe hypertension (Schmieder & Messerli, 2000). More LVH is seen with obesity, high dietary sodium intake, anemia of end-stage renal disease (ESRD), alcohol abuse, diabetes, and hypercholesterolemia (de Simone et al., 2001). Despite its cost, echocardiography is recommended in the 2013 European guidelines as part of the initial evaluation of all hypertensives (Mancia et al., 2013).

Associations

The association between LVH and hypertension is stronger for systolic levels, which contribute most of the relation between pulse pressure and LVH (Mule et al., 2003). Increased pulse pressure is related to LV mass independent of other pressure components

(de Simone et al., 2005). In addition to the stress and strain invoked by increased BP per se, other factors contribute, including the following:

- Genotype, which is a likely mechanism for the higher prevalence of LVH in black than in white hypertensives (Kizer et al., 2004).
- A polymorphism of the angiotensin type 2 receptor gene (-332G/A) (Alfakih et al., 2004).
- An important role of the renin-angiotensin system is supported by the impressive effect of ACEIs and ARBs in causing regression of LVH and preventing remodeling after an MI (Kenchaiah et al., 2004).
- In women, but not in men, an association between serum aldosterone and cardiac remodeling (Vasan et al., 2004) that could reflect increased renin-angiotensin activity.
- In view of the profibrotic effects of aldosterone described in Chapter 3, this may be involved in the increased collagen type 1 synthesis noted in patients with hypertensive heart failure (Querejeta et al., 2004).
- Increased cardiac sympathetic nervous activity (Schlaich et al., 2003).
- Higher nighttime BP level (Cuspidi et al., 2013).

Patterns

The patterns of LVH differ by the type of hemodynamic load: Volume overload leads to eccentric hypertrophy, whereas pure BP overload leads to an increase in LV wall thickness without concomitant increase in cavity volume, i.e., concentric hypertrophy (Fig. 4-5).

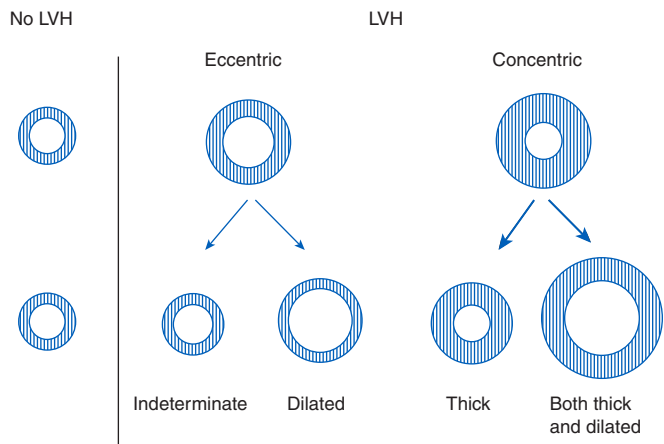


FIGURE 4-5 • Diagrammatic representation of the conventional two-tiered classification and the newly proposed four-tiered classification of LVH. Outer circle represents mean LV mass; inner circle, mean end-diastolic volume. (Adapted from Khouri MG, Peshock RM, Ayers CR, et al. A 4-tiered classification of left ventricular hypertrophy based on left ventricular geometry: The Dallas Heart Study. *Circ Cardiovasc Imaging* 2010;3:164–171.)

	No LVH	LVH			
		Eccentric		Concentric	
		Indeterminate	Dilated	Thick	Both thick and dilated
Increased LV mass/height ^{2.7}	-	+	+	+	+
Increased concentricity ^{0.67}	NA	-	-	+	+
Increased LV EDV/BSA	NA	-	+	-	+

In Bang et al.'s 2013 study of 939 patients with varying stages of hypertension, these percentages of various patterns were found by echocardiography: Normal geometry in 25%; concentric hypertrophy, nondilated in 29%, dilated in 14%; eccentric hypertrophy, nondilated in 12%, dilated in 20%.

Consequences

Even without LVH, hypertensives may have a significantly reduced coronary flow reserve from an impaired capacity for coronary vasodilation (Kawecka-Jaszcz et al., 2008). The presence of LVH is consistently and strongly related to subsequent cardiovascular morbidity and mortality (Krakoff, 2013). The increased risk for sudden death in hypertensives is likely connected to alterations in ventricular conduction and repolarization associated with LVH (Oikarinen et al., 2004).

Regression

Regression of LVH was noted in 52% of the 937 hypertensives treated for 4.8 years in the LIFE study (Gerdtts et al., 2008). Regression reduces the risk of stroke (Verdecchia et al., 2006). The effects of various antihypertensive agents are covered in Chapter 7.

Systolic and Diastolic Dysfunction

de Simone et al. (2004) use the term “inappropriate” left ventricular mass (LVM) when the LVM exceeds the theoretical value predicted by gender, body size, and stroke work. Such excessive LVM translates into concentric LV geometry and both systolic and diastolic dysfunction that, in turn, are the predecessors for systolic and diastolic heart failure. Patients with asymptomatic LV systolic dysfunction are at increased risk of heart

failure and death, even with only mildly reduced ejection fractions (Verdecchia et al., 2005). Similarly, diastolic dysfunction, defined as an echocardiographic normal ejection fraction but abnormal LV filling in an asymptomatic hypertensive with LVH, is a precursor to diastolic heart failure (Aurigemma & Gaasch, 2004).

Congestive Heart Failure

Hypertension is present in over two-thirds of patients who develop CHF (Yancy et al., 2006). Hypertension remains the major preventable factor in the disease that is now the leading cause of hospitalization in the U.S. for adults over age 65 (Hall et al., 2012). It is likely that antihypertensive drugs used in treatment do not completely prevent CHF but postpone its development by several decades and are responsible for the improved survival in CHF (Roger et al., 2004).

Most episodes of CHF in hypertensive patients are associated with diastolic dysfunction, as reflected in a preserved ejection fraction (Bursi et al., 2006) (Table 4-4). Vasani and Benjamin (2001) explain the susceptibility of hypertensives, particularly those with LVH, to diastolic heart failure in this manner:

When hemodynamically challenged by stress (such as exercise, tachycardia, increased afterload, or excessive preload), persons with hypertension are unable to increase their end-diastolic volume (i.e., they have limited preload reserve), because of decreased LV relaxation and compliance. Consequently, a cascade begins, in which the LV end-diastolic BP rises, left atrial pressure increases, and pulmonary edema develops.

Management of CHF in hypertensive patients is covered in Chapter 7.

TABLE 4-4

Characteristics of Patients with Systolic or Diastolic Heart Failure

Characteristics	Systolic Heart Failure	Diastolic Heart Failure
Age	All ages, typically 50–70 y	Frequently elderly
Sex	More often male	Frequently female
Left ventricular ejection fraction	Depressed, approximately 40% or lower	Preserved or normal, 40% or higher
Left ventricular cavity size	Usually dilated	Usually normal, often with concentric LVH
LVH on electrocardiography	Sometimes present	Usually present
Chest radiography	Congestion and cardiomegaly	Congestion with or without cardiomegaly
Gallop rhythm present	Third heart sound	Fourth heart sound

Coronary Heart Disease

As described in Chapter 1, hypertension is quantitatively the largest risk factor for CHD. The development of myocardial ischemia reflects an imbalance between myocardial oxygen supply and demand. Hypertension, by reducing the supply and increasing the demand, can easily tip the balance.

Clinical Manifestations

Hypertension may play an even greater role in the pathogenesis of CHD than is commonly realized for two reasons. First, hypertensives suffer more silent ischemia (Boon et al., 2003) and painless MI (Kannel et al., 1985) than do normotensives. Second, preexisting hypertension may go unrecognized in patients first seen after an MI. Although acute rises in BP may follow the onset of ischemic pain, the BP often falls immediately after the infarct if pump function is impaired.

Once an MI occurs, the prognosis is worsened in the presence of both preexisting and subsequent hypertension (Thune et al., 2008). On the other hand, an increase in post-MI mortality has been noted among those with acute coronary syndrome and systolic pressure below 120 mm Hg on admission (Lee et al., 2013).

Atrial Fibrillation

In the presence of atrial fibrillation, more BP measurements are needed to ascertain the level of BP (Pagonas et al., 2013). The likelihood of atrial fibrillation increases with increasing age, levels of BP, LVM, and left atrial diameter. When present, atrial fibrillation increases the risk of intracranial bleeding during anti-thrombotic therapy (Manolis et al., 2013). The risk of atrial fibrillation was reduced by over 60% in hypertensives who were adequately treated (Young-Xu & Ravid, 2004).

Aortic Stenosis

Among 193 patients with symptomatic aortic stenosis, hypertension was present in 32% and the additional workload was likely responsible for symptoms developing at larger valve areas and lower stroke work loss (Antonini-Canterin et al., 2003). On the other hand, the severity of aortic stenosis may be masked by the presence of coexisting hypertension (Kaden & Haghi, 2008). In those with systemic hypertension and low gradient severe aortic stenosis with preserved ejection

fraction, vasodilating antihypertensive therapy provided significant improvement (Eleid et al., 2013).

Large-Vessel Disease

Abdominal Aortic Aneurysm

The incidence of abdominal aortic aneurysms is increasing, likely as a consequence of the increasing number of elderly people who carry cardiovascular risks from middle age (Rodin et al., 2003). Since hypertension is one of these risk factors, onetime ultrasonographic screening is recommended for men over age 65 who have ever smoked (Earnshaw et al., 2004).

Aortic Dissection

As many as 80% of patients with aortic dissection have hypertension (Golledge & Eagle, 2008). The mechanism of dissection likely involves the combination of high pulsatile wave stress and accelerated atherosclerosis. The higher the pressure, the greater the likelihood of dissection.

Aortic dissection may occur either in the ascending aorta (proximal, or type A), which usually requires surgery, or in the descending aorta (distal, or type B), which usually can be treated medically (Golledge & Eagle, 2008). Hypertension is more frequently a factor with distal dissections, whereas Marfan syndrome, Ehlers-Danlos syndrome, and cystic medial necrosis are seen more frequently with the proximal lesion (Patel & Deeb, 2008).

Peripheral Vascular Disease

The presence of symptomatic PVD, usually manifested by intermittent claudication, poses a high risk of subsequent cardiovascular mortality (Arain & Cooper, 2008). By measurement of the ankle-brachial BP index (ABI) with a Doppler device, PVD was identified in 4.3% of U.S. adults over age 40, more frequently in those who were older, black, diabetic, smoker, or hypertensive (Selvin & Erlinger, 2004). Computerized tomographic angiography is the best procedure to establish the presence of PVD (Wennberg, 2013).

Takayasu Arteritis

Hypertension is present in nearly half of patients with Takayasu disease, an idiopathic, chronic inflammatory disease of large arteries that is reported most frequently in Japan and India (Weaver et al., 2004).

Carotid Artery Disease

The presence of a bruit over the carotid artery is indicative of twice the risk of MI and cardiovascular mortality compared with people who do not have a bruit (Pickett et al., 2008).

Increased carotid intima–media thickness is commonly used as a surrogate for hypertensive vascular disease and predicts the occurrence of ischemic strokes (Prati et al., 2008).

Cerebrovascular Disease

Stroke is the second leading cause of death worldwide, the leading cause of permanent neurologic disability in adults, and the most common indication for use of hospital and chronic care home beds (Donnan et al., 2008). The stroke death rate is even higher among blacks who live in the southeastern U.S., a rate similar to that noted in numerous other groups with inadequate health care worldwide (Donnan et al., 2008). Mortality rates from stroke have fallen markedly from the 1950s to the present in most industrialized countries, attributable to improved control of risk factors including hypertension (Towfighi & Saver, 2011). However, the incidence of stroke will likely continue to increase largely related to the increasing number of elderly people (Ovbiagele et al., 2013).

Role of Hypertension

Even more than with heart disease, hypertension is the major cause of stroke. About 50% of strokes are attributable to hypertension, the risk rising in tandem with increasing BP (Beauchet et al., 2013). Hypertensives are at three to four times greater risk for stroke and those with BP above 130/85 at 1.5 times greater risk than are normotensives. Beyond stroke, hypertension is associated with an increase in the incidence of dementia, both vascular and Alzheimer's (Faraco & Iadecola, 2013).

In hypertensives, nearly 80% of strokes are ischemic, caused by either arterial thrombosis or embolism, 15% are caused by intraparenchymal hemorrhage, and another 5% are caused by subarachnoid hemorrhage (Donnan et al., 2008). Transient ischemic attacks—acute episodes of focal loss of cerebral or visual function lasting less than 24 hours and attributed to inadequate blood supply—may arise from emboli from atherosclerotic plaques in the carotids or thrombi in the heart (Flemming et al., 2004) and are followed by a high risk of stroke (Daffertshofer et al., 2004).

ISH in the elderly is associated with a 2.7 times greater incidence of strokes than is seen in normotensive people of the same age (Qureshi et al., 2002). Elderly hypertensives more often have silent cerebrovascular disease (Vermeer et al., 2002) and cerebral white matter lesions on MRI (Verhaaren et al., 2013), which eventually may lead to brain atrophy and vascular dementia.

Brain microbleeds have been found in 15% of hypertensive patients, particularly in those with nocturnal hypertension detected by ambulatory monitors (Henskens et al., 2008). A widening pulse pressure during sleep is associated with a significantly increased risk of stroke (Kario et al., 2004), presumably reflecting the role of arterial stiffness (Laurent et al., 2003).

Whether hypertensive or normotensive before their stroke, the majority of stroke patients at the time they are first seen will have a transient elevation of BP that spontaneously falls within a few days (Venimos et al., 2004). Therefore, caution is advised in lowering the BP in the immediate poststroke period, as noted further in Chapter 7. On the other hand, as will be noted, long-term reduction of BP is the most effective protection against both initial and recurrent strokes (Donnan et al., 2008).

Cognitive Impairment and Dementia

Both high and low BPs are associated with impaired cognition even in the absence of clinically evident cerebrovascular disease (Birns & Kalra, 2009). A similar nonlinear relation has been noted with pulse pressure: Both excessively wide pulse pressure (reflecting arterial stiffness) and narrow pulse pressure (reflecting reduced cerebral perfusion) are associated with increased risk for Alzheimer disease and dementia (Qiu et al., 2003).

Renal Disease

Hypertension plays an important role in renal damage, whether manifested as proteinuria, reduced glomerular filtration rate (GFR), or progression to ESRD (Cozzolino et al., 2013).

Assessment

Microalbuminuria is widely recognized to be an early manifestation of renal damage from any cause (Cirillo et al., 2008). Even albumin levels below 30 mg/L or an albumin-to-creatinine ratio below 20 mg/g have been found to accompany and predict hypertension

and CVDs (Danziger, 2008). The presence of microalbuminuria likely reflects the presence of hypertension since it has been noted even in prehypertensives without diabetes or atherosclerotic vascular disease (Hsu et al., 2009).

Estimated glomerular filtration rate (eGFR) based on formulas including serum creatinine is increasingly being used as an indicator of renal damage, independent of microalbuminuria but additive to its presence as predictors of cardiovascular risk (Hallan et al., 2007). *Serum cystatin C* levels, both in absolute terms and as a replacement for serum creatinine to estimate GFR may be used to assess renal function. Cystatin C is a protein that is freely filtered by the glomerulus but largely reabsorbed or catabolized by the tubular epithelial cells. Since its level is not dependent on muscle mass, it may be a better maker of renal function than serum creatinine (Bloomfield et al., 2013).

Consequences

As more extensively described in Chapter 9, conventional beliefs have linked hypertension and chronic kidney disease (CKD) as a two-way street: Hypertension causes CKD and CKD causes hypertension. A commonly accepted sequence for hypertension causing CKD is a loss of renal autoregulation, which normally attenuates the transmission of increased systemic pressure to the glomeruli (Bidani & Griffin, 2004). As a consequence, patients with renal damage have an increased risk of both progressive renal dysfunction and CVDs (Färbon et al., 2008). Moreover, reduction of BP can slow if not stop the progression of renal diseases and accompanying cardiovascular events (Blood Pressure Lowering Treatment Trialists' Collaboration, 2013).

In the past, the progress of hypertension into CKD has been termed “hypertensive nephrosclerosis,” and this diagnosis was considered the second most common cause of CKD, below diabetic nephropathy. However, a common missense mutation in the *APOL1* gene, originally attributed to the nearby *MYH9* gene (Kao et al., 2008; Kopp et al., 2008), has been found in blacks from either south or west Africa (Skorecki & Wasser, 2013) and closely correlated with progression of renal disease (Parsa et al., 2013).

These findings have important clinical applications. In the African American Study of Kidney Disease and Hypertension (AASK) and Chronic Renal Insufficiency Cohort (CRIC) studies, intensive lowering of BP did not slow the progression of renal damage

(Parsa et al., 2013). Renal risk variants in *APOL1* were associated with the higher rates of ESRD and progression of CKD in the black patients in these two studies. The manner by which these genetic mutations contribute to hypertension and CRD remains unknown.

NATURAL HISTORY OF SPECIAL POPULATIONS

Before turning to evaluation, we describe groups of people whose hypertension, for various reasons, may follow a different course from that seen in the predominantly male, white, middle-aged populations observed in most clinical trials and long-term observational studies. These special groups include a major part of the hypertensive population: The elderly, women, blacks and other ethnic groups, diabetics, and the obese.

Elderly

Two patterns of hypertension are seen in the elderly: Combined systolic and diastolic—the carryover of primary (essential) hypertension common to middle age and ISH—the more frequent form in those over age 60. However, because the major consequences and, as is noted in Chapter 7, the therapy for both are quite similar, most of this discussion will not make a distinction between the two.

Prevalence of Hypertension

As noted in Chapter 1, whereas diastolic BPs tend to plateau before age 60 and drop thereafter, systolic BPs rise progressively. Therefore, the incidence of ISH—defined as systolic pressure of 140 mm Hg or more and diastolic pressure of 90 mm Hg or less—progressively rises with age. In the National Health and Nutrition Examination Survey III, the proportion of various types of hypertension seen with advancing age progressively shifted from diastolic and combined hypertension to ISH (Franklin et al., 2001). In those older than 60 years, ISH was the pattern of hypertension in 87% of those who were untreated. In Framingham, nearly half of those who developed ISH did not have antecedent diastolic hypertension and only 29% had a prior diastolic level of 95 mm Hg or higher (Franklin et al., 2005). Almost 90% of Framingham subjects who were normotensive at age 55 or 65 developed hypertension 20 years later (Vasan et al., 2002).

Risks of Hypertension

As seen in Table 4-3 in the data from the placebo-treated half of the elderly patients enrolled in eight RCTs over the last 20 years, mortality in elderly hypertensives is significant, particularly from strokes, even in the brief 2- to 5-year interval of these trials. As noted, the patients enrolled tend to be healthier than the general population, so the risks of both combined systolic–diastolic and ISH are even greater than shown in Table 4-3.

A different pattern appears in the very elderly who have more chronic debility. In the subjects aged 75 to 94 years followed up in the Framingham study, risks for all-cause and cardiovascular mortality increased at the lower levels of systolic BP (<120 mm Hg) (Kannel et al., 1997).

In addition to increased mortality seen with either low or high systolic BP in the very elderly, both are associated with the development of cognitive impairment (Waldstein et al., 2005).

Pathophysiology of Isolated Systolic Hypertension

The basic mechanism for the usual progressive rise in systolic BP with age is the loss of distensibility and elasticity in the large capacitance arteries, a process that was nicely demonstrated more than 75 years ago (Hallock & Benson, 1937) (Fig. 4-6). Increasing volumes of saline were infused into the tied-off aortas taken from patients at death whose ages ranged from the 20s to the 70s. The pressure within the aortas from the elderly subjects rose much higher with small increases in volume as compared to that in aortas from the younger subjects, reflecting the rigidity of the vessels.

Subsequently, the progressive rise in systolic pressure with age has been found to reflect a reduced cross-sectional area of the peripheral vascular bed and stiffer aorta and large arteries, producing an increased pulse wave velocity and an early return of pulse wave reflection in systole (Safar & Benetos, 2003). The early return of the reflected pressure wave augments aortic pressure throughout systole, increasing both systolic and pulse pressures, further increasing the work of the left ventricle while decreasing the diastolic aortic pressure that supports coronary blood flow (Pierini et al., 2000).

Postural Hypotension

As is covered in Chapter 7, therapy of hypertension in the elderly is vital but oftentimes must be tempered by

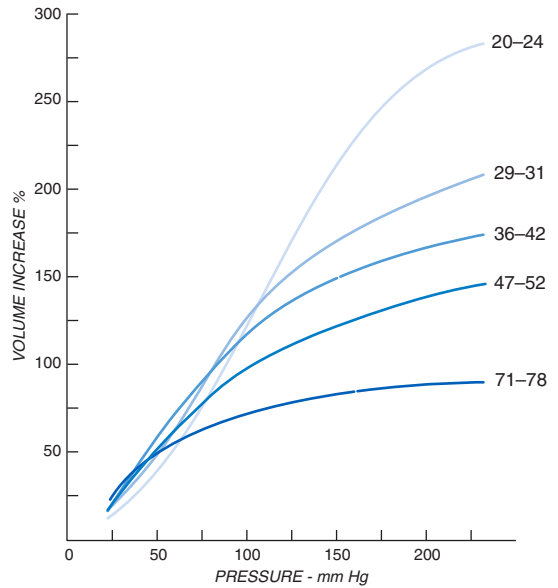


FIGURE 4-6 • Curves showing the relation of the percentage of increase in pressure to the increase in volume infused into aortas excised at autopsy from people in five different age groups. The curves were constructed from the mean values obtained from a number of aortas. (Reprinted from Hallock P, Benson IC. Studies of the elastic properties of human isolated aorta. *J Clin Invest* 1937;16:595–602.)

the need first to overcome coexisting postural hypotension, defined as a fall in systolic pressure of 20 mm Hg or more after 1 minute of quiet standing.

Although there are multiple, mainly neurologic, causes for this problem (Ejaz et al., 2004), the only predisposing factor for postural hypotension found in an unselected elderly population was hypertension (Räihä et al., 1995). As seen in Figure 4-7, the higher the basal supine systolic BP, the greater was the tendency for a postural fall (Lipsitz et al., 1985).

Mechanism

Normal aging is associated with various changes that may lead to postural hypotension. The two most common changes are venous pooling in the legs and reduced baroreceptor sensitivity (Jones et al., 2003). Even though elderly hypertensives have intact baroreceptor modulation of sympathetic nerve traffic, they have marked impairment of baroreceptor control of heart rate and of cardiopulmonary reflex control of the peripheral circulation (Grassi et al., 2000). In addition, splanchnic pooling of blood after eating may lead to profound postprandial hypotension (Puisieux et al., 2000).

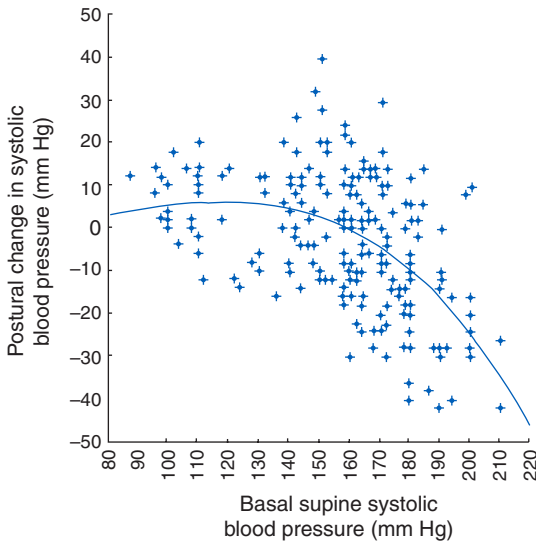


FIGURE 4-7 • Relationship between basal supine systolic blood pressure and postural change in systolic blood pressure for aggregate data from older subjects. (Modified from Lipsitz LA, Storch HA, Minaker KL, et al. Intra-individual variability in postural BP in the elderly. *Clin Sci* 1985;69:337-341.)

Women

Before age 50, women have a lower prevalence of hypertension than do men, but, after age 55, women have a greater age-related increase in proximal aortic stiffness, which leads to a higher incidence of systolic hypertension in older women (Pemu & Ofili, 2008). In addition, women have two other features that tend to lower diastolic BP and widen pulse pressure: First, shorter stature that causes a more rapid return of the pulse wave to augment the peak systolic pressure; second, a faster heart rate that induces a shorter diastolic period (Safar & Smulyan, 2004).

Although women at all ages have a lower incidence of heart attacks and strokes than do men, they maintain a strong, continuous, and linear association between systolic BP and cardiovascular events (Mason et al., 2004).

Blacks

Death from hypertension is the single most common reason for the higher mortality rate for blacks than for nonblacks in the U.S. (Minor et al., 2008). Blacks have more hypertension and suffer more from it, at least in part because of their lower socioeconomic status that results in reduced access to health care (Jha et al., 2003) and poorer nutrition (Stamler et al., 2013) along with a common genetic missense mutation

(Parsa et al., 2013). If appropriate therapy is provided, much of their excessive morbidity and mortality related to hypertension can be relieved.

Prevalence of Hypertension

The higher BP levels in U.S. blacks begin during childhood and adolescence and are established by early adulthood (Berenson et al., 2011). Most of the higher BPs in young blacks are attributed to a larger body weight and size (Toprak et al., 2009). In middle age, blacks and whites have similar incidences of hypertension given the same baseline BP and BMI (He et al., 1998). However, hypertension in blacks is a greater risk factor for coronary disease, strokes, and in particular, ESRD than in whites (Minor et al., 2008). In most studies, blacks have higher sleeping BPs, as recorded by ambulatory monitoring (Harshfield et al., 2002a,b).

Pathophysiology of Hypertension

There are numerous genotypic and phenotypic features found in black hypertensives that may explain their higher prevalence and greater degree of target organ damage. In particular, a common missense mutation in the *APOL1* gene, originally attributed to the nearby *MYH9* gene, has been found in a large percentage of blacks from southern and western Africa (Skorecki & Wasser, 2013). The *APOL1* alleles provided a past survival advantage by their association with protection from trypanosis. Those blacks with two alleles have been shown to have a high prevalence of hypertension and progression of CKD (Parsa et al., 2013).

Whatever else is responsible, poverty, racial discrimination, and barriers to health care obviously are involved in the higher hypertension-related morbidity and mortality seen among U.S. blacks (Jha et al., 2003). Stress and nutrition are involved.

Stress

As described in Chapter 3, there is an association between the stresses of low socioeconomic status and hypertension. A good example of the likely interaction between low socioeconomic status and a genetic trait is the finding that BP levels were significantly associated with darker skin color but only in those blacks in the lower levels of socioeconomic status (Klag et al., 1991).

Diet

Particularly among older black women, the higher prevalence of hypertension is clearly correlated with obesity (Minor et al., 2008). Although they have greater pressure sensitivity to sodium (Palacios et al., 2004), blacks do not appear to ingest more sodium than do nonblacks (Ganguli et al., 1999). However, their intake of both potassium and calcium is lower (Langford & Watson, 1990), they have more unprovoked hypokalemia (Andrew et al., 2002), and lower urinary potassium excretion apparently more than attributable to their lower intake of potassium (Turban et al., 2008).

Complications of Hypertension

Hypertension is not only more common in blacks but is also more severe, less well managed, and, therefore, more deadly. As best as can be ascertained, blacks at any given level of BP do not suffer more vascular damage than do nonblacks; rather, they display a shift to the right of the BP distribution, yielding a higher overall prevalence and a higher proportion of severe disease (Cooper et al., 1996). The only apparent exception is the much higher rate of ESRD in blacks as described under “Renal Disease” earlier in this chapter.

Other Ethnic Groups

Much less is known about the special characteristics of other ethnic groups as compared to blacks in the U.S., so only a few generalizations will be made about them.

Primitive Versus Industrialized Environment

People of any race living a rural, more primitive lifestyle tend to ingest less sodium, remain less obese, and have less hypertension. When they migrate into urban areas and adapt more modern lifestyles, they ingest more sodium, gain weight, and develop more hypertension (Cooper et al., 1999). Rather dramatic changes in the prevalence of hypertension and the nature of cardiovascular complications have been seen when formerly isolated ethnic groups move to an industrialized environment, as seen among South Asians who move to England (Khattar et al., 2000).

Persistence of Ethnic Differences

Although environmental changes often alter BP and other cardiovascular traits, some ethnic groups preserve

characteristics that presumably reflect stronger genetic influences. Examples include Bedouins in Israel (Paran et al., 1992) and Native Americans in the U.S. (Howard, 1996). In the U.S., Hispanics, particularly Mexican Americans, have a lesser prevalence of hypertension, despite their high prevalence of obesity, diabetes, and insulin resistance (Aranda et al., 2008).

Diabetes and Hypertension

The combination of diabetes and hypertension poses a major public health challenge, both increasing in incidence as the population grows older and fatter.

- Whereas the number of adults with overt diabetes in the U.S. is estimated to be 26 million, the number with prediabetes is estimated to be 79 million (Lee et al., 2012).
- Seventy-one percent of U.S. adult diabetics have hypertension (Geiss et al., 2002), and a significant number of hypertensives have unrecognized diabetes (Salmasi et al., 2004).
- Coexisting diabetes and hypertension are associated with greater degrees of arterial stiffness (Tedesco et al., 2004) leading to earlier rises in systolic and pulse pressures (Ronnback et al., 2004), the pattern of accelerated arterial aging.
- The presence of diabetes, either type 1 (Knerr et al., 2008) or type 2 (Mazzone et al., 2008) and even prediabetes increase the rate of atherosclerotic CVDs, including stroke (Lee et al., 2012).
- The microvascular complications of diabetes are also accelerated by hypertension, retinopathy in particular (Gallego et al., 2008).
- Even intensive combined control of both hypertension and diabetes has not been found to prevent microvascular complications (Ismail-Beigi et al., 2012), reinforcing the necessity of lifestyle modifications described in Chapter 6.

Obesity and Hypertension

Even in the absence of type 2 diabetes, obesity is one of the most common factors responsible for hypertension (Schlaich et al., 2009). In the National Health and Nutrition Examination Survey III, a progressive increase in the prevalence of hypertension was seen with increasing BMI at all ages (Thompson et al., 1999) (Fig. 4-8). The prevalence is increased further when obesity is predominantly abdominal (Allemann et al., 2001).

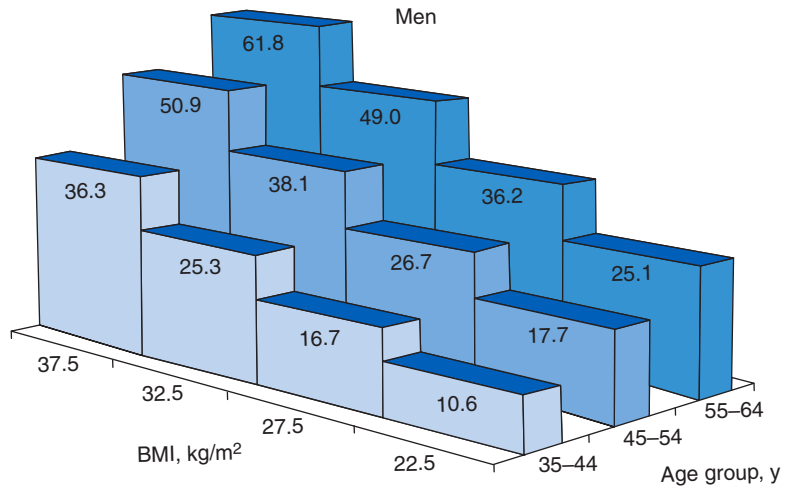


FIGURE 4-8 • Estimated risk (%) of hypertension by age group and body mass index (BMI) among men in the National Health and Nutrition Examination Survey III. (Modified from Thompson D, Edelsberg J, Colditz GA, et al. Lifetime health and economic consequences of obesity. *Arch Intern Med* 1999;159:2177–2183.)

ALTERING THE NATURAL HISTORY

Now that the possible mechanisms, natural history, major consequences, and special populations of untreated primary hypertension have been covered, an additional word about prevention is in order.

Most efforts to alter the natural history of hypertension involve both nondrug and drug therapies of existing disease. However, attempts to *prevent* hypertension must also be more widely promoted and followed. Without knowledge of the specific causes of this disease, no single preventive measure can be promoted with the assurance that it will work. However, to insist that specific causes be known before prevention is attempted is akin to saying that John Snow should not have closed the pump because he had no proof that *Vibrio cholera* organisms were the cause of death in those who drank the polluted water. The preventive measures likely to help—moderation in sodium intake, reduction of obesity, maintenance of physical conditioning, avoidance of stress, and greater attention to the other coexisting risk factors for premature CVD—will do no harm and may do a great deal of good.

Their value has been proved for prevention of diabetes (Diabetes Prevention Program Research Group, 2002; Tuomilehto et al., 2001) and supported for prevention of hypertension (Whelton et al., 2002). Nonetheless, with recognition of the difficulty of changing lifestyle habits, trials of antihypertensive drugs have been conducted to prove that they can at least slow, if not stop, the inexorable progress of hypertension (Julius et al., 2006; Luders et al., 2008;

Skov et al., 2007), but they have not shown that brief periods of therapy in middle-aged patients with stage 1 hypertension will relieve hypertension.

EVALUATION OF THE HYPERTENSIVE PATIENT

Having examined the natural history of various hypertensive populations, we now incorporate these findings into a game plan for evaluating the individual hypertensive patient.

There are three main reasons to evaluate patients with hypertension: (a) To determine the type of hypertension, specifically looking for identifiable causes; (b) to assess the impact of the hypertension on target organs; and (c) to estimate a patient's overall risk profile for the development of premature CVD. Such evaluation can be accomplished with relative ease and should be part of the initial examination of every newly discovered hypertensive. The younger the patient and the higher the BP, the more intensive the search for identifiable causes should be. Among middle-aged and older persons, greater attention should be directed to the overall cardiovascular risk profile, as these populations are more susceptible to immediate complications.

History

The patient history should focus on the duration of the elevated BP and any prior treatment, the current use of various drugs that may cause it to rise, and symptoms of target organ dysfunction (Table 4-5). Attention

TABLE 4-5

Important Aspects of the Patient's History

Duration of the hypertension	Presence of other risk factors
Last known normal BP	Smoking
Course of the BP	Diabetes
Prior treatment of the hypertension	Dyslipidemia
Drugs: types, doses, side effects	Physical inactivity
Intake of agents that may interfere	Concomitant diseases
Nonsteroidal anti-inflammatory drugs	Dietary history
Oral contraceptives	Weight change
Sympathomimetics	Fresh vs. processed foods
Adrenal steroids	Sodium
Excessive sodium intake	Saturated fats
Alcohol (>2 drinks/day)	Sexual function
Herbal remedies	Features of sleep apnea
Family history	Early morning headaches
Hypertension	Daytime somnolence
Premature CVD or death	Loud snoring
Familial diseases: pheochromocytoma,	Erratic sleep
renal disease, diabetes, gout	
Symptoms of secondary causes	Ability to modify lifestyle and maintain therapy
Muscle weakness	Understanding the nature of hypertension and
Spells of tachycardia, sweating, tremor	the need for regimen
Thinning of the skin	Ability to perform physical activity
Flank pain	Source of food preparation
Symptoms of target organ damage	Financial constraints
Headaches	Ability to read instructions
Transient weakness or blindness	Need for care providers
Loss of visual acuity	
Chest pain	
Dyspnea	
Edema	
Claudication	

should also be directed toward the patient's psychosocial status, including the willingness to make necessary changes in lifestyle and to take medication. An area of great importance is sexual dysfunction, often neglected until it arises after antihypertensive therapy is given. Erectile dysfunction, often attributed to antihypertensive drugs, may be present in as many as one-third of untreated hypertensive men and is most likely related to their underlying vascular disease (see Chapter 7).

A positive family history of hypertension is common, particularly in families with multiple affected members (Westerdahl et al., 2013).

Anxiety-Related Symptoms

Many of the symptoms described by hypertensives, such as bandlike headaches, dizziness and light-headedness, fatigue, palpitations, and chest discomfort,

reflect recurrent hyperventilation, a common problem among all patients (DeGuire et al., 1992) particularly among hypertensives who are anxious over their diagnosis and its implications (Kaplan, 1997). Anxiety and panic attacks are even more common among patients who had nonspecific intolerance to multiple antihypertensive drugs (Davies et al., 2003).

The situation is similar for symptoms of depression. Symptoms of depression (and anxiety) were not found to be more common prior to the onset of hypertension (Shinn et al., 2001) but were more common after the diagnosis was made (Scherrer et al., 2003).

Headache

In cross-sectional surveys, headache is among the most common of the symptoms that are reported (Middeke et al., 2008). These headaches had usually

been attributed to the psychological stress of having the “silent killer” (Friedman, 2002). However, data from prospective randomized placebo-controlled trials (RCTs) show that the prevalence of headache is often reduced when BP is lowered, irrespective of the drugs used to lower the BP (Law et al., 2005). It should be noted that sleep apnea is common among even minimally obese hypertensives, as described in Chapter 14, so early morning headaches may reflect not hypertension but nocturnal hypoxia.

Nocturia

Nocturia is more common in hypertensives, often the consequence of coexisting benign prostatic hypertrophy (Blanker et al., 2000) or simply a decreased bladder capacity (Weiss & Blaivas, 2000). At least theoretically, the altered pressure–natriuresis relationship described in Chapter 3 could delay urinary excretion, and a loss of concentrating ability may be an early sign of renal impairment.

Physical Examination

The physical examination should include a careful search for damage to target organs and for features of various identifiable causes (Table 4-6). Waist circumference should be measured, because values exceeding 88 cm (35 in.) in women and 102 cm (40 in.) in men are indicative of abdominal obesity and the metabolic syndrome (Wilson & Grundy, 2003) and serve as a cardiovascular risk factor independent of weight (Malik et al., 2004).

TABLE 4-6

Important Aspects of the Physical Examination

Accurate measurement of BP
 General appearance: distribution of body fat, skin lesions, muscle strength, alertness
 Funduscopy
 Neck: palpation and auscultation of carotids, thyroid
 Heart: size, rhythm, sounds
 Lungs: rhonchi, rales
 Abdomen: renal masses, bruits over aorta or renal arteries, femoral pulses, waist circumference
 Extremities: peripheral pulses, edema
 Neurologic assessment, including cognitive function

A heart rate of 80 or higher is more common in hypertensives and is a risk factor for CVD (Palatini, 2011).

Funduscopy Examination

Only in the optic fundi can small blood vessels be seen with ease, but this requires dilation of the pupil, a procedure that should be more commonly practiced using a short-acting mydriatic such as 1% tropicamide. Such routine funduscopy can portray the major changes of hypertensive retinopathy (Fig. 4-9) (Ong et al., 2013). However, recognition of the more subtle early changes that may appear even before hypertension is manifest requires digitized retinal photography (Sng et al., 2013).

The retinal changes have been most logically classified by Wong and Mitchell (2004) (Table 4-7). The changes progress from the initial arterial narrowing to sclerosis and then to hemorrhages and exudates, as shown in Figure 4-9. The striking association of retinal signs with the risk of stroke (Ong et al., 2013) makes a careful retinal exam an essential part of the initial evaluation of every hypertensive with follow-up exams as indicated.

Laboratory Tests

Routine Laboratory Testing

For most patients, a hematocrit, urine analysis (including microscopic exam and dipstick for proteinuria), automated blood chemistry (glucose, creatinine, electrolytes), uric acid and calcium, lipid profile (LDL and HDL cholesterol, triglycerides), and a 12-lead electrocardiography are all the routine procedures needed (Fig. 4-10) (Mancia et al., 2013). The blood is best obtained after an overnight fast to improve the diagnostic accuracy of the glucose and triglyceride levels. None of these usually yields abnormal results in the early, uncomplicated phases of primary hypertension, but they should always be obtained for a baseline. The serum creatinine or cystatin C should be used, along with the patient’s age, gender, and weight, to estimate the GFR (Matsushita et al., 2012). However, an estimated GFR below 60 need not be indicative of chronic renal disease in elderly patients and should be repeated and followed (Moynihan et al., 2013).

Additional Tests

A number of additional tests have been recommended in the 2013 European guidelines “based on the history,

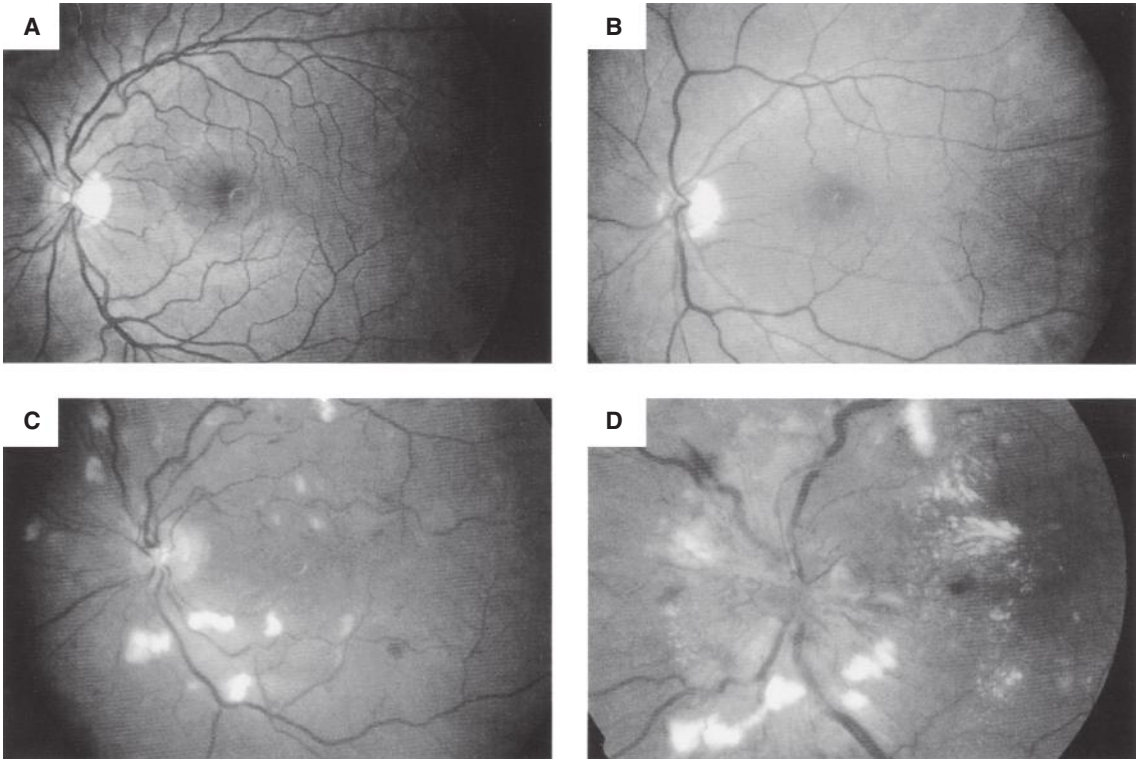


FIGURE 4-9 • Retinal photographs of progressively more severe hypertensive retinopathy. **A and B:** Grade A (nonmalignant). **C and D:** Grade B (malignant). (From Pache M, Kube T, Wolf S, et al. Do angiographic data support a detailed classification of hypertensive fundus changes? *J Hum Hypertens* 2002;16:405–410.)

physical examination, and findings from routine laboratory tests” (Mancia et al., 2013) (Table 4-8). As previously noted, funduscopy should be routine and, as described in Chapter 2, home BP monitoring should become routine. On the other hand, measurement of pulse wave velocity remains an investigational

procedure, and the remainder of these additional tests are recommended only if the history, physical exam, and routine lab tests support their need.

There are two reasons that additional testing should be limited. First, analyses of other commonly performed laboratory tests show surprisingly high costs

TABLE 4-7

Classification of Hypertensive Retinopathy

Grade of Retinopathy	Retinal Signs	Systemic Associations
None	No detectable signs	None
Mild	Generalized arteriolar narrowing, focal arteriolar narrowing, arteriovenous nicking, opacity (“copper wiring”) of arteriolar wall, or a combination of these signs	Modest association with risk of stroke, CHD, and death
Moderate	Hemorrhage (blot, dot, or flame-shaped), microaneurysm, cotton-wool spot, hard exúdate, or a combination of these signs	Strong association with risk of stroke, cognitive decline, and death from cardiovascular causes
Malignant	Signs of moderate retinopathy plus bilateral swelling of the optic disk	Strong association with death

Modified from Wong TY, Mitchell P. Hypertensive retinopathy. *N Engl J Med* 2004;351:2310–2317.

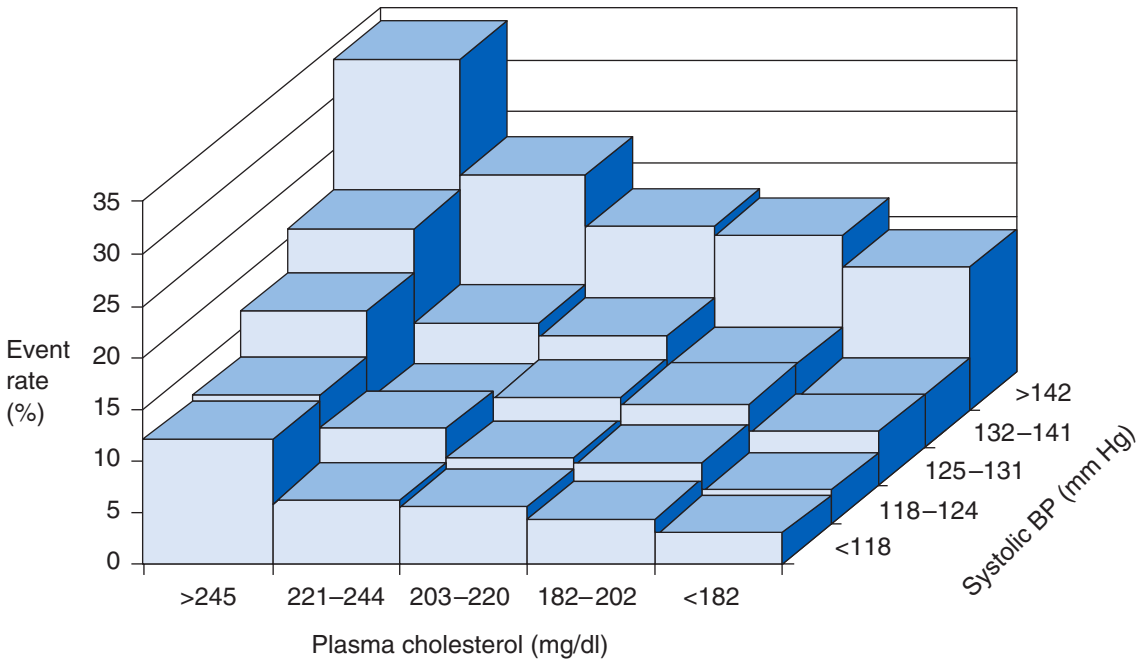


FIGURE 4-10 • The associations between systolic BP, plasma cholesterol, and mortality from CHD over an average 12-year follow-up among the 316,099 men screened for the Multiple Risk Factor Intervention Trial (MRFIT). (Data adapted from Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: Overall findings and differences by age for 316,099 white men. *Arch Intern Med* 1992;152:56–64.)

for one quality-adjusted life year (Boulware et al., 2003). More detailed analyses of the value of diagnostic testing have been recommended (Ferrante di Ruffano et al., 2012). As health care costs continue to rise, clinicians must be aware of the true costs of what they

often do to individual patients at a relatively small cost when these costs are applied to large populations.

The second reason why testing should be limited is the likelihood of false-positive results, particularly in patients with a low likelihood of having the condition being tested for. In such patients, a positive test result would more likely be a false positive rather than a true positive. Therefore, repeat and additional, ever-more expensive procedures would need to be done to rule out the diagnosis.

The bottom line is that individual practitioners dealing with individual patients should use testing selectively, recognizing both their hidden costs and their potential for false-positive results that mandate additional tests. Obviously, some tests such as blood glucose and lipids may be justified because they are needed for overall risk assessment; others for uncovering target organ damage, such as an ECG or an analysis for albuminuria. But additional tests should be reserved for recognition of conditions that can be helped by available therapies.

TABLE 4-8

Additional Tests Based on History, Physical Examination, and Findings from Routine Laboratory Tests

- Hemoglobin A_{1c} (if fasting plasma glucose is >5.6 mmol/L (102 mg/dL) or previous diagnosis of diabetes)
- Quantitative proteinuria (if dipstick test is positive)
- Urinary potassium and sodium concentration and their ratio
- Home and 24-h ambulatory BP monitoring
- Echocardiogram
- Holter monitoring in case of arrhythmias
- Carotid ultrasound
- Peripheral artery/abdominal ultrasound
- Pulse wave velocity
- Ankle-brachial index
- Funduscopy

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Search for Identifiable Causes

The frequencies of various identifiable causes of hypertension are quite low in the overall population with mild, asymptomatic hypertension. Nonetheless,

TABLE 4-9

Features of “Inappropriate” Hypertension

- Age of onset: <20 or >50 y
- Level of BP: >180/110 mm Hg
- Organ damage
 - Funduscopy grade II or beyond
 - Serum creatinine >1.5 mg/dL
 - Cardiomegaly or LVH as determined by electrocardiography
- Presence of features indicative of secondary causes
 - Unprovoked hypokalemia
 - Abdominal bruit
 - Variable pressures with tachycardia, sweating, tremor
 - Family history of renal disease
- Poor response to generally effective therapy

clues to the presence of an identifiable cause should be sought in the routine evaluation of every new hypertensive. If suggestive clues are found or if the patient has features of “inappropriate” hypertension (Table 4-9), additional workup for an identifiable cause should be performed.

The studies listed in Table 4-10 as initial usually will serve as adequate screening procedures and are usually available to every practitioner. If they are abnormal, the listed additional procedures should be performed, perhaps after referral to a hypertension specialist, along with whatever other tests are needed

TABLE 4-10

Overall Guide to Workup for More Common Identifiable Causes of Hypertension

Diagnosis	Diagnostic Procedure	
	Initial	Additional
Chronic renal disease	Urinalysis; serum creatinine; estimated GFR	Renography
Renovascular disease	Duplex sonography	Magnetic resonance or CT angiography; angiography
Coarctation	BP in legs	Echocardiogram; aortogram
Primary aldosteronism	Plasma and urinary potassium; plasma renin and aldosterone	Plasma or urinary aldosterone after saline load; adrenal venous sampling
Cushing syndrome	Morning plasma cortisol after 1 mg dexamethasone at bedtime	Urinary cortisol after variable doses of dexamethasone; adrenal CT scans and scintiscans
Pheochromocytoma	Plasma metanephrine	Urinary catechols; plasma catechols (basal and after 0.3 mg clonidine); adrenal CT scans and scintiscans

CT, computed tomography.

to confirm the diagnosis. More detail about these procedures is provided in their respective chapters.

Assessment of Overall Cardiovascular Risk

Once the cause and consequences of the hypertension have been evaluated, an assessment of the patient's overall cardiovascular risk status should be made. The proper management of hypertension should involve attention to all of the risk factors that can be altered. Patients at high risk should be counseled and helped to reduce all of their risk factors. For many patients, the BP may be the easiest of the risks to control, so this may be the first priority. As described more fully in the next chapter, the overall risk profile provides a more rational basis than an arbitrary BP level for determining whether and when to start treatment and the goal of therapy in the same manner as recently recommended for treatment of hypercholesterolemia (Stone et al., 2013).

The Framingham Formula

Most assessments are based on data from the Framingham Heart Study, the longest and most complete follow-up of a carefully studied, large population (D'Agostino et al., 2008) that also applies to young adults (Carson et al., 2013). The model includes age, gender, smoking, body mass index, parental history of hypertension, and systolic and diastolic BP. Although

age overwhelms all else in increasing risk (Wald et al., 2011), the other factors (other than parental history) are modifiable and therefore demand attention.

Patients should be advised in a clear, understandable manner about their own risk status, both to motivate them to take necessary lifestyle changes and medications and to bring them into the decision-making process, providing them with greater autonomy.

With the natural history in mind, we now turn to issues as to why, when, and how much therapies are needed for the appropriate management of hypertension.

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Management of Hypertension: Why, When, How Far

In the preceding four chapters, the epidemiology, natural history, and pathophysiology of primary (essential) hypertension were reviewed. We will now turn to its treatment, examining the benefits and costs of therapy in this chapter and the use of non-drug and drug treatments in the two chapters that follow.

In this chapter, three main questions are addressed:

- ▶ First, what is the evidence that treatment is beneficial?
- ▶ Second, at what level of blood pressure (BP) should active drug therapy be started? Lifestyle modifications, which will be examined in the next chapter, can be justified for everyone, hypertensive or not.
- ▶ Third, what is the goal of therapy and, further, are there different BP goals for different patients?

To answer these questions, in this chapter, only data comparing active drug therapy against untreated or placebo-treated patients are considered. In Chapter 7, data comparing one or another form of therapy are examined.

EVIDENCE FOR BENEFITS OF THERAPY

The evidence for benefits of therapy comes in part from epidemiologic and experimental evidence but mainly from the results of large-scale randomized controlled trials (RCTs).

Epidemiologic Evidence

Epidemiologic evidence, covered in Chapter 1, provides a clear conclusion: The risks of cardiovascular morbidity and mortality rise progressively with

increasing BP levels (Lewington et al., 2002). As an aside, it seems intuitive that reducing BP would decrease these risks to a similar degree. However, mortality rates remain higher in hypertensives treated to a lower BP than in subjects with the same BP without antecedent hypertension (Franklin et al., 2012). Reasons for this *residual risk* will be examined when evidence from trials of treatments is reviewed.

Despite this residual risk, community-wide surveys document that improved BP control has been accompanied by reduced BP-related mortality (Murphy & Xu, 2013), though racial and ethnic disparities persist (MMWR, 2013).

Interrupting the Progress of Hypertension

A 15- to 17-year longitudinal study of Welshmen (Miall & Chinn, 1973) and a 24-year follow-up of American aviators (Oberman et al., 1967) showed that hypertension begets further hypertension. In both studies, the higher the BP, the greater was the rate of change of pressure, pointing to an obvious conclusion: Progressive rises in BP can be prevented by keeping the pressure down. This conclusion is further supported by the results of the major placebo-controlled trials of antihypertensive therapy: Whereas 10% to 17% of those on placebo progressed beyond the threshold of diastolic pressure above 110 mm Hg, only a small handful of those on drug treatment did so (see Chapter 4, Tables 4-2 and 4-3).

Evidence from Natural Experiments in Humans

Vascular damage and the level of BP have been closely correlated in three situations: Unilateral renal vascular disease, coarctation, and pulmonary hypertension.

These three experiments of nature provide evidence that what is important is the level of the BP flowing through a vascular bed and not some other deleterious effect associated with systemic hypertension. Tissues with lower BP are protected; those with higher pressure are damaged.

- ▶ The kidney with renal artery stenosis is exposed to a lower pressure than is the contralateral kidney without stenosis. Arteriolar nephrosclerosis develops in the high-pressure nonstenotic kidney, occasionally to such a degree that hypertension can be relieved only by removal of the nonstenotic kidney, along with repair of the stenosis (Thal et al., 1963).
- ▶ The vessels exposed to the high pressure above the coarctation develop atherosclerosis to a much greater degree than do the vessels below the coarctation, where the pressure is low (Hollander et al., 1976).
- ▶ The low pressure within the pulmonary artery ordinarily protects these vessels from damage. When patients develop pulmonary hypertension secondary to mitral stenosis or certain types of congenital heart disease, both arteriosclerosis and arteriolar necrosis often develop within the pulmonary vessels (Heath & Edwards, 1958).

Evidence from Animal Experiments

Just as hypertension accelerates and worsens atherosclerosis in humans, animals that are made hypertensive develop more atherosclerosis than do normotensive animals fed the same high-cholesterol diet (Chobanian, 1990). In animals, the lesions caused by hypertension, including accelerated atherosclerosis, can be prevented by lowering the pressure with antihypertensive agents (Chobanian et al., 1992).

Evidence from Clinical Trials of Antihypertensive Therapy

The last piece of evidence—that there is benefit from lowering an elevated BP—is the most important. Over the last six decades, since oral antihypertensive therapy has become available, protection with antihypertensive therapy has been demonstrated at progressively lower levels of pressure and, more recently, in the very elderly (Beckett et al., 2008). The benefits of individual drugs against placebo are so compelling as to preclude the performance of such trials, so attention has turned to trials contrasting a set of one or two drugs against another set of one or two. The data in multiple

meta-analyses (Czernichow et al., 2011; Staessen et al., 2003; Turnbull et al., 2008a; Wang et al., 2005) validate the conclusion of the European societies' guidelines that “the main benefits of antihypertensive therapy are due to lowering of BP per se” (Mancia et al., 2014). As will be noted, this wide umbrella covers disparate groups of patients with different pretreatment levels of BP (Czernichow et al., 2011).

Problems in Applying Trial Results to Clinical Practice

Before examining the results of the multiple randomized clinical trials (RCTs) and their meta-analyses, which are used to inform guidelines for clinical practice, a few cautionary comments are in order. Practitioners must be aware of the features, both good and bad, of both the performance and the presentation of clinical trials since they are the foundation of *evidence-based medicine*, i.e., the decision to use a therapy based on systematic analyses of unbiased scientific evidence (Institute of Medicine, 2011b).

Problems with Trials

As noted, RCTs are required to assess reliably the modest effects of antihypertensive treatment on the major outcomes expected in typical hypertensive patients over a relatively short time, 3 to 5 years, wherein close observation remains possible. As noted by Schillaci et al. (2013),

Over the past 50 years, the remarkable progress in treatment and control of high BP, one of the most outstanding achievements of modern medicine, was driven by results of many large, event-based RCTs. The influential position of RCTs in clinical and therapeutic research as opposed to real-world observational studies (surveys, registries, and retrospective analyses of existing databases) originates from their high internal validity (i.e., the power to address clinical questions with a low level of internal bias).

As essential as they are, RCTs may be misleading, partly by their nature and partly because of human foibles (DeSimone et al., 2013). In particular, the financial sponsorship of clinical trials by drug marketers, although often essential for their performance, has been associated with selection of an inappropriate comparator and poorer quality of methods, selective reporting of outcomes, and more positive conclusions than seen in trials funded by nonprofit sources (Yank et al., 2007).

Beyond these often subtle and unrecognized biases toward the financial sponsor, a number of other factors may either, on the one hand, exaggerate or, on the other, diminish the apparent benefits of therapy as recently reviewed (DeSimone et al., 2013).

Possible Underestimations of Benefit

Results of trials may underestimate the true benefits of antihypertensive therapy for a number of reasons, including the following:

- *Mislabeling of Patients:* The ascertainment of hypertension for enrollment into trials is usually based on two or three sets of office-based BP measurements over 1 to 2 months. As amply noted in Chapter 2, such limited measurements are likely to capture a large number of transient or isolated clinic (white coat) hypertensives, thereby diminishing the efficacy of therapy, as all antihypertensive drugs lower BP more in relation to a higher starting BP and most drugs lower BP very little in the absence of persistent hypertension.
- *Intervention Too Late:* Hypertension may produce damages well before patients have sufficiently high BP to be eligible for enrollment. Even if effectively treated, these damages may be irreversible, particularly if other risk factors are also not corrected.
- *Too Short Duration of Treatment:* The duration of the trials is usually less than 5 years. However, the benefit of drugs may take much longer to become fully manifest, thereby minimizing the drugs' apparent efficacy.
- *Inadequate Therapy:* The approximately 12/6 mm Hg overall placebo-corrected decreases in BP, accomplished in most clinical trials, are likely too little to reduce the damages of hypertension maximally. The degree of protection clearly relates to the level of BP achieved during therapy and not to the pretreatment level (Czernichow et al., 2011). Because as many as 40% of patients in some trials did not reach the goal BP, the benefits may then be less than what could have been obtained by more intensive therapy (DeSimone et al., 2013).
- *Patients Lost to Follow-Up:* In some trials, as many as 25% of patients have been lost to follow-up before completion. In general, more high-risk patients are lost, weakening the evidence for benefit (Mancia, 2006).
- *Switching of Patients:* In all trials, a sizeable number of patients initially randomized to placebo were switched to active therapy because their BP rose beyond the predetermined ceiling of presumed

safety. Treatment of these high-risk patients in the control groups will underestimate the real benefit of active therapy.

- *Harm from Drugs:* The drugs available and chosen for almost all the earlier trials in subjects younger than 60 years old were high doses of diuretics and adrenergic inhibitors, mostly nonselective β -blockers. As is noted in Chapter 7, multiple metabolic abnormalities, which particularly aggravate lipid and glucose-insulin levels, have been amply documented with these therapies. These drug-induced abnormalities may have blunted or reversed the improvement in coronary risk provided by reduction of the BP.
- *Noncompliance with Therapy:* Patients assigned to active drug therapy may not have taken all of their medication and thereby have had less benefit. Although pill counts are usually performed, no truly accurate assessment of compliance is available.

Possible Overestimates of Benefit

On the other hand, antihypertensive therapy may be less effective than is seen in RCTs, because of *poor external validity*: The trial results may not be applicable to routine clinical practice, and the group data may not apply to individual patients. Data from clinical trials may overestimate the benefits of therapy as they are applied to the universe of hypertensives for the following reasons:

- *Inclusion of Inappropriate End Points:* To maximize the impact of therapy, multiple end points may be combined, some of questionable significance such as hospitalizations, which occur at the subjective discretion of the investigator (Lim et al., 2008). Lauer and Topol (2003) argue that only all-cause mortality should be the primary end point since it is objective, unbiased, and clinically relevant. As they note, "any end point that requires a measurement involving human judgment is inherently subject to bias."
- *Exclusion of High-Risk Patients:* In many early RCTs, patients with various symptomatic cardiovascular diseases, target organ damage, or major risk factors were excluded, leaving a fairly healthy population who may respond better than the usual mix of patients (Uijen et al., 2007).
- *Better Compliance with Therapy:* Patients enrolled in trials in which medications and all health care are free and follow-up is carefully monitored are likely to be more compliant with therapy than are patients in clinical practice. Therefore, they may achieve greater benefit.

- Overemphasis on Initial Reports:** The first report of a trial of a new drug is often more positive than are subsequent reports, but the first one is more likely to be cited and publicized (Ioannidis, 2005).
- Relative Versus Absolute Changes:** In most reports of RCTs, the reductions in coronary heart disease (CHD) and stroke are relative—i.e., they are the difference between the rates seen in treated versus untreated patients. However, as documented in Table 5-1, large relative differences may translate into small absolute differences. The 40% relative risk reduction by treatment of “mild” hypertension translates into only a 0.6% absolute risk reduction. The presentation of trial data as large relative reductions in risk is much more attractive to the public and the practitioners than that as the usually much smaller absolute reductions; however, the relative data may easily mislead the unwary into thinking that many more patients will be helped than is possible.

As shown in the far right column of Table 5-1, these investigators propose the use of the measure *number needed to treat (NNT)*, calculated as the inverse of the absolute risk reduction, because it “conveys both statistical and clinical significance to the doctor” and “can be used to extrapolate published findings to a patient at an arbitrary specified baseline risk” (Cook & Sackett, 1995).

The need for using absolute risk, or the NNT, is well demonstrated in Figure 5-1 (Lever & Ramsay,

1995). Figure 5-1A shows the quite similar reductions in relative risk for stroke in six major trials in the elderly and in the earlier Medical Research Council trial of younger hypertensives. Figure 5-1B shows the same data in absolute terms, clearly portraying the progressively greater benefit of therapy with increasing pretherapy risk, as reflected in the rates in the placebo groups.

The use of NNTs based on absolute risk reduction is clearly more accurate than the portrayal of relative risks. The NNT must be related to the duration of the trial. This is best done by using the *hazard difference*, expressed as mortality per unit of patient-time (Lubsen et al., 2000). However, in most recent reports, results are presented as *survival curves*, showing differences in outcomes that change over time, using the Kaplan-Meier life table methods for estimating the proportion of patients who experience an event by time since randomization (Pocock et al., 2002). When properly constructed, i.e., showing both the number of subjects remaining in the trial over time and a display of statistical uncertainty, such survival curves portray RCT results very well.

Admixture of Drugs: To achieve the preset goal of therapy, e.g., BP below 140/90, most trials comparing a drug versus placebo (as examined in this chapter) or one drug versus another (as examined in Chapter 7) must add additional drugs to the study drug. In some trials, 80% or more of the patients end up on two or more. What is ascribed to only the study drug may represent the effect of many others (Mancia et al., 2014).

TABLE 5-1

Calculations of Relative and Absolute Risk Reduction and Numbers Needed to Be Treated for Patients with Hypertension

Hypertension	Stroke in 5 Years				
	Control Group	Active Treatment Group	Relative Risk Reduction, $(P_c - P_a)/P_c$	Absolute Risk Reduction, $P_c - P_a$	Number Needed to Treat, $1/(P_c - P_a)$
Diastolic \leq 115 mm Hg					
Event rate (P)	0.20	0.12	0.40	0.08	13
Total number of patients	16,778	16,898			
Diastolic \leq 110 mm Hg					
Event rate (P)	0.015	0.009	0.40	0.006	167
Total number of patients	15,165	15,238			

Modified from Cook RJ, Sackett DL. The number needed to treat: A clinically useful measure of treatment effect. *BMJ* 1995;310:452–454. Based on the results of Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke and coronary heart disease. Part 2: Short-term reductions in blood pressure. *Lancet* 1990;335:827–838.

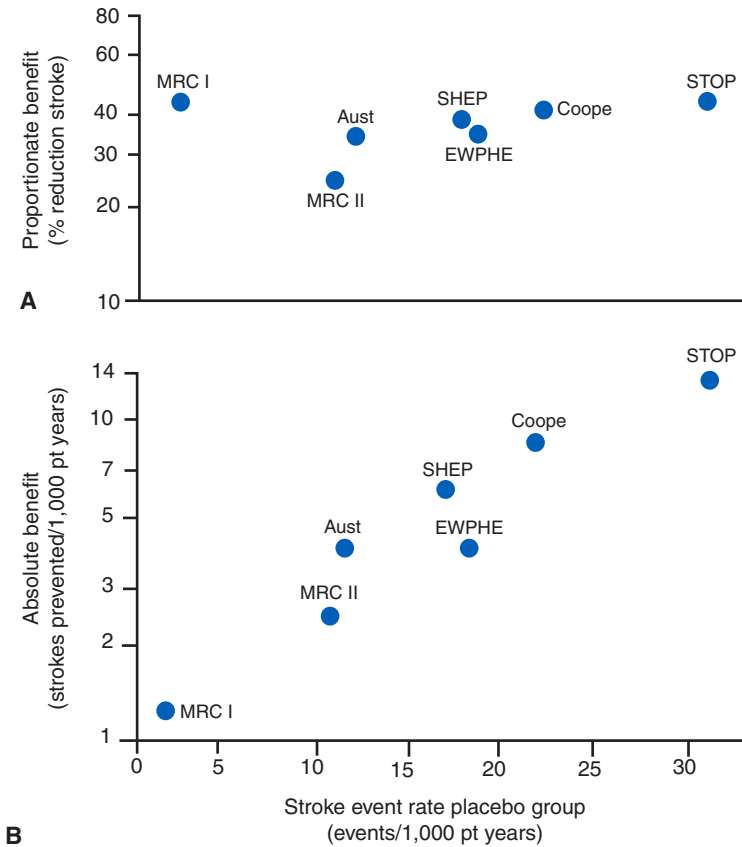


FIGURE 5-1 • Comparison of (A) proportionate (relative) and (B) absolute benefit from reduction in the incidence of stroke in six trials in the elderly and in one other trial (Medical Research Council I [MRC-I]) having a similar design but in which the absolute stroke risk was much lower. Event rates are for fatal and non-fatal stroke combined. Aust, Australian study; EWPHE, European Working Party on High BP in the Elderly trial; Coope, Cooper and Warrender; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients with Hypertension. (Modified from Lever AF, Ramsay LE. Treatment of hypertension in the elderly. *J Hypertens* 1995;13:571–579.)

Reliance on Conventional Clinic-Based BP Measurements

In all RCTs, outcomes are related to changes in conventional clinic-based measurement of BP, which (as detailed in Chapter 2) can both overestimate out-of-office BP due to white-coat hypertension and underestimate out-of-office BP due to masked hypertension. Drug treatment can convert sustained hypertension (i.e., high BP both in and out of the office) to a form of masked (i.e., partially treated) hypertension, by lowering clinic BP more than ambulatory BP (Franklin et al., 2013). While daytime ambulatory BPs and nocturnal BPs are superior to conventional office BPs as predictors of target organ damage and clinical outcomes (O'Brien et al., 2013), few RCTs have included ambulatory BP monitoring and no RCT has tested whether treatment of masked HTN improves outcomes.

Solutions to the Problems of Trials

Ambulatory BP monitoring needs to become a standard part of future RCTs. Those who perform and report RCTs must follow established guidelines such as the

Consolidated Standards of Reporting Trials (CONSORT) (Schulz et al., 2010). However, clinicians themselves must be prepared to assess the validity of trial data, since in the words of Montori (Montori et al., 2004),

Science is often not objective. Emotional investment in particular ideas and personal interest in academic success may lead investigators to overemphasize the importance of their findings and the quality of their work. Even more serious conflicts arise when for-profit organizations, including pharmaceutical companies, provide funds for research and consulting, conduct data management and analyses, and write reports on behalf of the investigators.

Montori et al. (2004) provide this set of guides for clinicians to avoid being misled by biased presentation and interpretation of trial data:

- Read the “Methods and Results” sections. Remember that the “Discussion” section often offers inferences that differ from those a dispassionate reader would draw.
- Read abstracts and comments in objective secondary publications such as the *ACP Journal Club*,

Evidence-Based Medicine, UpToDate, and The Medical Letter.

- Beware of faulty comparators. A weak comparator is often chosen in comparative trials, perhaps the most egregious being the β -blocker atenolol (Carlberg et al., 2004).
- Beware of composite end points; as noted previously, all-cause mortality can hardly be fudged.
- Beware of small treatment effects, particularly when the data are reported as differences in relative risks. If the 95% confidence interval (CI) crosses the midline, beware.
- Beware of subgroup analyses. A number of provisos should be met to ensure that apparent differences in subgroup responses are real, particularly that only a small number of hypotheses were tested that were specified before the results became available.

Meanwhile, students and practitioners need to take better advantage of available sources of evidence-based clinical information (Zwolsman et al., 2012). The Cochrane Library is now the most prolific provider, but more and more sources are available, many at no cost.

Problems with Meta-Analyses and Systematic Reviews

Meta-analyses and systematic reviews of multiple RCTs are often the highest level of evidence used by expert panels whether formulating clinical practice guidelines, formulary composition, payment schedules, or textbook content (Thompson & Higgins, 2005). Unfortunately, biases may affect them as well. As Kicinski (2013) notes,

When some study outcomes are more likely to be published than others, the literature that is available to doctors, scientists, and policy makers provides misleading information. It is clear that statistically significant results supporting the hypothesis of the researcher often have a greater chance of being published and fully reported. One consequence of underreporting is that it influences the sample of studies that is available for a meta-analysis. When publication bias occurs, the validity of the meta-analysis is uncertain.

To reduce underreporting of *negative trials*, since 2005, the International Committee of Medical Journal Editors has required that all clinical trials be registered prospectively in the public domain (www.clinicaltrials.gov) as a condition for publication, and, since 2007, the U.S. Food and Drug Administration (FDA) has required the registration of all trial results (Kicinski, 2013).

An even bigger issue perhaps is an author's personal bias in setting the criteria as to which trials to include and which to exclude from meta-analysis. If there are only a small number of trials on a given topic, restrictive inclusion criteria can eliminate a single trial and sway the overall conclusion about the putative treatment effect as being positive or negative.

Even under the best of conditions, meta-analyses and systemic reviews of RCTs may not be able to provide adequate information about long-term outcomes of chronic diseases such as hypertension, since almost all RCTs are of relatively short-term duration.

Problems with Guidelines

The most authoritative recommendations on how to best manage hypertension are the guidelines issued by national, or international, expert committees.

However, there are problems with current guidelines, including these:

- There are increasing numbers of hypertension guidelines, and their recommendations differ.
- They are too long-winded to be used when needed, although shorter "Practice Guidelines" are now being provided and software applications develop to incorporate *point-of-care* recommendations into electronic health records (Vandvik et al., 2013).
- They fail to take patients' beliefs and abilities into account (Vandvik et al., 2013).
- The participants in guideline committees may be too narrow in outlook, may be beholden to commercial interests, or may not include the most critical observers.

Realizing these issues, the Institute of Medicine (Institute of Medicine, 2011a) issued the following standards for improving the trustworthiness of clinical practice guidelines:

- Establish transparency in the guideline development process.
- Manage conflicts of interest among panel members.
- Establish committees that are multidisciplinary and include affected patients and representatives of patient advocacy groups.
- Utilize systemic reviews to evaluate the evidence.
- Delineate the evidence foundation and grade the strength of the evidence for each recommendation (see below).
- Articulate recommendations unambiguously.
- Submit the guideline recommendations for external review by the full spectrum of stakeholders

including scientific experts, clinical experts, specialty societies, federal government agencies, patients, and public representatives.

- Update the recommendations continually as new evidence comes to light.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system has become an international standard for grading the quality of the evidence and the corresponding strength of the recommendation (Guyatt et al., 2011).

Using the criteria shown in Table 5-2, the *quality of the evidence* for any specific recommendation is rated as:

- High**—Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate**—Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low**—Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low**—Any estimate of effect is very uncertain.

This rating system is quite reproducible (Mustafa et al., 2013).

Then, the *strength of the recommendation* is rated as:

- Strong For**—The panel is highly confident that desirable consequences outweigh undesirable consequences.
- Strong Against**—The panel is highly confident that the undesirable consequences outweigh the desirable consequences.
- Weak For**—The panel is less confident that the desirable consequences outweigh the undesirable consequences.
- Weak Against**—The panel is less confident that the undesirable consequences outweigh the desirable consequences.

Table 5-3 shows the somewhat different grading systems developed on one hand by the National Heart Lung and Blood Institute (NHLBI) and on the other by the American College of Cardiology (ACC)/American Heart Association (AHA) (Eckel et al., 2013).

Despite problems with trials, meta-analyses, and guidelines, we must use them to determine the most effective way to manage hypertension. The following will examine the evidence that lowering BP with drugs provides benefit, starting with the most severe degree of hypertension and ending with prehypertension.

As will become obvious, the evidence of benefit becomes progressively more difficult to document as the baseline level of BP and the overall degree of risk decrease. Investigators seldom live long enough or have

TABLE 5-2

GRADE System for Assessing Quality of Evidence

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial	High —Further research is very unlikely to change our confidence in the estimate of effect	Risk of bias –1 Serious –2 Very serious	Large effect +1 Large +2 Very large
	Moderate —Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	Inconsistency –1 Serious –2 Very serious Indirectness –1 Serious –2 Very serious	Dose response +1 Evidence of a gradient All plausible confounding +1 Would reduce a demonstrated effect or
Observational study	Low —Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate	–1 Serious –2 Very serious Imprecision –1 Serious –2 Very serious	+1 Would suggest a spurious effect when results show no effect
	Very low —Any estimate of effect is very uncertain	Publication bias –1 Likely –2 Very likely	

Adapted from Guyatt G, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings Tables. *J Clin Epidemiol* 2013;64:383–394.

TABLE 5-3

American College of Cardiology (ACC)/American Heart Association (AHA) and National Heart Lung and Blood Institute (NHLBI) Grading Systems for Evidence Quality and Strength of Recommendations

		SIZE OF TREATMENT EFFECT												
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	CLASS IIa <i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i> IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; additional registry data would be helpful</i> Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>No Benefit or CLASS III Harm</i> <table border="1"> <tr> <td></td> <td>Procedure/ Test</td> <td>Treatment</td> </tr> <tr> <td>COR III: No benefit Harm</td> <td>Not Helpful</td> <td>No Proven Benefit</td> </tr> <tr> <td>COR III: Harm</td> <td>Excess Cost w/o Benefit or Harmful</td> <td>Harmful to Patients</td> </tr> </table>		Procedure/ Test	Treatment	COR III: No benefit Harm	Not Helpful	No Proven Benefit	COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients
	Procedure/ Test	Treatment												
COR III: No benefit Harm	Not Helpful	No Proven Benefit												
COR III: Harm	Excess Cost w/o Benefit or Harmful	Harmful to Patients												
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses 									
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trials or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trials or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Evidence from single randomized trial or nonrandomized studies 									
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Only expert opinion, case studies, or standard of care 									
	Suggested phrases for writing recommendations	should be recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	<table border="1"> <tr> <td>COR III: No Benefit is not recommended is not indicated should not be performed/administered/ other is not useful/beneficial/effective</td> <td>COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/administered/ other</td> </tr> </table>	COR III: No Benefit is not recommended is not indicated should not be performed/administered/ other is not useful/beneficial/effective	COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/administered/ other							
COR III: No Benefit is not recommended is not indicated should not be performed/administered/ other is not useful/beneficial/effective	COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/administered/ other													
Comparative effectiveness phrases [†]	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B												

From Eckel RH, et al. 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013. doi: 10.1161/01.cir.0000437740.48606.d1

funds enough to obtain “hard” outcome data on patients with minimally elevated BP or little cardiovascular risk.

Trial Results

Trials in Malignant Hypertension

The benefits of drug therapy in malignant hypertension were easy to demonstrate in view of its predictable, relatively brief, and almost uniformly fatal course in untreated

patients. Starting in 1958, a number of studies appeared showing a significant effect of medical therapy in reducing mortality in malignant hypertension (see Chapter 8).

Trials in Less Severe Hypertension

Demonstrating that therapy made a difference in non-malignant, primary hypertension took a great deal longer. However, during the late 1950s and early 1960s,

reports began to appear that suggested that therapy of nonmalignant hypertension was helpful (Hodge et al., 1961; Hood et al., 1963; Leishman, 1959). The first placebo-controlled, albeit small, study by Hamilton et al. (1964) showed a marked decrease in complications over a 2- to 6-year interval for 26 effectively treated patients as compared to 31 untreated patients.

Veterans Administration Cooperative Study

The first definitive proof of the protection provided by antihypertensive therapy in nonmalignant hypertension came from the Veterans Administration Cooperative Study begun in 1963. The value of therapy in the 73 men with diastolic BPs of 115 to 129 mm Hg given hydrochlorothiazide, reserpine, and hydralazine versus the 70 men given placebo became obvious after less than 1.5 years, with a reduction in deaths from four to zero and, in major complications, from twenty-three to two (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1967).

Along with the men with diastolic BPs of 115 to 129 mm Hg, another 380 with diastolic BPs between 90 and 114 mm Hg also were assigned randomly to either placebo or active therapy. It took a longer time—up to 5.5 years, with an average of 3.3 years—to demonstrate a statistically clear advantage of therapy in this group (Veterans Administration Cooperative Study Group on Antihypertensive Agents, 1970). A total of 19 of the placebo group, but only eight of the treated group, died of hypertensive complications, and serious morbidity occurred more often among the placebo group. Overall, major complications occurred in 29% of the placebo group and 12% of the treated group.

The promising results of the Veterans Administration study prompted the initiation of a number of additional controlled trials of therapy of hypertension. Data from trials completed before 1995, primarily with diuretics and β -blockers, are separated from those completed since 1995, primarily with angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), and angiotensin II receptor blockers (ARBs).

Trials Before 1995

The 21 trials listed in Table 5-4 included a total of 56,078 patients followed up for an average of 5 years (Psaty et al., 1997; 2003). In all these trials, the primary drugs were either β -blockers or diuretics; in trials done before the mid-1980s, almost all used higher doses of

diuretic. It should be noted that the entry BP criterion for all of the trials before the Systolic Hypertension in the Elderly Program Pilot Study (SHEP-P) in 1989 was the diastolic level, reflecting the greater emphasis placed, until recently, on diastolic rather than systolic blood pressure (SBP) as the major determinant of risk.

The trials published before 1985 mainly involved younger patients; those in the early 1990s enrolled elderly hypertensives with either combined hypertension or isolated systolic hypertension (ISH), who will be examined separately.

Separation of the Data by Doses

Psaty et al. (1997) separated the nine trials that involved high doses of diuretic (equivalent to 50 mg or more of hydrochlorothiazide) from the four that involved lower doses (equivalent to 12.5 to 25.0 mg hydrochlorothiazide) and the four that used a β -blocker as the primary drug (Fig. 5-2). The Hypertension Detection and Follow-up Program study was considered separately, as it was not placebo controlled: Half of the patients were more intensively treated (stepped care); the other half were less intensively treated (referred care).

The separation of the data by doses clearly reveals the lack of protection from CHD by high doses of diuretic and β -blockers, whereas all therapies had a significant impact on stroke. The later four studies with lower doses of diuretic showed excellent protection against CHD.

Conclusion

Based on these early trials—primarily in middle-aged patients with combined systolic and diastolic hypertension—the evidence was clear: Reductions in BP of 10 to 12 mm Hg systolic and 5 to 6 mm Hg diastolic for a few years conferred relative reductions of 38% for stroke and 16% for CHD (Collins & MacMahon, 1994).

Placebo-Controlled Trials After 1995

After 1995, a new series of trials have been completed, and more started, to determine the effects of the newer antihypertensive agents—ACEIs, ARBs, and CCBs—and to broaden the patient population to those with associated conditions including coronary disease, diabetes, and renal insufficiency (Table 5-5).

Figure 5-3 is a 2003 overview of data from 31 RCTs showing the relation between odds ratios for cardiovascular events and differences in SBP

TABLE 5-4

Randomized Placebo-Controlled Trials of Antihypertensive Drug Treatment Published Before 1995

Trial (Reference)	Number of Patients	Entry BP, mm Hg	Mean Age, Years	Duration, Years	Primary Drugs
VA Coop I (1967)	143	186/121	51	1.5	D-high
VA Coop II (1970)	380	163/104	51	3.3	D-high
Carter (1970)	97	>160/110	60–79	4.0	D-high
Barracough et al. (1973)	116	—/109	56	2.0	D-high
Hypertension-Stroke (1974)	452	167/100	59	2.3	D-high
USPHS (Smith, 1977)	389	148/99	44	7.0	D-high
VA-NHLBI (Perry et al., 1978)	1,012	—/93	38	1.5	D-high
HDFP (1979)	10,940	170/101	51	5.0	D-high
Oslo (Hegeland, 1980)	785	155/97	45	5.5	D-high
Australian (Management Comm, 1980)	3,427	165/101	50	4.0	D-high
Kuramoto et al. (1981)	91	168/86	76	4.0	D-high
MRC-I (1985)	17,354	161/98	52	5.0	β-B/D-high
EWPHE (Amery et al., 1985)	840	182/101	72	4.7	D-low
HEP (Coope & Warrender, 1986)	884	197/100	60	4.4	β-B
SHEP-P (Perry et al., 1989)	551	172/75	72	2.8	D-low
SHEP (1991)	4,736	170/77	72	4.5	D-low
STOP-H (Dahlöf et al., 1991)	1,627	195/102	76	2.0	β-B
MRC-II (1992) et al.	4,396	185/91	70	5.8	β-B/D-low
Dutch TIA (1993)	1,473	157/91	52% > 65	2.6	β-B
PATS (1995)	5,665	154/93	60	2.0	D-high
TEST (Eriksson, 1995)	720	161/89	70	2.6	β-B

β-B, beta-blocker; BP, blood pressure; D-high, diuretic dose ≥50 mg hydrochlorothiazide; D-low, diuretic dose <50 mg hydrochlorothiazide; EWPHE, European Working Party on Hypertension in the Elderly; HDFP, Hypertension Detection and Follow-up Program; MRC, Medical Research Council; NHLBI, National Heart, Lung, and Blood Institute; PATS, Poststroke Antihypertensive Treatment; SHEP, Systolic Hypertension in the Elderly Program; SHEP-P, SHEP Pilot Study; STOP-H, Swedish Trial in Old Patients with Hypertension; TEST, Tenormin after Stroke and TIA; USPHS, U.S. Public Health Service; VA, Veterans Administration.

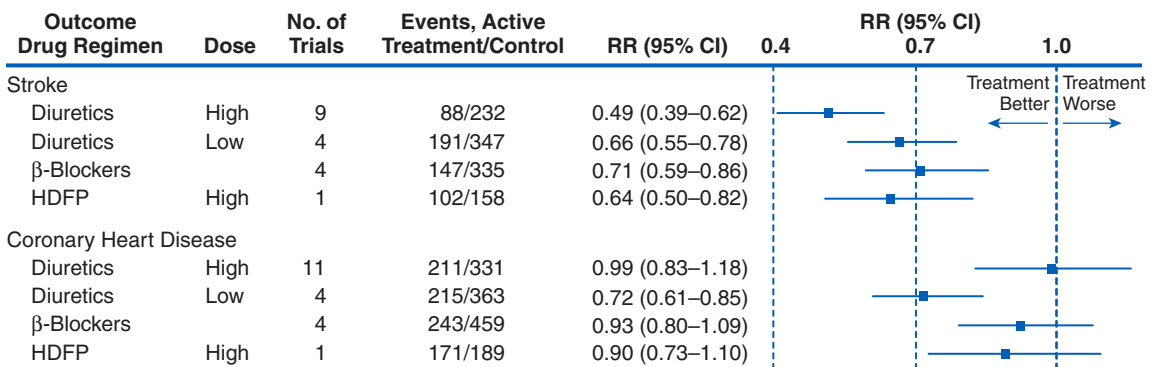


FIGURE 5-2 • Meta-analysis of randomized, placebo-controlled clinical trials in hypertension according to first-line treatment strategy. For these comparisons, the numbers of participants randomized to active therapy and placebo were 7,758 and 12,075 for high-dose diuretic therapy; 4,305 and 5,116 for low-dose diuretic therapy; and 6,736 and 12,147 for β-blocker therapy. HDFP, Hypertension Detection and Follow-up Program; RR, relative risk; CI, confidence interval. (Adapted from Psaty BM, Smith NL, Siscovick DS, et al. Health outcomes associated with antihypertensive therapies used as first-line agents. A systematic review and meta-analysis. *JAMA* 1997;277:739–745.)

TABLE 5-5

Randomized Placebo-Controlled Trials of Antihypertensive Drug Therapy Published After 1995

Trial (Reference)	Primary Drugs	No. of Patients (Condition)	Mean Age, Years	Baseline BP, mm Hg	Final BP, mm Hg	Δ BP vs. Placebo, mm Hg	Relative Risk Reduction
ACEI vs. Placebo							
BENEDICT (Ruggenenti et al., 2004)	Trandolapril	604 (HTN + DM2)	61	151/87	139/81	-2/-2	-47% microalbuminuria ($p < 0.01$)
REIN (GISEN Group, 1997)	Ramipril	352 (HTN + CKD + Uprot)	49	150/92	144/88	-1/-1	-56% renal decline ($p = 0.03$)
PROGRESS (2004)	Perindopril ± indapamide	6,105 (stroke ± HTN)	64	147/86	139/83	-9/-4	-28% strokes ($p < 0.01$)
DIAB-HYCAR (Marre et al., 2004)	Ramipril	4,912 (DM2 + U prot ± HTN)	65	146/82	142/80	-2/0	-14% proteinuria ($p < 0.07$)
ADVANCE (2007)	Perindopril + indapamide	11,140 (DM2 ± HTN)	58	145/81	139/74	-6/-2	-18% CV mortality ($p = 0.03$)
HOPE (2000)	Ramipril	9,297 (RFs ± HTN)	66	139/79	136/76	-3/-2	-26% CV death ($p < 0.001$)
EUROPA (2003)	Perindopril	12,218 (RFs ± HTN)	60	137/82	128/78	-5/-2	-20% CV death ($p = 0.0003$)
PEACE (2004)	Trandolapril	8,290 (CAD)	64	134/78	130/74	-3/-1	CV death $p = NS$
PART 2 (MacMahon et al., 2000)	Ramipril	617 (CAD, PAD)	61	133/79	127/74	-6/-4	Carotid IMT ($p = NS$), -4% LVMI ($p = 0.04$)
PREVEND-IT (Asselbergs et al., 2004)	Fosinopril	864 (U microalb)	51	129/76	129/76	-1/-2	-26% U alb ($p < 0.001$), CV events ($p < 0.1$)
SCAT (Teo, 2000)	Enalapril	460 (CAD)	61	128/77	122/74	-4/-3	QCA ($p = NS$)

ARB vs. Placebo

IDNT (Lewis et al., 2001)	Irbesartan	1148 (DM2 + CKD + HTN)	59	160/87	140/77	-2/-3	-20% renal decline ($p = 0.02$)
IRMA-2 (Parving et al., 2001)	Irbesartan	590 (DM2 + UMicroalb + HTN)	58	153/90	142/83	-2/0	-70% renal decline ($p < 0.001$)
RENAAL (Brenner et al., 2001)	Losartan	1,513 (DM2 + CKD + HTN)	60	152/82	140/74	-1/0	-28% ESRD
PROFESS (Yusuf et al., 2008)	Telmisartan	20,332 (stroke)	66	144/73	136/71	-4/-2	New stroke $p = NS$
CGB vs. Placebo							
Syst-Eur (Staessen et al., 1997)	Nitrendipine	4,695 (elderly HTN)	70	174/86	151/79	-11/-5	-42% stroke ($p = 0.003$)
SYST-CHINA (Liu et al., 1998)	Nitrendipine	2,394 (elderly HTN)	67	171/86	151/81	-9/-3	-38% stroke ($p = 0.01$)
SCOPE (Lithell et al., 2003)	Candesartan	4,964 (elderly HTN)	76	166/90	145/80	-3/-2	-10% CV event ($p = 0.19$), -28% nonfatal stroke ($p = 0.04$)
STONE (Gong et al., 1996)	Nifedipine	1,632 (elderly HTN)					-59% stroke + severe arrhythmia ($p < 0.01$)
IDNT (Lewis et al., 2001)	Amlodipine	1,148 (DM2 + CKD + HTN)	59	159/87	140/77	-1/-3	$p = NS$ renal decline
BENEDICT Ruggenenti et al., 2004	Verapamil	604 (HTN + DM2)	63	150/86	141/82	+1/+2	Microalbuminuria ($p = NS$)
PREVENT (Pitt, 2000)	Amlodipine	825 (CAD)	57	129/79	122/75	-5/-4	$p = NS$ QCA
Thiazide vs. Placebo							
HYVET (Beckett et al., 2008)	Indapamide ± perindopril	3,845 (octogenarian HTN)	84	173/91	143/78	-15/-6	-34% CV events ($p < 0.01$), -30% stroke ($p = 0.06$)

DM2, type 2 diabetes mellitus; HTN, hypertension; U prot, proteinuria; U mircoalb, urinary microalbuminuria; RFs, risk factors for atherosclerotic cardiovascular disease; CV, cardiovascular; QCA, quantitative coronary angiography; IMT, intimal-medial thickness.

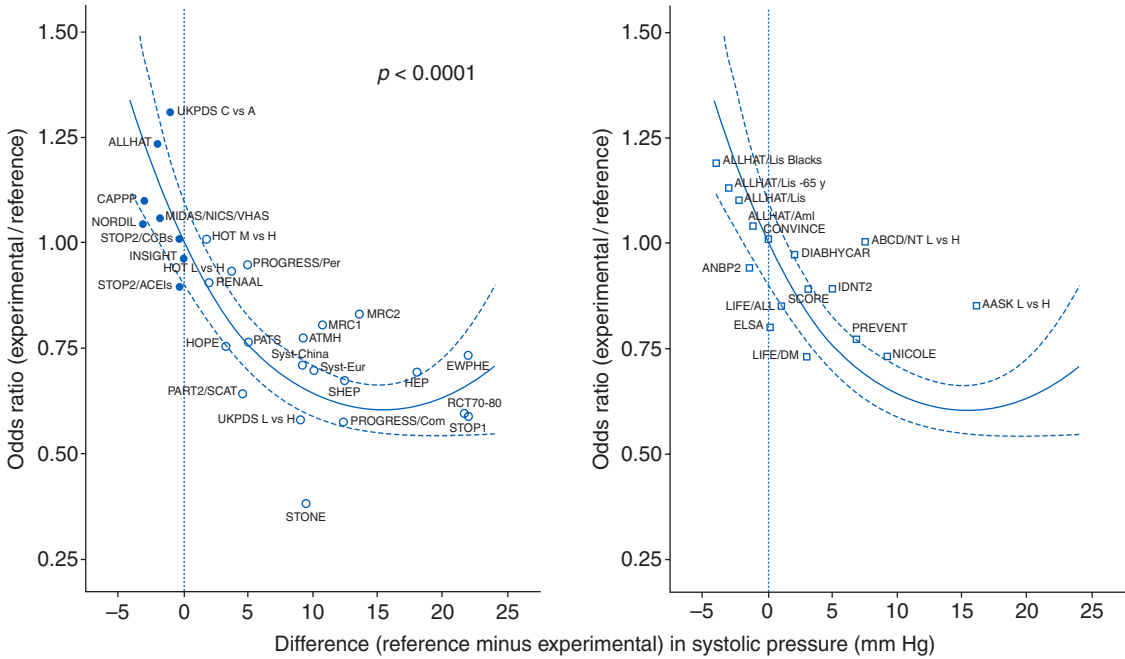


FIGURE 5-3 • Relationship between odds ratio for cardiovascular events and corresponding differences in SBP in trials published before (left) and after (right) 2000. Odds ratios were calculated for experimental versus reference treatment. BP differences were obtained by subtracting achieved levels of experimental groups from those in reference groups. Negative values indicate tighter BP on control than on reference treatment. The regression lines were plotted with 95% CI and were weighted for the inverse of the variance of the individual odds ratios. (Modified from Staessen JA, Wang JG, Thijs L. Cardiovascular prevention and blood pressure reduction: A quantitative overview updated until 1 March 2003. *J Hypertens* 2003;21:1055–1076.)

(Staessen et al., 2003). The figure portrays data from 15 of the 21 placebo-controlled trials published before 1995 that are listed in Table 5-2, the others being too small or too short to be included. Most of the placebo-controlled trials published before 2003 are included. In addition, data from some of the comparative trials to be covered in Chapter 7 are included, since the purpose of the graph is to show the degree of protection with varying differences of SBP. In some of the comparative trials, lesser SBP reduction was seen with the “experimental” drug, with resultant increases in cardiovascular events.

The message of Figure 5-3 is clear: The degree of BP reduction is the primary determinant of cardiovascular protection, not the type of drug that provided the reduction in BP. As discussed later in the chapter, subsequent meta-regression analyses after 2003 by the Blood Pressure Lowering Treatment Trialists’ Collaboration all have confirmed this conclusion: A few mm Hg additional reduction in SBP is accompanied by large additional reductions in cardiovascular (CV) disability and death.

The only apparent exception, to be described in more detail in Chapter 7, is that β -blocker-based therapy has not been as protective against stroke as

other drugs, despite equal reduction in BP (Carlberg et al., 2004).

In placebo-controlled trials of ACEIs, ARBs, and CCBs, published before 2003, the only apparent difference is lesser protection against heart failure by CCBs (Turnbull, 2003) (Fig. 5-4). Subsequent trials with the CCB amlodipine have shown better protective effects with this agent (Wang et al., 2007).

Trial Results: Special Populations

Trials in the Elderly with Isolated Systolic Hypertension (ISH)

Although both the earlier and the later trials listed in Tables 5-2 and 5-3 include some elderly patients with ISH, defined in most of these trials as a SBP 160 mm Hg or higher with a diastolic BP below 95 mm Hg, the fact that such patients make up the largest portion of hypertensive patients now and will do so, to an even greater degree, in the future as our population ages, justifies a closer, separate look at the data on their therapy. Staessen et al. (2000) have provided a meta-analysis of these trials, which are listed in Table 5-6.

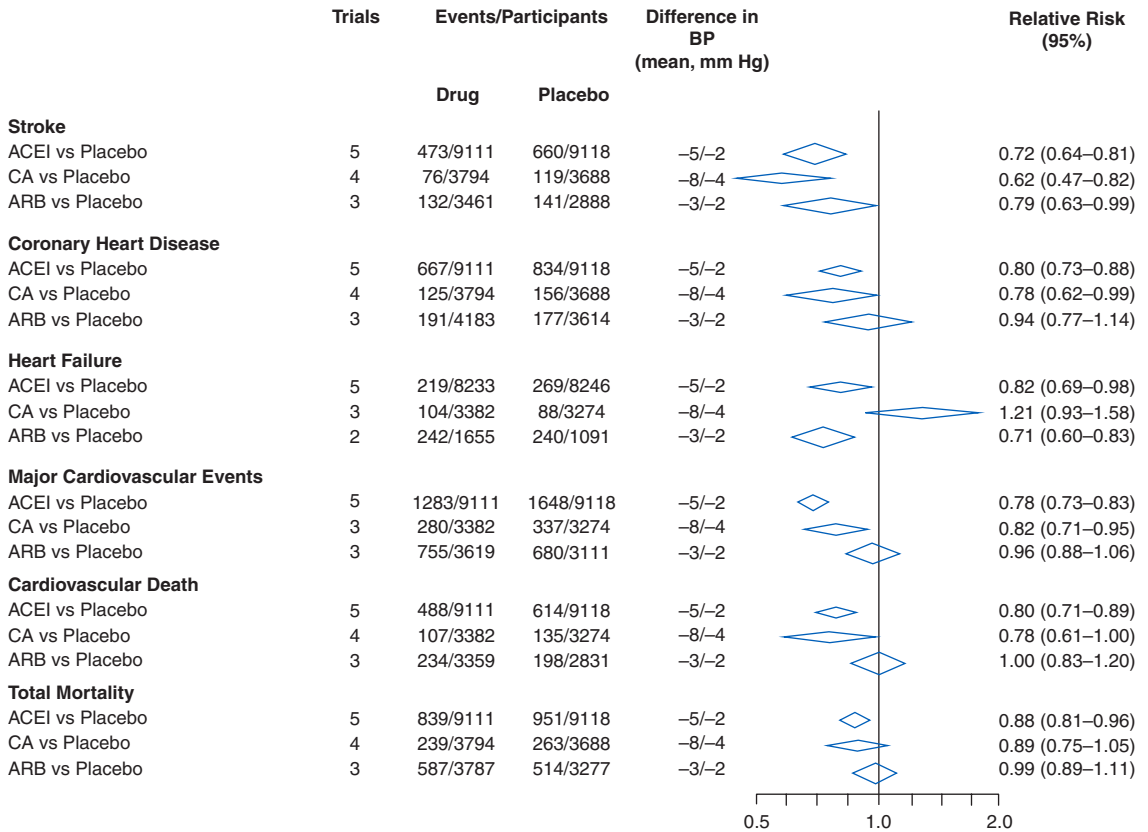


FIGURE 5-4 • Comparisons of the effects of therapy based on ACEI, angiotensin-converting enzyme inhibitor; CA, calcium antagonist; ARB, angiotensin II receptor blocker; and all versus placebo on cardiovascular events and mortality. (Modified from Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: Results of prospectively-designed overviews of randomised trials. *Lancet* 2003;362:1527–1535.)

TABLE 5-6

Randomized Placebo-Controlled Trials of Antihypertensive Drug Treatment in Elderly Patients with Isolated Systolic Hypertension above 160 mm Hg^a

Trial (Reference)	Number of Patients	Entry BP, mm Hg	Mean Age, Years	Duration, Years	Primary Drugs
EWPHE (Amery et al., 1985)	172	178/92	73	4.3	Diuretic
MRC-I (1985)	428	174/92	62	5.2	β-B/Diuretic
HEP (Coope & Warrender, 1985)	349	191/85	70	3.6	β-B
SHEP (1991)	4,736	170/77	72	4.4	Diuretic
STOP-H (Dahlöf et al., 1991)	268	194/91	76	1.9	β-B/diuretic
MRC-II (1992)	2,651	182/83	70	6.1	β-B/diuretic
Syst-Eur (Staessen et al., 1997)	4,695	174/85	70	2.0	CCB
Syst-China (Liu et al., 1998)	2,394	170/86	67	3.0	CCB

^aDiagnosis of systolic hypertension based on SBP above 160 and diastolic BP below 95 mm Hg in all trials except SHEP, which required a diastolic BP of ≤90 mm Hg.

β-B, beta-blocker; CCB, calcium channel blocker; EWPHE, European Working Party on Hypertension in the Elderly; MRC, Medical Research Council; SHEP, Systolic Hypertension in the Elderly Program; STOP-H, Swedish Trial in Old Patients with Hypertension; Syst-China, Systolic Hypertension in China trial; Syst-Eur, Systolic Hypertension in Europe trial.

The 2008 Hypertension in the Very Elderly Trial (HYVET) is discussed separately.

Figure 5-5 summarizes the data from these eight trials of 15,693 elderly patients with ISH. The average BP at entry was 174/83 mm Hg, and the mean fall in BP over the median 3.8-year follow-up was 10/4 mm Hg. Therapy significantly reduced all-cause and cardiovascular mortality by 13% and 18%, respectively, but had an even greater impact on morbidity: Coronary events were reduced by 23% and strokes by 30%.

In these trials, the absolute benefits of active therapy were greater in men, older patients, and those with prior cardiovascular complications, reflecting the higher initial risk status of such patients. To prevent one major cardiovascular event, the numbers of patients that needed to be treated for 5 years were 18 men versus 38 women, 19 patients who were 79 years or older versus 39 patients who were 60 to 69 years old, and 16 of those with prior cardiovascular complications versus 37 of those without (Staessen et al., 2000). Moreover, in a 15-year follow-up of a portion of the participants in the SHEP trial, a persistent reduction in fatal plus nonfatal cardiovascular events was found among the original drug-treated group compared to the placebo group, 58% versus 79%, despite the eventual use of antihypertensive

therapy in 65% of the placebo group, compared to 72% of the active group (Sutton-Tyrrell et al., 2003).

As impressive as these data are, they must be recognized as covering only the higher range (stage 2) of ISH, i.e., systolics of 160 mm Hg or higher, which has uniformly been the criterion for entry into the trials shown in Table 5-4 and Figure 5-5. Most ISH is between 140 and 159 mm Hg, and most premature cardiovascular events occur in patients in that range rather than in those with higher SBP (Chaudhry et al., 2004). As of now, there still are no placebo-controlled RCTs documenting the benefit for those with stage 1 ISH. Yet, when meta-regression analyses include RCTs with active comparator groups, it becomes clear that small additional reductions in SBP (as little as a few mm Hg) between groups are accompanied by sizeable reductions in CV events for patients younger and older than age 65 (Turnbull et al., 2008a).

HYVET Trial in Those Over Age 80

Data are now available on the effect of therapy for patients over the age of 80 years, percentage-wise the fastest growing demographic group (Beckett et al., 2008). The HYVET included 3,845 hypertensives over age 80 with a sustained SBP of 160 mm Hg or higher. Their mean seated BP was 173/91 mm Hg. Half were assigned to placebo and the other half to active therapy, starting with the diuretic indapamide and adding the ACEI perindopril, if needed, to achieve the goal of 150 mm Hg. With the average additional decrease in BP of 15/6 mm Hg over placebo, the actively treated half achieved significantly greater protection against stroke, heart failure, and all-cause mortality after a median follow-up of only 1.8 years, causing the trial to be stopped prematurely by the data and safety monitoring board.

These impressive results are in keeping with the observation that older patients derive greater *absolute* benefit from any reduction in BP than do younger patients. As shown by Wang et al. (2005), the relative slopes of decreasing events with therapy are similar in the younger, older, and very old, but since the older start at higher degrees of risk, they achieve a greater absolute benefit (Fig. 5-6). Wang et al. (2005) further show that the lowering of systolic pressure is the critical element of therapy, regardless of the magnitude of the fall in diastolic pressure.

The results of all published antihypertensive RCTs on major cardiovascular events in patients under age 65, and those 65 years and older (not including

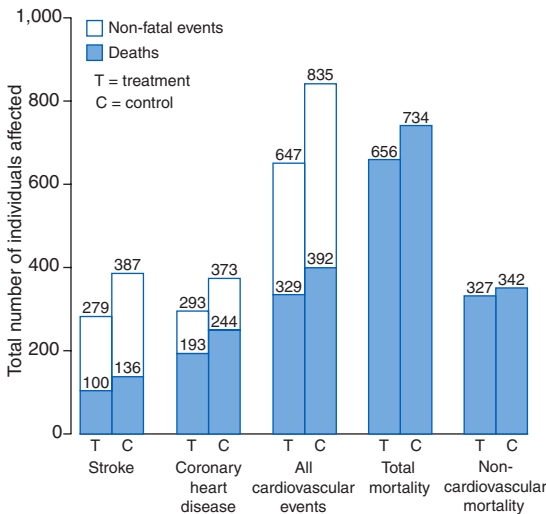


FIGURE 5-5 • Summarized results in 15,693 older patients with ISH above 160 mm Hg enrolled in eight trials of antihypertensive drug treatment. BP at entry averaged 174/83 mm Hg. During follow-up (median, 3.8 years), the mean difference in BP between the treated and control patients was 10.4 mm Hg systolic and 4.1 mm Hg diastolic. (Modified from Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: Meta-analysis of outcome trials. *Lancet* 2000;355:865–872.)

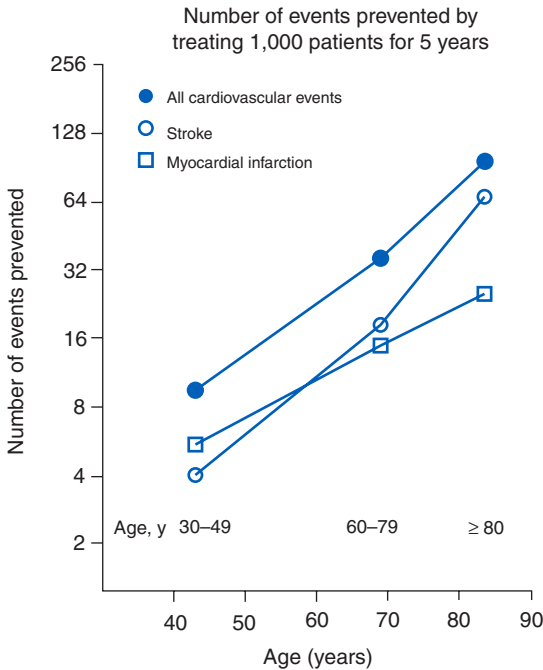


FIGURE 5-6 • Absolute benefits in the prevention of fatal and nonfatal cardiovascular events, stroke, and MI in three age groups. Symbols represent the number of events that can be prevented by treating 1,000 patients for 5 years. (Modified from Wang JG, Staessen JA, Franklin SS, et al. Systolic and diastolic blood pressure lowering as determinants of cardiovascular outcome. *Hypertension* 2005;45:907–913.)

HYVET), show similar risk reductions (Table 5-7) (Turnbull et al., 2008a). Thus, age per se is not a defining issue: Patients at any age with a reasonable

life expectancy deserve antihypertensive drug therapy if their SBP is 160 mm Hg or higher.

The data in Table 5-7 cover RCTs with either an ACEI or CCB versus placebo. The trials with an ARB were not placebo controlled.

Trials in Women

Meta-analysis of 31 RCTs by the Blood Pressure Lowering Treatment Trialists’ Collaboration of 31 RCTs found that all major classes of antihypertensives produce similar BP reductions in men and women and no evidence for gender-based differences in the CV protection afforded (Turnbull et al., 2008b).

Trials in Black Hypertensives

Non-Hispanic black patients have been underrepresented in most hypertension RCTs with the exception of ALLHAT and AASK. BP in black hypertensives responds less to monotherapy with renin-inhibiting drugs than it does in white hypertensives, and, in the ALLHAT trial, black hypertensives on the ACEI lisinopril had more heart failure and strokes than those on the diuretic chlorthalidone, which caused a larger fall in BP (Wright et al., 2005). In the long-term follow-up of the AASK cohort, the group originally randomized to the more stringent BP goal of <130/80 had slower progression of chronic kidney disease (CKD) to end-stage renal disease (ESRD) than the group originally randomized to the less

TABLE 5-7

Mean Differences in BP Between Randomized Groups in Younger and Older Adults

Treatment Comparison	Age < 65 (n = 96,466)		Age ≥ 65 (n = 94,140)	
	Age (Years)	Difference in SBP/DBP (mm Hg)	Age (Years)	Difference in SBP/DBP (mm Hg)
ACEI vs. placebo	57	-4.6/-2.1	70	-4.2/-2.0
CA vs. placebo	58	-7.2/-2.9	72	-9.3/-3.8
More vs. less ^a	57	-4.3/-3.5	70	-3.5/-3.4
ARB vs. other	56	-1.7/-0.3	75	-2.0/-1.2
ACEI vs. D/BB	55	1.3/0.2	73	2.0/0.5
CA vs. D/BB	58	1.1/-0.2	72	0.5/-0.4
ACEI vs. CA	59	0.9/0.6	73	1.0/1.0

^aMore vs. less intensive BP-lowering regimen.

SBP/DBP, systolic/diastolic blood pressure; ACEI, angiotensin-converting enzyme inhibitor; CA, calcium antagonist; ARB, angiotensin receptor blocker; D/BB, diuretic or β-blocker.

From Blood Pressure Lowering Treatment Trialists’ collaboration. *BMJ* 2008;336:1121.

stringent BP goal of <140/90 mm Hg but only in those with proteinuria (Appel et al., 2010).

Trials in Diabetic Patients

Fifteen RCTs of antihypertensive therapy in patients with type 2 diabetes mellitus or impaired fasting glucose are summarized in Table 5-8 (Bangalore et al., 2011). The two largest trials deserved special mention. In the Action in Diabetes and Vascular Disease: Preterax and Diamicon-MR Controlled Evaluation (ADVANCE) trial (see Tables 5-5 and 5-8), the relative risk of CV death fell by 18% when BP was reduced from 144/81 mm Hg to 139/79 mm Hg with a fixed combination of perindopril and indapamide versus placebo (Patel et al., 2007). In the Action to Control

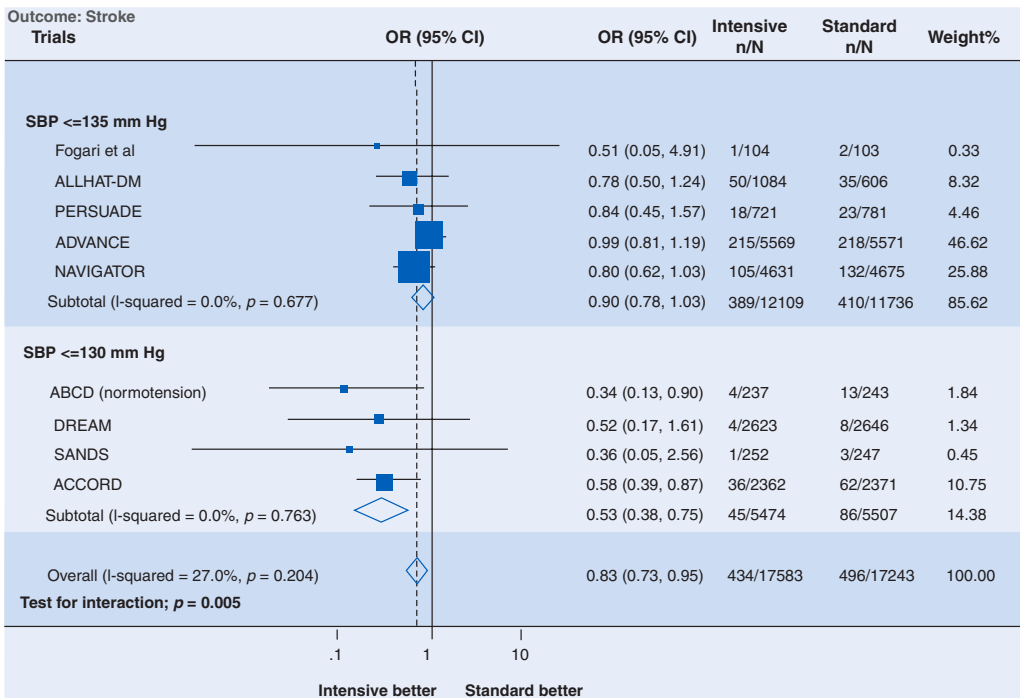
Cardiovascular Risk in Diabetes (ACCORD) trial, the risk of stroke fell by 50%, while the risk of coronary events was unchanged when SBP was reduced to 119 mm Hg rather than to 133 mm Hg (Cushman et al., 2010). The added benefit of more intensive BP reduction on stroke but not myocardial infarction (MI) in patients with diabetes is supported by two separate meta-analyses, the first of which is shown in Figure 5-7, (Bangalore et al., 2011; McBrien et al., 2012) but not by a more restrictive Cochrane review, which found no added benefit of intensive BP lowering on stroke or MI (Arguedas et al., 2013). Post hoc analysis of the diabetic subgroup (9,603 patients) in ONTARGET showed a progressive reduction in the risk of stroke but not MI with progressively lower achieved SBP down to a value of 111 mm Hg (Redon et al., 2012).

TABLE 5-8

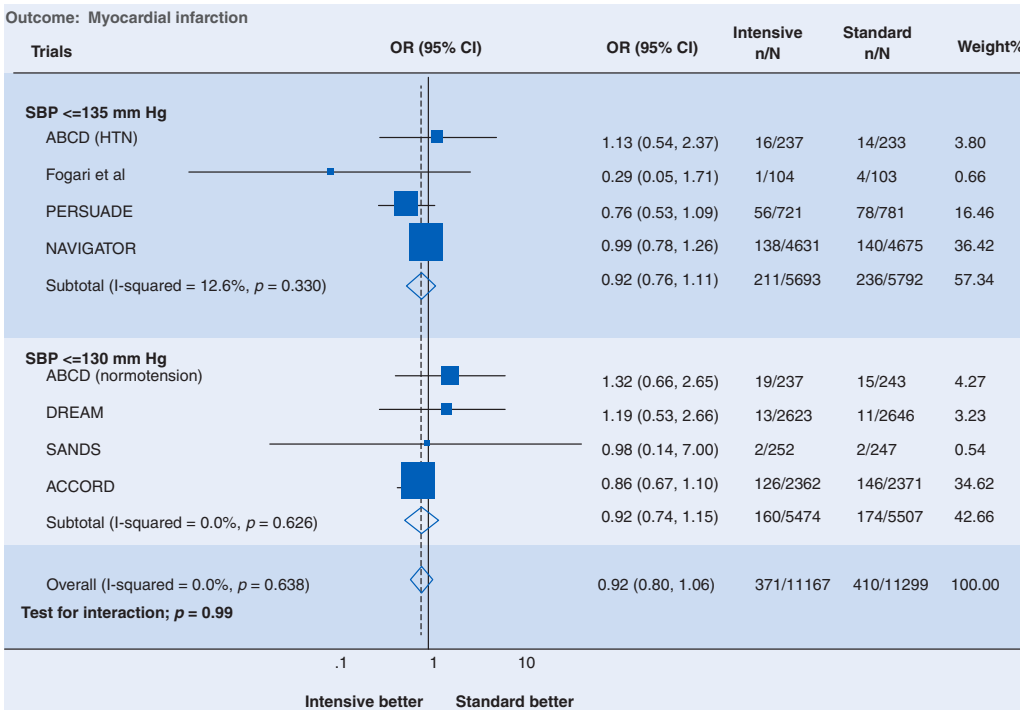
Randomized Controlled Trials of Antihypertensive Drug Therapy in Patients with Type 2 Diabetes or Impaired Fasting Glucose

Trial (Reference)	Comparison	No. of Patients	Mean Age, Years	Final Systolic BP (mm Hg)	Final Diastolic BP (mm Hg)
ABCD (hypertension) (Schrier et al., 2007)	More vs. less intensive BP lowering	470	58	133 vs. 139	78 vs. 86
ABCD (normotension) (Schrier et al., 2007)	More vs. less intensive BP lowering	480	59	128 vs. 137	75 vs. 81
ABCD-2 V (Estacio et al., 2006)	More vs. less intensive BP lowering	129	56	118 vs. 124	75 vs. 80
ACCORD (Cushman et al., 2010; Chew et al., 2010)	More vs. less intensive BP lowering	4,733	66	119 vs. 134	64 vs. 71
ADVANCE (Patel et al., 2007)	Perindopril-indapamide vs. placebo	11,140	66	135 vs. 140	74 vs. 76
ALLHAT (new diabetic) (Barzilay et al., 2004)	Doxazosin vs. chlorthalidone	1,690	67	139 vs. 134	77 vs. 75
Chan et al. (1992)	Enalapril vs. nifedipine	102	58	137 vs. 132	72 vs. 73
DIRECT Project 2 (2009)	Candesartan vs. placebo	1,905	57	119 vs. 123	73 vs. 76
DREAM (Bosch et al., 2006)	Ramipril vs. placebo	5,269	55	128 vs. 132	78 vs. 80
Fogari et al. (2002)	Fosinopril/amlodipine vs. amlodipine	207	62	132 vs. 140	82 vs. 87
GUARD (Bakris et al., 2008)	Benazepril/amlodipine vs. benazepril/HCTZ	304	58	130 vs. 132	88 vs. 87
NAVIGATOR (McMurray et al., 2010)	Valsartan vs. placebo	9,306	64	133 vs. 136	78 vs. 80
PERSUADE (Daly et al., 2005)	Perindopril vs. placebo	1,502	62	132 vs. 137	77 vs. 78
SANDS (Howard et al., 2008)	More vs. less intensive BP lowering	499	56	117 vs. 129	67 vs. 73

BP, blood pressure; ABCD, Appropriate Blood Pressure Control in Diabetes; ABCD-2 V, ABCD-2 Valsartan; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon-MR Controlled Evaluation; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; DIRECT, Diabetic Retinopathy Candesartan Trials; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; GUARD, Gauging Albuminuria Reduction with Lotrel in Diabetic Patients with Hypertension; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; PERSUADE, Perindopril Substudy in Coronary Artery Disease and Diabetes; and SANDS, Stop Atherosclerosis in Native Diabetics Study. Adapted from Bangalore S, Kumar S, Lobach I, et al. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: Observations from traditional and bayesian random-effects meta-analyses of randomized trials. *Circulation* 2011;123:2799-2810.



A



B

FIGURE 5-7 • Intensive versus standard BP control and (A) stroke and (B) MI. Results are further stratified by achieved systolic pressure in the intensive group. The size of the data marker represents the weight of each trial. OR indicates odds ratio; CI, confidence interval; SBP, systolic blood pressure; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; PERSUADE, Perindopril Substudy in Coronary Artery Disease and Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon-MR Controlled Evaluation; NAVIGATOR, Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research; ABCD, Appropriate Blood Pressure Control in Diabetes; DREAM, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; SANDS, Stop Atherosclerosis in Native Diabetics Study; and ACCORD, Action to Control Cardiovascular Risk in Diabetes. (From Bangalore S, Kumar S, Lobach I, et al. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: Observations from traditional and bayesian random-effects meta-analyses of randomized trials. *Circulation* 2011;123:2799–2810, p. 9)

Trials in Patients with Chronic Kidney Disease

In patients with CKD, the goals of antihypertensive therapy are to reduce the risks of both ESRD and CV events. In two trials of patients with diabetic nephropathy (IDNT and RENAAL), those treated with an ARB had slowed progression of renal damage (Brenner et al., 2001; Lewis et al., 2001)—a conclusion that has been confirmed by a recent meta-analysis (Khan et al., 2013). The achieved BPs in the active treatment groups of IDNT and RENAAL were 140/74–77, with small additional reductions in BP from addition of an ARB being associated with 20% to 28% reduction in the rate of renal decline or incident ESRD (see Table 5-5). Available data on nondiabetic CKD are limited with a recent meta-analysis of only 2,272 participants of

3 trials (REIN, AASK, and MDRD) showing suggestive but inclusive evidence that a BP target of <130/80 mm Hg might afford greater renal protection than a BP target of <140/90 mm Hg but only in the subset of patients with proteinuria (300 to 1,000 mg of protein per 24 hours) (Upadhyay et al., 2011).

A recent meta-analysis of 152,290 participants of 26 RCTs compared the CV benefits of antihypertensive therapy in patients with eGFR above or below 60 mL/min/1.73 m²; mean baseline BP ranged from 141/82 to 170/104 mm Hg, while mean achieved BP ranged from 135/78 mm Hg to 151/81 mm Hg (Table 5-9) (Ninomiya et al., 2013). Patients with CKD derived the same relative CV risk reduction as non-CKD patients but greater reduction in absolute risk. The benefit was tied to BP reduction rather than drug class, even when comparing ACEIs and CCBs (Fig. 5-8).

TABLE 5-9

Mean Baseline Characteristics and Follow-Up Differences in BP Between Randomized Groups According to Different eGFR

Treatment Comparison	No. of Patients	Mean Age, Years	Baseline eGFR (mL/min/1.73 m ²)	Baseline BP (mm Hg)	Final BP (mm Hg)
All Trials					
eGFR ≥ 60	121,995	63	81	156/91	141/81
eGFR < 60	30,295	68	52	160/90	144/80
Active Treatment vs. Placebo					
ACEI vs. placebo					
eGFR ≥ 60	42,896	62	82	141/82	135/78
eGFR < 60	11,399	67	52	145/82	137/77
CCB vs. placebo					
eGFR ≥ 60	4,252	66	77	164/85	151/81
eGFR < 60	1,855	70	52	169/84	143/83
More Intensive vs. Less Intensive Regimens					
eGFR ≥ 60	16,687	60	81	168/104	142/83
eGFR < 60	3,979	65	52	170/104	143/83
Comparisons of Drug Classes					
ACEI vs. diuretic or β-blocker					
eGFR ≥ 60	36,540	63	81	156/90	143/83
eGFR < 60	8,686	71	51	162/89	146/81
CCB vs. diuretic or β-blocker					
eGFR ≥ 60	34,838	64	81	159/93	144/83
eGFR < 60	7,671	70	52	163/91	147/82
ACEI vs. CCB					
eGFR ≥ 60	19,520	67	83	153/87	141/80
eGFR < 60	5,022	72	51	161/88	147/80

ACEI, angiotensin-converting enzyme inhibitor.

Adapted from Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: Meta-analysis of randomized controlled trials. *BMJ* 2013;347:15680. doi: 10.1136/bmj.55680

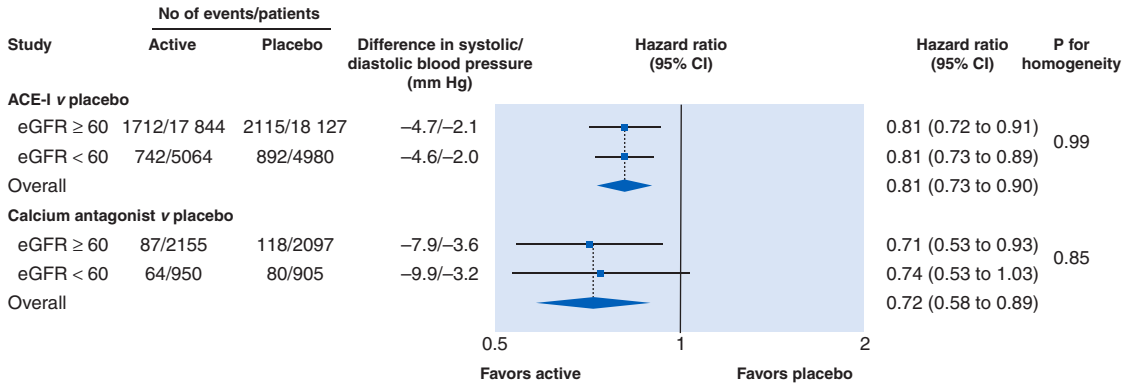


FIGURE 5-8 • Effects of angiotensin-converting enzyme inhibitor or calcium antagonist–based regimens versus placebo for risk of major cardiovascular events according to kidney function status. P value for homogeneity indicates consistency of effect of treatment regimen among subgroup. Overall mean difference in systolic and diastolic BP during follow-up in actively treated/first listed regimens versus control/second listed regimens, calculated by weighting difference observed in each contributing trial by number of patients in trial. Negative values indicate lower mean systolic and diastolic BP during follow-up in actively treated/first listed groups than in control/second listed groups. (From Blood Pressure Lowering Treatment Trialists' Collaboration. Blood pressure lowering and major cardiovascular events in people with and without chronic kidney disease: Meta-analysis of randomized controlled trials. *BMJ* 2013;347:15680. doi: 10.1136/bmj.55680)

Trials in Cardiac Patients

In addition to the documentation that coronary artery disease (CAD) morbidity and mortality have been significantly prevented by low-dose diuretics, CCBs, ACEIs, and ARBs reviewed earlier in this chapter (Figs. 5-2 and 5-4), additional RCTs have examined the effect of antihypertensive agents for secondary prevention of CAD.

Angina and Coronary Disease

Nitrates, β -blockers, and CCBs had been used for many years on the basis of efficacy in reducing symptoms with little or no hard outcome data. When given to patients with high CV risk profiles, whether hypertensive or normotensive, addition of an ACEI reduced major CV events more than placebo (with ramipril) in the Heart Outcomes Protection Evaluation (HOPE) study (Yusuf et al., 2000) or (with perindopril) in the European Trial on Reduction of Cardiovascular Events with Perindopril in Stable Coronary Artery Disease (EUROPA) study (Fox, 2003) but not (with trandolapril) in the Prevention of Events with Angiotensin-Converting Enzyme Inhibitor (PEACE) trial (Braunwald et al., 2004), in which most patients with stable coronary disease were on background statin therapy and other CV reduction therapies. The CAMELOT trial (Nissen et al., 2004) showed that amlodipine, but not enalapril, further protected patients with CAD even when they were normotensive. It is unclear whether the added benefit with amlodipine seen in this rather

small study was due to the drug's antiischemic rather than antihypertensive effect.

Congestive Heart Failure

In ALLHAT, the ACEI was somewhat less effective than the diuretic chlorthalidone in primary prevention of heart failure, but this may be an artifact of the design in which preexisting diuretic therapy was withdrawn in the ACEI arm (ALLHAT Officers and Coordinators, 2002). Multiple trials, a few placebo controlled and mostly of short duration, have shown reduction in hospitalizations and mortality in patients with chronic heart failure with diuretics, β -blockers, ACEIs, ARBs, aldosterone antagonists, and, in blacks, a combination of hydralazine and nitrate. However, none of these trials were hypertensive treatment trials as medication was not titrated to lower BP. In the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE), the ARB did not reduce CV events more than placebo (Massie et al., 2008). In the recent TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial, results presented at the 2013 AHA Scientific Sessions (Pfeffer and on behalf of the TOPCAT Investigators, 2013) indicate that spironolactone did not reduce the primary outcome of cardiovascular death, heart failure hospitalization, or surviving a cardiac arrest in patients with heart failure and preserved ejection fraction; however, spironolactone did reduce the major burden

faced by these patients—the risk of repeated hospitalizations for heart failure.

Trials in Patients with Stroke

In the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial of patients who had survived ischemic or hemorrhagic stroke, outpatient SBP reduction by 12 mm Hg to a value of 135 mm Hg with an ACEI/diuretic (perindopril/indapamide) combination reduced the relative risk of recurrent ischemic stroke by 36% and recurrent hemorrhagic stroke by 76% more than placebo; however, a smaller reduction in BP of only 5 mm Hg with perindopril monotherapy showed no stroke protection (PROGRESS Collaborative Group, 2001). Similarly, in the subsequent Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial of patients with ischemic stroke, no statistical benefit was found when SBP was reduced by only 4 mm Hg with ARB (telmisartan) monotherapy versus placebo (Yusuf et al., 2008).

Along with antihypertensive therapy, reduction of blood cholesterol with statins has provided another 21% reduction in stroke incidence in high-risk patients (Heart Protection Study, Collins et al., 2004), a 48% reduction in patients with high C-reactive protein levels and LDL cholesterol < 130 mg/dL (Ridker et al., 2008), and a 27% reduction in hypertensives (Sever et al., 2003). Statin therapy also is effective in secondary stroke prevention (Amarenco et al., 2006).

Cognitive Function

Strong observational data suggest that antihypertensive therapy reduces the risk of dementia, but the data from RCTs still are inconclusive (Gorelick et al., 2012). The only specific drug that has been shown in an RCT to prevent dementia is the CCB nitrendipine in the Syst-Eur trial (Gorelick et al., 2012).

An Overview of the Benefits of Therapy

Despite all of the preceding evidence that treatment of hypertension reduces cardiovascular disease, the overall role of antihypertensive therapy in the impressive falls in coronary and stroke mortality seen in most developed societies over the past 40 years turns out to be rather small. Recall from Chapter 1 that the best available evidence gives the treatment of hypertension only 3% and population-wide lowering of BP 9.5% of

the credit for the 62% decline in men and the 45% decline in women in coronary mortality in England and Wales between 1981 and 2000 (Unal et al., 2004).

The reasons for this limited role are multiple, including

- Suboptimal hypertension control rates in the population despite gradual improvement
- Inability to provide effective preventive therapy before the inexorable progress of hypertension-related complications
- Inadequate attention to concomitant risk factors, leaving a large residual of risk even among those treated

These issues and others are addressed in the remainder of this chapter and in Chapter 7, but first we will examine one of the more attractive aspects of treating hypertension, namely, its cost-effectiveness.

Cost-Effectiveness of Treating Hypertension

The treatment of hypertension is among the most cost-effective measures now available for preventing avoidable death (Stason, 2009). Using various mathematical modeling techniques and Markov decision analyses, most recent estimates find that treatment of hypertension provides additional quality-adjusted life-years (QALYs) for a far lower cost than treatment of dyslipidemia or diabetes. In patients with diabetes, the message is clear: Control of hypertension actually has a net cost savings, whereas control of hyperglycemia and control of hypercholesterolemia—though cost-effective (i.e., <\$50,000 per QALY)—still entail a net-positive cost (CDC Diabetes Cost-Effectiveness Group, 2002). The cost savings from fewer hospitalizations and less long-term care for stroke, coronary events, and microvascular complications of diabetes outweigh the costs of office visits and drugs to manage hypertension.

Traditional cost-effectiveness analyses are performed from the theoretical societal perspective using long-term (e.g., 10- to 30-year) projections. However, from a more practical perspective, payers are interested in short-term projections, because enrollee turnover is high, and achievement of quality metrics, which trigger reimbursement. Using the National Committee on Quality Assurance's Health Care Effectiveness Data and Information System (HEDIS) database, which enables health plans to monitor and report quality metrics of the care delivered to enrollees,

Nuckols et al. (2011) estimated that to increase the United States (U.S.) hypertension control rate from 50% currently to 70%, health plan expenditures for office visits and medications would cost an additional \$170 per hypertensive patient per year (from \$29.5 billion to \$42 billion nationally).

This additional cost may fall soon due to several recent trends:

- New drug development in hypertension has slowed considerably, and drug costs will continue to decline as more drugs become generic and \$4 per month formularies expand.
- Physician office visits for hypertension will decrease with the expansion of telemedicine programs, increased utilization of nonphysician care providers and low-cost medical assistants, and emergence of self-medication titration protocols.
- Affordable Care Act initiatives are moving away from fee-for-service payments to bundled payments based on achievement of quality metrics (HEDIS scores).

High HEDIS scores for high BP management should be easier for physicians to achieve if policy makers adopt the new more relaxed guideline recommendations about when drug therapy should be started and the goals of therapy (see Table 5-10 and accompanying text).

WHEN SHOULD DRUG THERAPY BE STARTED?

Before addressing the question, “When should drug therapy be started?,” one caveat must always be recalled: An initially elevated office BP, above 140 mm Hg systolic or 90 mm Hg diastolic, must always be confirmed either by home or ambulatory BP monitoring—as emphasized by both the new European guidelines (Mancia et al., 2014) and updated UK guidelines (Krause et al., 2011)—or remeasured at least three times over at least 4 weeks to ensure that hypertension is present. Only if the office level is very high (>180/110 mm Hg) or if symptomatic target organ damage is present should therapy be begun before the diagnosis is carefully established.

On the other hand, in view of the risks of even “high-normal” BP or “prehypertension” (Vasan et al., 2001), therapy in the future may be indicated for many more patients even without hypertension as currently defined. Yet, the desire to expand the

number of people receiving BP-lowering medication already has begun to collide with societal needs to limit health care expenditures and increasing demands for evidence-based practice guidelines. The late John Swales (Swales, 2000), who served in the UK government for 3 years, wrote of this issue:

The lower the blood pressure level at which treatment is recommended, the smaller the probability of the individual benefiting and the greater the number of patients eligible for treatment. There is a continuous inverse relationship between individual benefit and the total cost of health care. At some point, a decision has to be made that the cost of treating a low level of risk is not justified.

Rationale for Risk-Based Guidelines

Guidelines for the institution of therapy have been based solely on the level of BP, giving rise to major irrationalities and inconsistencies. As noted by Jackson et al. (1993),

This has led to the situation in which a 60-year-old woman with a diastolic BP of 100 mm Hg but no other risk factors (her absolute risk of cardiovascular disease is about 10% in 10 years) may meet the criteria for treatment, whereas a 70-year-old man with multiple risk factors but a diastolic BP of 95 mm Hg (his absolute risk is about 50% in 10 years) may not. The treatment of these two patients would be expected to reduce the absolute risk in the 60-year-old woman by nearly 3% in 10 years (30% of 10%) but in the 70-year-old man by approximately 17% (30% of 50%).

In the previous edition of this textbook, we noted:

All [other hypertension guidelines] but the U.S. JNC-7 continue to use overall risk assessment in determining the threshold to start therapy. The failure of JNC-7 to utilize even a crude profile will almost certainly be corrected in the new JNC-8 Report.

Our prediction did not turn out. No mention is made of overall risk assessment in the 2014 report from the JNC 8 committee (James et al., 2014), the 2013 guidelines from the American Society of Hypertension (ASH)/International Society of Hypertension (ISH) (Weber et al., 2014), or the 2013 hypertension guidelines from the ACC/AHA/CDC (Go et al., 2014). In contrast, the 2013 ESH/ESC guidelines (Mancia et al., 2014) and the 2011 UK guidelines (Krause et al., 2011) use both global risk and BP level to decide when and how therapy should be started.

New Risk-Based Cholesterol Guidelines

At the same time, the situation has changed dramatically with the 2013 ACC/AHA cholesterol treatment guidelines (Stone et al., 2013), which are rigorously based on risk assessment. A large paradigm shift, treating to LDL cholesterol targets, is no longer recommended; rather, clinicians should determine whether a patient falls into one of four mutually exclusive high-risk groups for atherosclerotic cardiovascular disease (ASCVD) and should initiate statin therapy as follows:

- ▶ Patients with *clinical* ASCVD should receive high-intensity (age < 75) or moderate-intensity (age ≥ 75) statin therapy.
- ▶ Patients with *LDL-C* ≥ 190 mg/dL should receive high-intensity statin therapy.
- ▶ Patients with *diabetes* (type 1 or type 2; age 40 to 75 years) with LDL-C of 70 to 189 mg/dL and without clinical ASCVD should receive at least moderate-intensity statin therapy or possibly high-intensity statin therapy when estimated 10-year ASCVD risk is ≥7.5%.
- ▶ Patients ages 40 to 79 years without clinical ASCVD or diabetes but with LDL cholesterol levels of 70 to 189 mg/dL and *estimated 10-year ASCVD risk* ≥7.5% should receive moderate- or high-intensity statin therapy.

Most hypertensive patients will fall into one of these groups and will benefit from moderate- or high-intensity statin therapy. High-intensity statin therapies are atorvastatin (40 to 80 mg) or rosuvastatin (Crestor; 20 to 40 mg). Moderate-intensity statin therapies include atorvastatin (10 to 20 mg), rosuvastatin (5 to 10 mg), simvastatin (20 to 40 mg), pravastatin (40 to 80 mg), and several others. “Statin-intolerant” patients still may benefit from lower doses.

Ten-year ASCVD risk—which includes both coronary events and stroke—is determined using an online calculator (Fig. 5-9) that can be accessed through the following Web site: <http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx>.

New Pooled Cohort ASCVD Risk Calculator (Fig. 5-9)

Despite its great familiarity, the Framingham Heart Study risk calculator is derived from a single white cohort. New equations were developed to estimate the

10-year risk for developing a first ASCVD event (non-fatal MI, CHD death, or fatal or nonfatal stroke) using pooled data from several large, racially and geographically diverse, modern NHLBI-sponsored cohort studies, including the ARIC (*Atherosclerosis Risk in Communities*) study, the Cardiovascular Health Study, and the CARDIA (*Coronary Artery Risk Development in Young Adults*) study, combined with applicable data from the Framingham Original and Offspring Study cohorts.

State-of-the-art statistical methods were used to derive and internally validate the Pooled Cohort Equations, which provide gender- and race-specific estimates of the 10-year risk for ASCVD for African American and White men and women 40 to 79 years of age. The variables that statistically merited inclusion in the risk assessment equations are age, total and HDL cholesterol, SBP (including treated or untreated status), diabetes, and current smoking status.

New Evidence-Based Hypertension Guidelines

New guidelines from seven expert committees have been published since 2010 (Table 5-10). Several new changes are notable:

- ▶ The new guidelines are increasingly more evidence based than in the past.
- ▶ The 2014 report from the JNC 8 panel members (James et al., 2014) may be the most strictly evidence-based set of guidelines produced to date (Bauchner et al., 2014). Treatment recommendations are based on strict interpretation of data only from RCTs in hypertension; major RCTs of anti-hypertensive agents were excluded from consideration if the study population included patients with high ASCVD risk with or without hypertension. Unlike past JNCs, the 2014 report of the JNC 8 panel members (referred to as “JNC 8”) is not a comprehensive set of practice guidelines. It does not address important practical issues such as medication compliance or home and ambulatory BP monitoring. Before the report was finalized in 2013, the National Institutes of Health (NIH) decided it would no longer sanction professional practice guidelines (James et al., 2014). While the final report underwent peer review before being published by JAMA (Peterson et al., 2014), “JNC 8” differs from the preceding JNCs in that it is sanctioned neither by the NIH nor by any professional

	A	B	C	D	E												
1			Enter patient values in this column														
2	Risk Factor	Units	Value	Acceptable range of values	Optimal values												
3	Sex	M (for males) or F (for females)	m	M or F													
4	Age	years	50	20-79													
5	Race	AA (for African Americans) or WH (for Whites or others)	wh	AA or WH													
6	Total Cholesterol	mg/dL	200	130-320	170												
7	HDL-Cholesterol	mg/dL	30	20-100	50												
8	Systolic Blood Pressure	mm Hg	140	90-200	110												
9	Treatment for High Blood Pressure (if SBP >120)	Y (for yes) or N (for no)	n	Y or N	N												
10	Diabetes	Y (for yes) or N (for no)	n	Y or N	N												
11	Smoker	Y (for yes) or N (for no)	n	Y or N	N												
12																	
13	Your 10-Year ASCVD Risk (%)	0.0	<p>10-Year and Lifetime ASCVD Risks</p> <table border="1"> <thead> <tr> <th>Risk Category</th> <th>Predicted Risk (%)</th> </tr> </thead> <tbody> <tr> <td>Your 10-Year ASCVD Risk</td> <td>0.0</td> </tr> <tr> <td>10-Year ASCVD Risk (%)</td> <td>2.1</td> </tr> <tr> <td>Row 15</td> <td>0.0</td> </tr> <tr> <td>Your Lifetime ASCVD Risk (%)</td> <td>2.1</td> </tr> <tr> <td>Lifetime ASCVD Risk (%)</td> <td>5.0</td> </tr> </tbody> </table>			Risk Category	Predicted Risk (%)	Your 10-Year ASCVD Risk	0.0	10-Year ASCVD Risk (%)	2.1	Row 15	0.0	Your Lifetime ASCVD Risk (%)	2.1	Lifetime ASCVD Risk (%)	5.0
Risk Category	Predicted Risk (%)																
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Your Lifetime ASCVD Risk (%)	2.1																
Lifetime ASCVD Risk (%)	5.0																
14	10-Year ASCVD Risk (%) for Someone Your Age with Optimal Risk Factor Levels (shown above in column E)	2.1															
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16	Your Lifetime ASCVD Risk* (%)	0.0															
17	Lifetime ASCVD Risk (%) for Someone at Age 50 with Optimal Risk Factor Levels (shown above in column E)	5.0															
18																	
19	*This is the lifetime ASCVD risk for an individual at age 50 years with your risk factor levels. In rare cases, 10-year risks may exceed lifetime risks given that the estimates come from different approaches.																
20																	
21	Abbreviations: AA= African American; ASCVD = Atherosclerotic cardiovascular disease, defined as CHD death, nonfatal myocardial infarction, or fatal or non fatal stroke; F = Female; M [= Male; N = No; WH = White; Y = Yes.																
22																	
23																	
24																	

FIGURE 5-9 • 2013 AHA/ACC atherosclerotic cardiovascular disease (ASCVD) risk calculator. (From Goff DC, Lloyd-Jones DM, Bennett G, Coady S et al., 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013; 01.cir.0000437741.48606.98 [pii];10.1161/01.cir.0000437741.48606.98 [doi])

TABLE 5-10

Thresholds for Initiation of Drug Therapy in Current Guidelines

Level of Risk	"JNC 8" (James et al., 2014)	ASH/ISH (Weber et al., 2014)	ACC/AHA/ CDC (Go et al., 2014)	ESH/ESC (Mancia et al., 2014)	CHEP (Hackam et al., 2013)	UK NICE (Krause et al., 2011)	ISHIB (Flack et al., 2010)
"Elderly"	≥150/90 (60+ y)	≥150/90 (80+ y)	≥140/90	≥160 systolic (80+ y)	≥150/90 (80+ y)	≥150/90 (80+ y)	Not specified
General, no risk factors or organ damage	≥140/90	≥140/90	≥140/90	≥150/90	≥160/100	≥140/90	≥135/85
General, + risk factors or organ damage	≥140/90	≥140/90	≥140/90	≥140/90	≥140/90	≥140/90	≥130/80
Diabetes	≥140/90	≥140/90	≥140/90	≥140/90	≥130/80	≥140/90	≥130/80
CKD	≥140/90	≥140/90	≥140/90	≥140/90	≥140/90	≥140/90	≥135/80

JNC 8, 2014 Report of the Committee Members Appointed to the 8th Joint National Committee; ASH, American Society of Hypertension; ISH, International Society of Hypertension; AHA, American Heart Association; ACC, American College of Cardiology; CDC, Centers for Disease Control and Prevention; CHEP, Canadian Hypertension Education Program; UK, United Kingdom; NICE, National Institute for Health and Clinical Excellence; ISHIB, International Society of Hypertension in Blacks.

medical society and thus does not constitute the official U.S. hypertension guidelines. As a result, other practice guidelines appeared in 2014 from the American Society of Hypertension (ASH)/International Society of Hypertension (ISH) (Weber et al., 2014) and from the ACC/AHA/CDC (Go et al., 2014).

- ▶ Most of the new evidence-based guidelines have raised the threshold for initiation of drug therapy in the hypertensive “elderly” to ≥150/90 mm Hg (160 systolic by the 2013 ESH/ESC guidelines) (Mancia et al., 2014) and in patients with diabetes or CKD from ≥130/80 to ≥140/90 mm Hg (except for the 2013 Canadian guidelines, which kept the ≥130/80 mm Hg threshold for diabetes) (Hackam et al., 2013).
- ▶ Only “JNC 8” defines “elderly” as 60 years or older, whereas the other guidelines define elderly as 80 years or older (see Table 5-9). Several JNC 8 panel members did not support this definition and wrote a minority view position paper (Wright et al., 2014), citing the following evidence supporting a treatment threshold of 140 mm Hg systolic for patients aged 60 to 79:
 - ▶ Increasing the treatment threshold to 150 mm Hg systolic and the treatment target to 140 to 149 mm Hg (rather than 10 mm Hg lower) will likely reduce the

intensity of antihypertensive therapy in the large population at the highest risk for hypertensive complications including black adults (as incorporated into the new ASCVD risk calculator in Figure 5-7).

- ▶ The evidence supporting the new higher (systolic of 150 mm Hg) threshold was based on insufficient evidence.
- ▶ The higher SBP goal in persons aged 60 year or older runs the considerable risk of increasing population-level BPs and reversing the progressive decline in CV disease, especially stroke.

All but the three sets of guidelines from the U.S. use global ASCVD risk in deciding when to initiate therapy. The UK guidelines continue to be most conservative, reserving drug therapy in stage 1 hypertension only for those with clinical CV disease, target organ damage, diabetes, CKD, or an estimated 10-year CV disease risk of ≥20% (Krause et al., 2011). As seen in Table 5-11, the 2013 European guidelines (Mancia et al., 2014) use risk factors, target organ damage, and the presence of overt clinical disease to determine the overall degree of risk, using a stratification chart to classify risk from “low” to “very high” (Table 5-12). In turn, the level of risk is used to decide upon the need to begin therapy or to continue to monitor.

TABLE 5-11

Factors Other than BP Level that Influence Global Cardiovascular Risk in Patients with Hypertension

Risk Factors

- Male
- Age (men \geq 55 y, women \geq 65 y)
- Smoking
- Dyslipidemia
- Impaired fasting glucose (100–125 mg/dL)
- Obesity (BMI \geq 30 kg/m² or waist circumference: men \geq 102 cm, women \geq 88 cm)
- Family history or premature CVD (men aged < 55 y, women aged < 65 y)

Asymptomatic Target Organ Damage

- LVH by ECG or transthoracic echocardiography
- CKD (eGFR \leq 60 mL/min/1.73 m²)
- Microalbuminuria (albumin/creatinine ratio 30–300 mg/g)
- Ankle–brachial index < 0.9
- Pulse wave velocity > 10 m/s

Diabetes Mellitus (fasting plasma glucose \geq 126 mg/dL \times 2; or HBA1C \geq 7%; or postload plasma glucose > 198 mg/dL)

Established Cardiovascular or Renal disease

- Stroke or TIA
- CAD: MI, angina, myocardial revascularization
- Heart failure (with decreased or preserved ejection fraction)
- Intermittent claudication (symptomatic peripheral artery disease)
- CKD with eGFR < 30 mL/min/1.73 m²
- Advanced retinopathy: hemorrhages or exudates, papilledema

LVH, left ventricular hypertrophy; CKD, chronic kidney disease; CAD, coronary artery disease; TIA, transient ischemic attack; GFR, glomerular filtration rate

Adapted from Mancia G et al. 2014 ESH/ESC Guidelines for the management of arterial hypertension. *J Hypertens* 2013;31:1281–1356.

Should the Threshold Be Lower?

However, as easier to take and more effective drugs have become available, some have argued that they be given to people who are not yet hypertensive in an attempt to prevent both the onset of elevated BP and the vascular damage that may develop before the level goes beyond the 140/90 mm Hg threshold. The rationale includes the inability of current therapy, as used in clinical practice, for those with BP greater than

140/90 to provide more than partial protection, about 40% against strokes, but only 25% against heart disease.

Stevo Julius, in particular, has argued that drug therapy should be started earlier despite the lack of evidence of benefit, a lack that is attributable to the absence of long-term trials in subjects with BP below 140/90 mm Hg. To provide such evidence, the TROPHY (Trial of Preventing Hypertension) trial (Julius et al., 2006) was begun in 1999 using an ARB in half of 809 patients whose BP was between 130 and 139 mm Hg systolic and 85 and 89 mm Hg diastolic. During the 2 years on the ARB, the number of those progressing to hypertension, i.e., BP 140/90 or higher, was 66% lower than in those on placebo. However, 2 years after the ARB was discontinued, there was only a 16% lesser onset of hypertension in the previously tested group compared to the placebo group.

Lower Thresholds for Higher-Risk Patients?

The 2003 JNC 7 report (Chobanian et al., 2003) recommended 140/90 mm Hg as the threshold for starting drug therapy for most hypertensive patients and a lower threshold of 130/80 mm Hg for those with diabetes mellitus or CKD because these comorbid conditions are associated with very high CV risk. Then, the 2008 AHA/ACC position statement on treatment of hypertension in patients with coronary disease (Rosendorff et al., 2007) expanded the 130/80 threshold to include patients with known or suspected coronary disease or peripheral arterial disease or those requiring primary prevention for a high global CV risk. Now, the JNC 8 panel members (James et al., 2014) and the new European guidelines panel (Mancia et al., 2014) conclude that these earlier recommendations for the 130/80 mm Hg treatment target had been based largely on expert opinion.

On the other hand, recent meta-regression analyses by the BP Lowering Treatment Trialists show that additional reduction in BP (systolic or diastolic) produces additional reduction in the risk of CV disease regardless of the initial BP level, even at an initial SBP < 140 mm Hg or an initial diastolic BP < 80 mm Hg (Fig. 5-10) (Czernichow et al., 2011). These analyses support the utilization of BP-lowering medication in high-risk patients with and without hypertension.

TABLE 5-12

Stratification of Total Cardiovascular Disease Risk by BP and Other Factors

Other risk factors, asymptomatic organ damage	Blood Pressure (mm Hg)			
	High-normal SBP 130–139 or DBP 85–89	Grade 1 HTN SBP 140–159 or DBP 90–99	Grade 2 HTN SBP 160–179 or DBP 100–109	Grade 3 HTN SBP ≥ 180 or DBP ≥ 110
No other RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to moderate risk	Moderate to high risk	High risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥ 4, or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

SBP, systolic blood pressure; DBP, diastolic blood pressure; RF, risk factor; OD, organ disease; CVD, cardiovascular disease; CKD, chronic kidney disease.

Adapted from Mancia G et al. 2014 ESH/ESC Guidelines for the management of arterial hypertension. *J Hypertens* 2013;31:1281–1356.

Overall Management

The bottom line is this: Most hypertensives have fairly mild, asymptomatic hypertension, and the benefits of treatment—measured as the reduction of hard end points—progressively decline the milder the degree of hypertension. Many patients receive relatively little benefit yet are exposed both to the adverse side effects and to the fairly large financial costs of therapy. Therefore, for maximal patient benefit, a management strategy based on overall risk is rational and appropriate. On the other hand, those at higher degrees of risk likely achieve better protection when treated at lower levels of BP. The situation would obviously change if and when the earlier use of antihypertensive drug therapy is shown to prevent the progression of BP and cardiovascular damage in those with BPs lower than the currently accepted lower threshold for institution of therapy.

Now that the rationale for the institution of therapy has been described, let us turn to the issue of how far to lower the pressure.

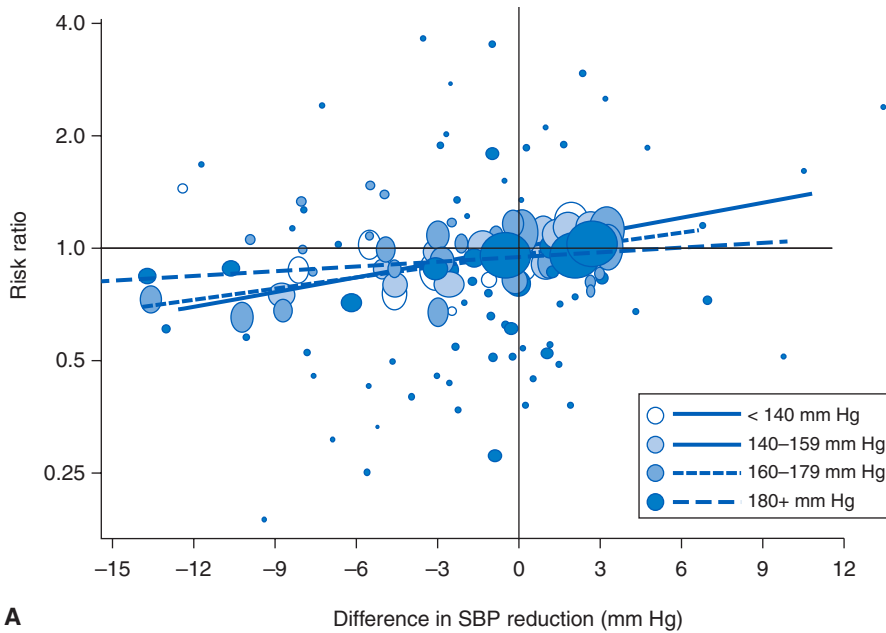
GOAL OF THERAPY

Logically, the goal of therapy should be to lower BP below the threshold for starting therapy. Until recently, the general attitude was “the lower, the better.” JNC 7

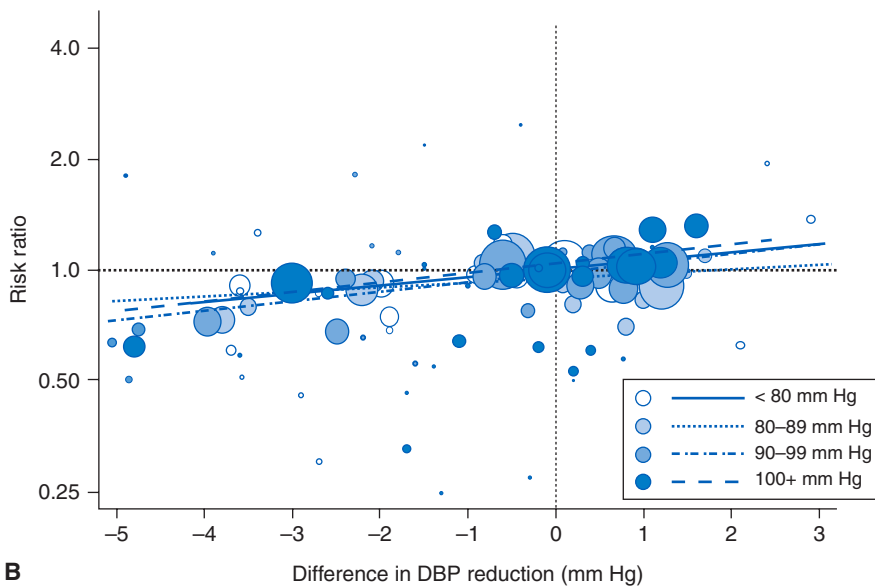
emphasized the impressive observational data from the Prospective Trialists' Collaboration (Chapter 1, Figure 1-1) (Lewington et al., 2002) showing that the risks of fatal CHD and fatal stroke increase logarithmically beginning at a BP as low as 115/75 mm Hg. However, the JNC 8 report concluded that RCTs do not support benefits of reducing BP to less than the 140/80 for patients ≥ age 60 or below 130/80 for patients less than age 60 or those with diabetes or CKD.

The small number of RCTs that prospectively compared more intense with less intense antihypertensive therapy are summarized as follows (Table 5-13):

- Stroke:** In the recent SPS3 trial, no difference was found in the risk of total CV events in patients with recent lacunar infarcts when SBP was lowered to 127 mm Hg rather than 138 mm Hg, but the risk of subsequent hemorrhagic stroke was reduced by more than 60% (Benavente et al., 2013).
- Diabetes:** In the ACCORD trial, no difference was found in coronary events in patients with diabetes whose SBP was reduced to 119 mm Hg compared with 133 mm Hg but, once again, a greater reduction in stroke (Cushman et al., 2010), even though ACCORD may have been underpowered; very few CV events occurred in the diabetic study patients, most of whom received treatment with statins and other CV risk reduction measures. Moreover,



A



B

FIGURE 5-10 • Comparison of the associations between BP change and the risk ratio reduction in total major cardiovascular events according to categories of (A) systolic blood pressure (SBP) and (B) diastolic blood pressure (DBP) of 201,566 participants in 32 RCTs. The area of each circle is proportional to inverse variance of log odds ratio. Fitted line represents summary meta-regression for total major cardiovascular events. Each regression line is for a different level of baseline blood pressure. (From Czernichow S, Zanchetti A, Turnbull F, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: Meta-analysis of randomized trials. *J Hypertens* 2011;29:4–16.)

reliance on clinic BP presents particular problems in trials of diabetic patients due to the high prevalence of masked hypertension (Franklin et al., 2013), an issue not assessed in ACCORD. As mentioned earlier in this chapter, two meta-analyses

also concluded that in patients with diabetes, protection from stroke but not MI improves with a greater magnitude of BP reduction (Bangalore et al., 2011; Reboldi et al., 2011), whereas a more restrictive Cochrane review (that excluded the

TABLE 5-13

Randomized Trials Comparing More Intense with Less Intense Antihypertensive Therapy

Trial (Reference)	Primary Drugs	No. of Patients (Condition)	Mean Age, Years	Baseline BP, mm Hg	Less Intense— Final BP, mm Hg	More Intense— Final BP, mm Hg	Relative Risk Reduction
SPS3 (Benavente et al., 2013)	Thiazide, ACEI/ARB, CCB, BB	3,020 (recent lacunar stroke)	63	143/79	138 systolic	127 systolic	–63% intracerebral hemorrhage ($p = 0.03$), $p = \text{NS}$ all CV events
AASK (Appel et al., 2010)	Ramipril, amlodipine, metoprolol	1,094 (HTN + CKD)	55	150/96	141/86	130/78	Renal decline: $p = \text{NS}$ except for subgroup with proteinuria: –27% renal decline ($p = 0.01$)
ACCORD (2010)		4,733 (DM2 ± HTN)	62	139/76	135/71	119/64	$p = \text{NS}$ overall CV events, –41% stroke ($p = 0.01$)
HOT (Hansson et al., 1998)	Felodipine + ACEI + BB	18,790 (general HTN)	62	170/105	144/85	142/83, or 140/81	–28% strokes $p = \text{NS}$ CV events
HOT-DM2 (Hansson et al., 1998)	Felodipine + ACEI + BB	1,501 (HTN + DM2)	62	107/105	144/85	142/83, or 140/81	–50% CV events ($p = 0.005$)
ABCD-V (Estacio et al., 2006)	Valsartan	(DM2-NT)	57	126/84	124/80	118/75	Less albuminuria ($p < 0.007$)
ABCD-N (Schrier et al., 2002)	Nisoldipine, enalapril	480 (DM2-NT)	59	137/84	137/81	128/75	Less albuminuria ($p < 0.009$), less retinopathy ($p = 0.019$), less stroke ($p = 0.03$)
ABCD-H (Estacio et al., 1998)	Nisoldipine, enalapril	470 (DM2 + HTN)	57	158/76	146/90	139/82	$p = \text{NS}$ CV events
UKPDS-38 (1998)	Captopril ± atenolol	1,148 (HTN + DM2)	56	160/94	154/87	144/82	–32% DM-related death ($p < 0.019$), –44% stroke ($p = 0.013$), –37% microvascular disease ($p = 0.0092$)

positive ADVANCE trial) concluded that there is low-quality evidence for intensive BP reduction for even stroke protection in patients with diabetes mellitus (Arguedas et al., 2013).

In the words of Bangalore et al. (2011),

The present body of evidence suggest that intensive BP control (systolic BP < 135 mmHg) reduces the risk for macrovascular (death, stroke) events in patients with type 2 diabetes mellitus/impaired fasting glucose/impaired glucose tolerance. A treatment goal of 130 to 135 mmHg, similar to the achieved BP of 133.5 mmHg in the standard therapy group of the ACCORD trial, is therefore acceptable and more aggressive goals to 120 mmHg can be considered in patients at higher risk of stroke. However, a systolic BP < 130 mmHg, there may be target organ heterogeneity, and these cerebrovascular benefits have to be balanced against an increased risk of SAEs [serious adverse events] and a lack of benefit for cardiac, renal, and retinal outcomes.

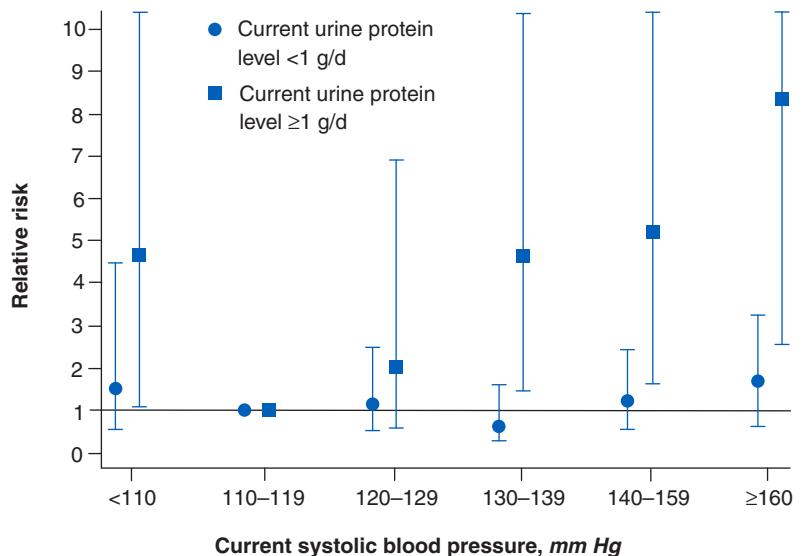
- CKD:** In the cohort follow-up of the AASK trial, more intensive antihypertensive therapy to a BP of 130/78 rather than less intensive therapy to 141/86 mm Hg during the trial led to persistently slower rate of renal decline in the subset of patients with proteinuria (Appel et al., 2010). Additional studies, though not designed to address the issue of goal of therapy, found protection with SBP below 130 mm Hg only in those with proteinuria greater than 1.0 g per day and no added protection from systolics as high as 160 down to less than 110

for those with less proteinuria (Jafar et al., 2003) (Fig. 5-11).

Additional points should be noted:

- The report of the JNC 8 committee members relaxed the recommendations for starting and intensifying therapy after reviewing the mean baseline BP levels and mean achieved BP levels for randomized groups and associated primary outcomes. Clearly, some patients in these trials achieved lower BPs and some higher BPs than the mean values. By making use of such patient-specific data, the meta-regression analysis in Figure 5-10 shows additional benefits from lowering BP by as much as 15/5 mm Hg even from a baseline BP < 140/80 mm Hg (Czernichow et al., 2011).
- The meta-analysis shown in Figure 5-10 also includes trials that were excluded from analysis by the JNC 8 committee because all patients were not hypertensive and thus had lower mean baseline BPs. They are included in Tables 5-5 and 5-12.
- The ongoing NIH-funded Systolic Blood Pressure Intervention Trial (SPRINT) is designed specifically to evaluate more intense versus less intense treatment of ISH (ClinicalTrials.gov Identifier: NCT01206062).
- In the meantime, debate continues over the possible importance of a J-curve for both systolic and diastolic BP, i.e., a reduction in risk as BP is lowered down to some critical level that is inadequate to maintain perfusion of vital organs, resulting in an increased risk as the pressure is lowered further.

FIGURE 5-11 • The relative risk for CKD progression in patients with a current urine protein excretion of 1.0 g/day or greater represents 9,336 patients (223 events), and the relative risk for patients with a current urine excretion less than 1.0 g/day represents 13,274 patients (88 events). The reference group for each is defined at a systolic BP of 110 to 119 mm Hg. CIs are truncated, as shown. (Modified from Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease: The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis. *Ann Intern Med* 2003;139:244–252.)



Evidence for a J-Curve

An association between reduction of BP and ischemic injury was first suggested by Stewart (1979), who reported a fivefold increase in MI among patients whose diastolic BP was reduced to less than 90 mm Hg (Korotkoff phase 4). Stewart's report was largely neglected until Cruickshank et al. (1987) reported the same phenomenon.

The evidence for a J-curve was recently reviewed by Mancia and Grassi (2014) and summarized as follows:

In a classic cardiac catheterization lab study, acute reduction of diastolic BP to <90 mm Hg by intravenous nitroprusside caused a progressive fall in coronary sinus blood flow in hypertensive patients with LVH (who have impaired coronary vasodilator reserve), whereas reduction of diastolic BP to <70 mm Hg had no effect on coronary sinus flow in hypertensive patients without LVH (Polese et al., 1991). The point is clear: Patients with hypertensive heart disease are susceptible to subendocardial ischemia if diastolic BP is lowered too far and too fast as can occur when treating hypertensive crises with intravenous medication. This is particularly true in hypertensives with CAD in whom autoregulation is impaired in the disease arteries.

But does intensive chronic oral antihypertensive therapy run the risk of triggering ischemic events in ambulatory hypertensive patients in office-based practice? There is suggestive evidence but no iron clad proof.

In the words of Mancia and Grassi (2014),

The question is not whether a J-curve phenomenon exists: it obviously does, with an ascending limb that will reach 100% mortality at zero BP. It should rather be whether the ascending limb can become manifest at the BP values achieved with [oral] drugs that lower BP.

The evidence in favor of the J-curve comes from *post hoc observational analysis* of RCTs. Data from active treatment and comparator groups are combined to maximize sample size, and then hazard ratios are plotted for patients binned by progressively lower levels of BP achieved with treatment. A partial list of recent analyses providing the most compelling evidence for J-curves includes the following:

- In the INVEST (International Verapamil SR/Trandolapril) trial of hypertensive patients with established CAD, the incidence of ASCVD death decreased progressively in patients whose diastolic

BP was lowered from 120 mm Hg to 80–89 mm Hg and then increased progressively in those with achieved diastolic BP below 80 mm Hg (Fig. 5-12) (Messerli et al., 2006). Consistent with the notion that the coronaries are perfused only in diastole such that diastolic BP constitutes coronary perfusion pressure, the analyses show that the J-curve was less pronounced in patients who had undergone coronary revascularization and more pronounced for diastolic than SBP and for MI rather than stroke.

- In the large ONTARGET trial of patients who had very high ASCVD risk but were not all hypertensive, the incidence of ASCVD events decreased when BP was reduced with treatment (ramipril, telmisartan, or both) from 145/82 at baseline to 133/76 mm Hg and then increased when on-treatment BP reached lower values of 125/72 or 116/68 mm Hg (Mancia et al., 2011).
- In the PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes) trial of secondary stroke prevention with telmisartan (vs. placebo), the risk of a second stroke (or total ASCVD) gradually declined when SBP was reduced from a baseline of ≥ 150 mm Hg to either 130–139 mm Hg or 120–129 mm Hg but increased again when reduced to <120 mm Hg (Ovbiagele et al., 2011).

Evidence Against a J-Curve

Cruickshank's concept has not gone unchallenged. As recently reviewed by Verdecchia et al. (2014), the evidence against the J-curve includes the following:

- Post hoc observational analysis loses the intended balance of baseline characteristics between randomized groups. Patients with the lowest achieved BP sometimes are the sickest to begin with, leading to *reverse causality*: Generalized inanition or advanced illness of any kind—whether severe heart failure or cancer—caused the low BP rather than intensive antihypertensive therapy causing clinical organ ischemia. Thus, in some reports, the J-limb is burned off by multivariate analyses that account for such baseline illness characteristics, while, in others, the J-limb is lessened but survives.
- Post hoc analyses of RCTs also suffer from dwindling sample size at the critically interesting lower levels of BP < 130/80 mm Hg, leading to large standard deviations around the point estimates that are taken to represent the ascending limb of the J-curve

(Fig. 5-12) (Messerli et al., 2006). The point is this: If BP is rarely lowered below 130/80 mm Hg in RCTs—in which motivated patients are given free medication by a forced-titration protocol implemented by a dedicated team of trained nurses and physicians—this occurrence is even rarer in everyday clinical practice.

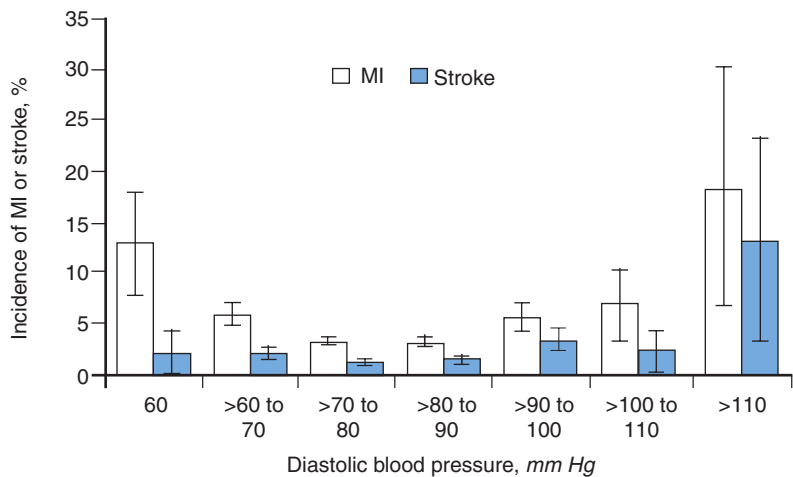
- Diastolic J-curves have been seen in post hoc analysis of placebo arms of RCTs, indicating that the low diastolic BP cannot be treatment induced but rather is caused by untreated ISH, which carries a high risk of fatal and nonfatal ASCVD.
- Post hoc analysis of the diabetic subgroup of INVEST did not show a J-curve in ASCVD events but did show a systolic J-curve for all-cause mortality, which argues in favor of reverse causality and against treatment-induced ischemia (Cooper-DeHoff et al., 2010). Post hoc analysis of the diabetic subgroup of ONTARGET showed a progressive reduction in stroke risk down to achieved

SBP of 110 mm Hg with no evidence of a J-curve; for MI and overall ASCVD events, no benefit was seen by lowering SBP < 130 mm Hg but also no clear harm (Redon et al., 2012).

- In the primary prespecified analysis of the ACCORD trial (Cushman et al., 2010), no J-curve was found in coronary events in patients with diabetes whose SBP was reduced to 119 mm Hg compared with 133 mm Hg and there was a greater reduction in stroke.

Recommendations for the Goal of Therapy

As we lack clinical trials that address rigorously some key issues in important ethnic and age groups, guideline reports will continue to generate debate. Having reviewed the large—but still incomplete—body of evidence from RCTs, meta-analyses, and observational data as well as several new sets of guidelines, we offer



MI

Patients with MI, <i>n</i>	23	135	387	255	71	14	8
Total patients, <i>n</i>	177	2239	11 324	7378	1214	201	43
Mean systolic blood pressure, <i>mm Hg</i>							
Patients with MI	127.0	131.9	135.2	143.8	158.3	166.9	191.4
Patients without MI	126.2	129.6	131.4	139.3	155.2	170.3	185.7

Stroke

Patients with stroke, <i>n</i>	4	50	151	116	44	5	6
Total patients, <i>n</i>	175	2253	11 320	7366	1217	199	45
Mean systolic blood pressure, <i>mm Hg</i>							
Patients with stroke	112.2	132.7	136.3	143.8	161.1	171.1	177.9
Patients without stroke	126.7	129.6	131.5	139.3	155.2	169.9	187.9

FIGURE 5-12 • Incidence of total MI and total stroke by diastolic blood pressure strata. (From Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: Can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med* 2006;144:884–893.)

the following recommendations about the goals of antihypertensive therapy:

- Hypertensive Elderly.** Seated office BP should be reduced to <150/90 mm Hg. For most patients 80 years of age or older with ISH, office SBP should be reduced to 140 to 145 mm Hg. This is only a general rule of thumb, as the definition of “elderly” and the goal of therapy should be highly individualized based on each patient’s overall health and personal goals. A seated SBP in the 150 mm Hg range may be the best goal for a frail 70-year-old who is prone to orthostatic and postprandial hypotension, whereas a seated SBP of 130 mm Hg may be best for a healthy robust 85-year-old whose chief concern is to avoid a disabling stroke. Home BP monitoring should be routinely conducted in elderly patients to avoid overtreatment or undertreatment of high BP due to white-coat reactions and treatment-induced masked hypertension, which are very common in the elderly.
- Nonelderly General Hypertensive Patients.** Seated office BP should be reduced to <140/90 mm Hg. Seated home BP should be checked—infrequently—and reduced to <135/85 mm Hg.
- Hypertensive Patients with Diabetes and/or CKD.** Seated office BP should be reduced to <140/90 mm Hg. Orthostatic BP should be checked regularly to avoid overtreatment, and home BP should be checked regularly to avoid undertreatment as masked hypertension is very common and predicts hypertensive complications. Seated home BP should be reduced to <135/85 mm Hg. Ambulatory BP monitoring, if available, should be considered in patients with CKD because nocturnal hypertension is common and predicts hypertensive complications.

Lower-than-usual BP goals (seated office BP < 135/85 or <130/80 mm Hg and seated home BP < 130/80 mm Hg) may be considered in some groups, including the following:

- Non-Hispanic black patients, who are at greater risk for hypertensive complications, premature disability, and death.** Ambulatory BP monitoring should be considered to detect nocturnal hypertension, which is common and predicts hypertensive complications.
- Patients with proteinuric CKD, though frequent monitoring will be needed to avoid acute kidney injury necessitating a more relaxed BP goal.**
- Diabetic or other high-risk patients for whom stroke prevention is an overriding concern.**

The Overriding Need: Adequate Therapy

Despite the concerns over a J-curve, we should not lose sight of the fact that a big reason for the lesser protection found among most treated hypertensives reflects undertreatment, not overtreatment. Clearly, it is essential that most patients have their SBP brought down to 140 mm Hg and their diastolic BP to the 80 to 85 mm Hg range to provide the demonstrated benefits of therapy.

Importance of Population Strategies

Most of our current efforts are directed at the individual patient with existing hypertension. Clearly, we also need to advise the larger population to do those things that may protect against the development of hypertension, an approach directed toward the “sick populations” rather than only the sick individuals. At this time, such population strategies should not involve medications but rather should be based on lifestyle modifications. The next chapter describes these modifications.

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Treatment of Hypertension: Lifestyle Modifications

The title of this chapter reflects a major problem in the management of hypertension: “Modification” means making a change, which for people with hypertension for as many as 60 years may be exceedingly hard to accomplish. What is needed is “maintenance,” to reflect the presence of healthy lifestyles that only need to be continued.

Nonetheless, the successful adoption of healthy lifestyles is able to prevent cardiovascular diseases and reduce mortality even in the elderly (Rizzuto et al., 2012). But what is needed is population-wide change (Estruch et al., 2013). As Geoffrey Rose noted in his 1992 book, a small change by the population, such as a 2-mm Hg reduction in blood pressure that would be seen after population-wide modest reduction in sodium intake, would provide more benefit than the drug treatment of all those already hypertensive.

The critical need for such changes is heightened by the increasing risks for hypertension and its complications faced by low-income people in the near future (Danaei et al., 2013). The evidence that lifestyle changes in all societies influence both blood pressure (Tzoulaki et al., 2012) and overall cardiovascular risk (Moodie et al., 2013) is incontrovertible. Carefully considered guidelines to improve society-wide cardiovascular health are available (Pearson et al., 2013).

There is an obvious attraction for broad, governmental actions to mandate everyone’s behavior rather than attempting hard-to-make individual changes. However, such mandates may be counterproductive, as editorialized about the attempt to prohibit the sale of large quantities of sugar-rich drinks in New York city (Mariner & Annas, 2013). A proper balance between encouragement of individual choices and governmental dictates may be hard to achieve, but there will always be a need for mandates to “challenge corporate and industrial practices that place profit above public

health” (Fairchild, 2013). The remarkable reduction in cigarette smoking in the United States (U.S.) came about mainly by a nationwide abolition of their promotion by the cigarette producers after they were hit by a massive financial penalty. Even the threat of governmental action may help as seen in the voluntary reduction in the amount of salt added by food processors in the United Kingdom (U.K.) (Brinsden et al., 2014), largely from the continual campaign by a tenacious physician, Graham MacGregor. In the U.S., much of the pressure for governmental action, such as the removal of trans fat, comes from the Center for Science in the Public Interest.

Most of the lifestyle changes listed in Table 6-1 do more than lowering the blood pressure. As reviewed in detail by the 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk (Eckel et al., 2014), most of them provide greater protection against cardiovascular diseases than would be provided by the lowering of blood pressure alone (Mozaffarian et al., 2011). But to be fully effective, they must be begun much earlier than after people become hypertensive. In the most widely studied experimental model of spontaneous hypertension, the spontaneously hypertensive rat (SHR), preventive measures must be given within the first 6 weeks after birth, analogous to early adolescence in humans. Assuming that the SHR is a model for human hypertension, healthy lifestyles must be adopted much earlier.

POTENTIAL FOR PREVENTION

Lifestyle modifications may prevent or at least delay the onset of hypertension. Three long-term, well-controlled preventive trials involving subjects with high-normal blood pressure, i.e., prehypertension, have shown that individual and combined lifestyle changes lower blood

TABLE 6-1

Lifestyle Therapy to Reduce the Possibility of Becoming Hypertensive and to Reduce BP and to Reduce the Risk of BP-Related CV Complications in Hypertensive Patients

- Healthy diet: high in fresh fruits, vegetables, low-fat dairy products, dietary and soluble fiber, whole grains, and protein from plant sources; low in saturated fat, cholesterol, and salt
- Reduction in sodium intake to <100 mmol/day
- Attaining and maintaining ideal body weight (BMI 18.5–24.9 kg/m²)
- A waist circumference of <102 cm (men) and <88 cm (women)
- Regular physical activity: accumulation of 30–60 min of moderate-intensity dynamic exercise, 4–7 days/week
- Low-risk alcohol consumption (≤2 standard drinks per day and <14 standard drinks per week for men and <9 standard drinks per week for women).
- A smoke-free environment

pressure and reduce the incidence of hypertension, as summarized in Table 6-2 (Hypertension Prevention Trial Research Group, 1990; Stamler et al., 1989; Trials of Hypertension Prevention Collaborative Research Group, 1992, 1997).

The effects of multiple lifestyle changes have also been examined in two groups of patients with somewhat higher BPs. The Trial of Nonpharmacologic Interventions in the Elderly (TONE) enrolled 975 men and women aged 60 to 80 years whose hypertension was controlled on one antihypertensive drug (Whelton et al., 1998). They were randomly assigned to reduced sodium intake, weight loss, both of these, or no intervention (i.e., usual care). After 3 months, their antihypertensive drug was withdrawn. Over the ensuing 30 months, the proportion of patients who remained normotensive without antihypertensive drugs was only 16% in those on usual care,

more than 35% in those on one of the two interventions, and 43.6% in those on both interventions (Fig. 6-1). These impressive effects were achieved with relatively small amounts of dietary sodium reduction (an average of 40 mmol/day) or weight reduction (an average of 4.7 kg).

Another trial involved 412 adults whose average age was 48 years and who had a BP between 120 and 159 mm Hg systolic and 80 to 95 mm Hg diastolic (Sacks et al., 2001). They were randomly given one of two already prepared diets, one typical of the U.S. diet, i.e., the controls, and the other composed of more fruits, vegetables, and low-fat dairy foods, the Dietary Approaches to Stop Hypertension (DASH) diet portrayed in Table 6-3. In addition, they were randomly given one of three levels of sodium intake: High (150 mmol/day), intermediate (100 mmol/day), or low (50 mmol/day).

TABLE 6-2

Trials of Lifestyle Modifications on the Incidence of Hypertension

Trial (Reference)	No. of Subjects	Duration (Year)	Weight Loss (kg)	Reduction of Incidence (%)
Primary prevention trial (Stamler et al., 1989)	201	5	2.7	54
Hypertension Prevention Trial (Hypertension Prevention Trial Research Group, 1990)	252	3	1.6	23
Trials of hypertension prevention				
I. (Trials of Hypertension Prevention Collaborative Research Group, 1992)	564	1.5	3.9	51
II (Trials of Hypertension Prevention Collaborative Research Group, 1997)	595	4.0	1.9	21

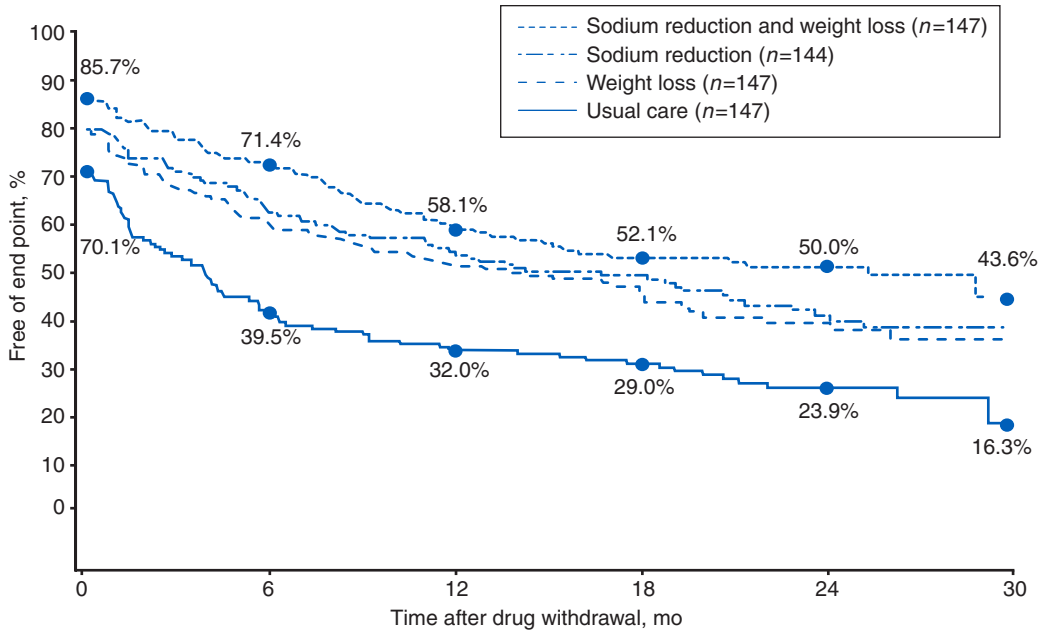


FIGURE 6-1 • Percentages of the 144 participants assigned to reduced sodium intake, the 147 assigned to weight loss, the 147 assigned to reduced sodium intake and weight loss combined, and the 147 assigned to usual care (no lifestyle intervention) who remained free of cardiovascular events and high BP and in whom no antihypertensive agent was prescribed during follow-up. (Modified from Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons. *JAMA* 1998;279:839–846.)

Each diet was consumed for 30 consecutive days, while weight was kept constant. Figure 6-2 shows significant falls in systolic blood pressure (SBP) noted with the DASH diet at every level of sodium intake as

compared to the control diet and significant falls in SBP with progressively lower sodium intakes on either diet. The effects were seen in normotensives and hypertensives, men and women, blacks and nonblacks,

TABLE 6-3

DASH Diet

Food Group	Daily Serving	Examples and Notes
Grains	7–8	Whole wheat bread, oatmeal, popcorn
Vegetables	4–5	Tomatoes, potatoes, carrots, beans, peas, squash, spinach
Fruits	4–5	Apricots, bananas, grapes, oranges, grapefruit, melons
Low-fat or fat-free dairy foods	2–3	Fat-free (skim)/low-fat (1%) milk, fat-free/low-fat yogurt, fat-free/low-fat cheese
Meats, poultry, fish	≤2	Select only lean meats, trim away fats; broil, roast, or boil; no frying; and remove skin from poultry
Nuts, seeds, dry beans	4–5/week	Almonds, peanuts, walnuts, sunflower seeds, soybeans, lentils
Fats and oils	2–3	Soft margarines, low-fat mayonnaise, vegetable oil (oil, corn, canola, or safflower)
Sweets	5/week	Maple syrup, sugar, jelly, jam, hard candy, sorbet

DASH eating plan available at: http://www.nhibi.nih.gov/health/public/heart/hpb/dash/new_dash.pdf

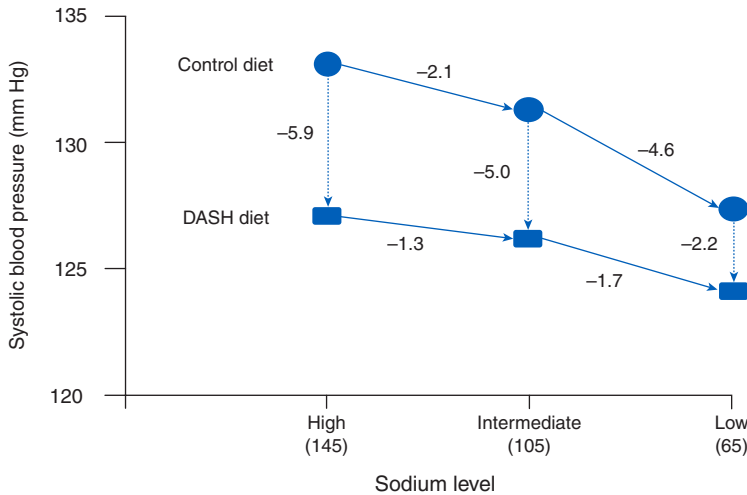


FIGURE 6-2 • Reduction of SBP by Dietary Approaches to Stop Hypertension, the DASH diet, and reduced sodium intake. The mean SBP are shown for the high-sodium control diet. The three dietary sodium levels are expressed in terms of millimoles per day. The solid lines indicate changes in BP for various sodium levels, and the dotted arrows show the mean differences in BP between the two diets at each level of sodium intake. The order in which participants were given the sodium levels was random, with a crossover design. There was a significant difference in SBP between the high-sodium and low-sodium phases of the control diet (mean, -6.7 mm Hg) and the DASH diet (mean, -3.0 mm Hg). (Modified from Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N Engl J Med* 2001;344:3–10.)

and were accompanied by falls in diastolic blood pressure (DBP) as well.

As impressive as these results are, they may not be applicable to the “real” world since the latter two were short studies that were tightly controlled. A more realistic view of what can be expected comes from the PREMIER trial wherein participants were assigned to the DASH diet but prepared their own meals (Elmer et al., 2006). Not surprisingly, at the end of 18 months, neither the extent of dietary change nor the reduction in BP was as great as seen in the original DASH trial. The additional fall in BP compared to the group only given advice was -1.1 – -0.9 mm Hg.

Although there is no doubt that the unhealthy lifestyle of people in most developed societies contribute to our high incidence of hypertension, diabetes, and cardiovascular disease (Moodie et al., 2013), multiple barriers make correction of these unhealthy practices difficult. As noted by Chobanian et al. (2003):

Barriers to prevention include cultural norms; insufficient attention to health education by health care practitioners; lack of reimbursement for health education services; lack of access to places to engage in physical activity; larger servings of food in restaurants; lack of availability of healthy food choices in most schools, worksites, and restaurants; lack of exercise programs in

schools; large amounts of sodium added to foods by the food industry and restaurants; and the higher cost of food products that are lower in sodium and calories. Overcoming the barriers will require a multipronged approach directed not only at high-risk populations but also to communities, schools, worksites, and the food industry.

Obviously, removal of these barriers will be difficult and will require major environmental changes, which demand a political advocacy and governmental financing that is sorely lacking.

As rational as lifestyle modifications seem to be, both for prevention and treatment of hypertension, their value must be put into perspective. As Pickering (2004) notes:

Given that healthcare practitioners have limited resources to improve hypertension control, it would seem appropriate to focus on the intervention that has the greatest chance of success; there can be little doubt that drug treatment wins hands down. This conclusion is not intended to negate the importance of lifestyle changes such as the DASH diet, and patients should certainly be encouraged to adopt them, but if behavioral medicine is to progress, practitioners need to find more cost-effective methods for instituting and maintaining behavior change. In the mean time, doctors are still going to need to take out the prescription pad.

PROTECTION AGAINST CARDIOVASCULAR DISEASE

The larger issue of whether these lifestyle modifications will, in fact, reduce morbidity and mortality in hypertensive patients may never be settled. The difficulty of demonstrating such protection in the various therapeutic trials using much more potent antihypertensive drugs was described in Chapter 5. Other than for the dramatic impact that smoking cessation and the rapid weight loss achieved by bariatric surgery (Adams et al., 2012) have had upon cardiovascular disease, it may not be possible to document the efficacy of most lifestyle modifications, which are less potent and more difficult to monitor than is drug treatment (Harrap, 2012). Lifestyle modifications must be accepted on the evidence that they will lower the BP and other risk factors without risk and with a reasonable chance of adoption by most patients.

With recognition that only societal changes will lead to major changes, the effects of individual lifestyle modifications on hypertension will now be examined. In the latter part of the chapter, some maneuvers that are not “lifestyle” are covered since they are not antihypertensive drugs as are covered in the next chapter.

AVOIDANCE OF TOBACCO

Smoking cessation is the most effective, immediate way to reduce cardiovascular risk, adding 10 years to the life span of women who quit (Pirie et al., 2013). However, an effect on BP has not been generally thought to be involved in this risk reduction because chronic smokers as a group have a lower BP than do nonsmokers (Mikkelsen et al., 1997), likely because smokers weigh less than do nonsmokers. In addition, the role of a pressor effect of smoking was missed because of the almost universal practice of having smokers abstain from smoking for some time before measuring their BP, usually because medical facilities are smoke free. Thus, the significant, immediate, and repetitive pressor effect of smoking had been missed because it lasts for only 15 to 30 minutes after each cigarette. Only with ambulatory BP monitoring has the major pressor effect of smoking been recognized (Oncken et al., 2001). Smoking exacerbates the effects of hypertension on mortality (Ge et al., 2012), increasing arterial stiffness (Jatoi et al., 2007) and impairing nitric oxide (NO) synthase (Argacha et al., 2008).

Unfortunately, the rate of cigarette smoking in the U.S. has not continued to decrease while use of other tobacco products has gone up (Centers for Disease Control and Prevention [CDC], 2012a). The use of smokeless tobacco and cigars, if their smoke is inhaled, also increases the risk of myocardial infarction (Teo et al., 2006).

Hypertensives who use tobacco must be repeatedly and unambiguously told to quit and given assistance in doing so. Nicotine replacement therapies may help even if they cause sympathetic stimulation, and the partial nicotine agonist, varenicline, may help in relieving withdrawal symptoms and blocking the desire to continue smoking (Sobieraj et al., 2013). If the patient continues to smoke, all antihypertensive drugs except nonselective β -blockers may attenuate the smoking-induced rise in BP.

WEIGHT REDUCTION

Most adults in the U.S., as many as 80% of African American women, are overweight, defined as a BMI more than 25, and more than 30% are obese, defined as a BMI more than 30 (Ogden et al., 2014). The nature of modern life, with more caloric intake and less physical activity, engenders more obesity, which is now a worldwide epidemic (Swinburn et al., 2011), particularly ominous in children (Ogden et al., 2014). Any degree of weight gain, even to a level that is not defined as overweight, is associated with an increasing incidence of hypertension (Shihab et al., 2012) and, even more strikingly, of type 2 diabetes. As more completely described in Chapter 3, the hypertensive effect of weight gain is mainly related to increased abdominal or visceral fat (Ostchega et al., 2012), usually as part of the metabolic syndrome (Safar et al., 2013), accompanied by impaired endothelial function in turn associated with sympathetic activation, reduced NO synthesis, and adipocyte-derived factors (Nguyen Dinh Cat et al., 2011).

Despite increasing awareness of the problem, dietary habits among U.S. adult hypertensives continue to worsen (Mozaffarian et al., 2011). Because the maintenance of significant weight loss is so difficult for most who are obese, physicians, patients, and society at large must do more to prevent weight gain, particularly among children in whom obesity and the metabolic syndrome are increasing so rapidly (Ogden et al., 2014). Societal changes are needed to stop the epidemic.

Clinical Data

Once achieved, obesity is extremely hard to overcome, except by bariatric surgery. Even though significant weight loss can be achieved by multiple behavioral motivations (Unick et al., 2013), most success is short-lived, at least in part by persistence of appetite-stimulating hormones in the blood (Sumithran et al., 2011). In view of the limited success of diets and appetite-suppressing drugs, bariatric surgery is being more widely practiced (Vest et al., 2013).

Real prevention will most likely require societal changes that must be based on governmental restrictions, as attempted (apparently unsuccessfully) on the sale of super-sized sugar-loaded beverages (Fairchild, 2013). As noted by Gostin (2007):

Despite the undoubted political risks, should public health agencies push for strong measures to control obesity, perhaps even banning hazardous foods? The justification lies with the epidemic rates of overweight and obesity, the preventable morbidity and mortality, and the stark health disparities based on race and socioeconomic status. If the problem were related to pathogens, tobacco, or lead paint, most would support aggressive measures to protect innocent individuals from hazards created by others. But comfort foods also have hidden hazards—it is difficult to tell if they are laden with fat and, if so, what kind. Although the public dislikes paternalism, it is at least worth considering whether such an approach is ever justified to regulate harms that are apparently self-imposed, but also are deeply socially embedded and pervasively harmful to the public.

DIETARY SODIUM REDUCTION

No food in its natural state is high in sodium. Salt was originally added to preserve foods that spoil without refrigeration. Although infants do not prefer saltier liquids, the presence of increased salt in virtually all processed food quickly leads to an acquired preference. Food processors are able to bulk up their products with water held by the salt. Soft drink and beer drinkers are enticed to consume more fluid to quench the saltiness of food and bar condiments. Of the average daily sodium intake of 4,323 mg by U.S. men and of 2,918 mg by U.S. women (Yang et al., 2011), 77% comes from that added in the processing (Centers for Disease Control and Prevention, CDC, 2012b).

Rigid restriction of dietary sodium intake was one of the first effective therapies for hypertension (Kempner, 1948). However, after thiazides were introduced during the late 1950s and their mode of action was shown to involve a mild state of sodium depletion, both physicians and patients eagerly adopted this form of therapy in place of dietary sodium reduction. In discarding rigid salt restriction, physicians disregarded the benefits of modest reduction both for its inherent antihypertensive effect and for its potential of reducing diuretic-induced potassium loss.

Moderate dietary sodium reduction is advocated by most individual experts, national and international guideline reports, governmental health agencies, and medical organizations, including the American Heart Association (Pearson et al., 2013). Unfortunately, the one official U.S. document that prevents this desired societal change is the U.S. Food and Drug Administration regulation that continues to designate salt as “an ingredient recognized as safe (GRAS),” thereby allowing food processors to add as much salt as they wish. Unlike many other countries that have begun to address dietary sodium intake (Brinsden et al., 2014), the U.S. refuses to do so. As a consequence, the amount of sodium in fast foods sold in the U.S. is often more than twice the amount in the same item in the U.K. (Roehr, 2012). The CDC (CDC, 2012b) estimate that moderate reduction of dietary sodium could prevent as many as 11 million new cases of hypertension in the U.S., and Coxson et al. (2013) estimate a decrease of mortality of 0.7 and 1.2 million over 10 years.

Evidence for Antihypertensive Effect

Moderate sodium reduction to a level of 2.4 g/day (6 g NaCl per day, 100 mmol/day) has been shown to reduce blood pressure in hypertensives by a mean of 5.4/2.8 mm Hg (He et al., 2013) and to provide a possible preventative effect (Forman et al., 2012). An earlier meta-analysis showed a significant fall in BP, greater in hypertensives than in normotensives, that correlates with the degree of sodium reduction (He & MacGregor, 2003) (Fig. 6-3). This analysis was restricted to 26 trials that lasted 4 weeks or longer, but very similar results were found in their later analysis of 34 trials (He et al., 2013).

In another meta-analysis of data from both normotensive and hypertensive subjects, Aburto et al. (2013a) showed an overall reduction of 3.4/1.5 mm Hg. In neither of the 2013 meta-analyses were any significant adverse effects seen in blood lipids, catecholamines, or renal function.

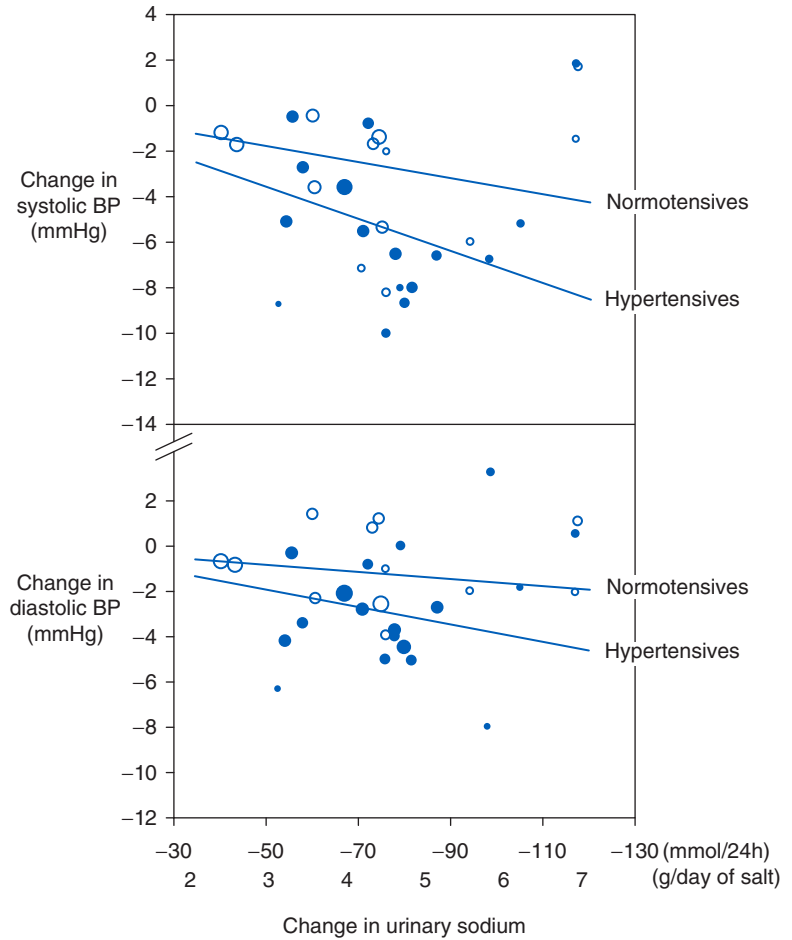


FIGURE 6-3 • Relationship between the net change in 24-hour urinary sodium excretion and BP in a meta-analysis of 26 trials. Open circles, normotensive. Solid circles, hypertensives. The slope is weighted by the inverse of the variance of the net change in BP. The size of the circle is proportional to the weight of the trial. (Modified from He FJ, MacGregor GA. How far should salt intake be reduced? *Hypertension* 2003;42:1093–1099.)

The likely inability to maintain enough dietary sodium reduction to achieve a meaningful effect on BP by most people over a long period of time has led to a concerted effort to convince food processors to reduce the amount of sodium added to processed foods and drinks, the source of about three-fourths of current sodium consumption (Frisoli et al., 2012). In the meantime, patients should be advised to read the label on processed products, avoiding those with more than 300 mg per portion. In addition, a number of books and Web sites, such as the American Heart Association Heart (heart.org), provide advice and recipes for lower-sodium diets.

Mechanisms of Antihypertensive Effect

Despite considerable research, neither the mechanisms by which excessive sodium intake raises BP nor the mechanisms by which moderate sodium restriction

lowers BP are completely characterized (Kotchen et al., 2013). However, the structure and function of the heart and kidneys may be improved after prolonged, moderate sodium reduction: Left ventricular hypertrophy decreases (Rodriguez et al., 2011), glomerular hyperfiltration and proteinuria are reduced (Agarwal, 2012), arterial stiffness and oxidative stress are lessened (Hummel et al., 2012), and endothelial function improves (Jablonski et al., 2013).

Sodium Sensitivity

The fall in BP with reduced sodium intake tends to be greater in those with lower plasma renin and higher atrial natriuretic peptide levels (Melandar et al., 2007). The BP sensitivity to sodium tends to be enhanced in hypertensives, blacks, and older people, all associated with lower renin, so that these patients tend to respond more to sodium reduction presumably because they have a lesser reactive increase in renin

(Weinberger, 1996). In addition, this sensitivity is greater in adults who had a low birth weight (de Boer et al., 2008). Blacks, who are more likely to have been of low birth weight and therefore have impaired nephrogenesis, tend to be more sodium sensitive (Schmidlin et al., 2007). Compared to those who are salt resistant, more sodium-sensitive people developed hypertension over a 15-year follow-up (Barba et al., 2007), and they have more cardiovascular disease and shorter survival (Franco & Oparil, 2006), associated with less insulin resistance (Laffer & Elijovich, 2013).

Sodium sensitivity may have a genetic mechanism. In a study of 185 subjects, 55 of whom were hypertensive and 34 sodium sensitive, Carey et al. (2012) found polymorphisms in the sodium bicarbonate cotransporter gene that were closely associated with sodium sensitivity. An association with multiple genetic variants in the endothelial system was reported in a study of Chinese men (Defago et al., 2013).

Despite these associations, there seems to be no need to ascertain the individual patient's degree of sodium sensitivity before recommending moderate sodium reduction, particularly as testing may not be reliable or reproducible (Gerdtz et al., 1999). Those who respond more to sodium reduction likely are more sodium sensitive, but there is no harm, and as noted in Table 6-4, there are other potential benefits of moderate sodium reduction in all hypertensives. All should be encouraged to reduce their levels to the 100 mmol/day goal, particularly since there is no certain way to predict who will develop hypertension.

Additional Benefits of Sodium Reduction

In addition to lowering BP, other benefits have been observed with moderate sodium reduction, as summarized in Table 6-4.

Enhancement of Efficacy of Antihypertensive Drugs

Moderate sodium reduction clearly increases the antihypertensive efficacy of all classes of antihypertensive drugs, with the possible exception of calcium channel blockers, which have a mild natriuretic effect (Chrysant et al., 2000). Lower sodium intake improves the kinetic and dynamic effects of ARBs and β -blockers (Azizi et al., 2013). This potentiation was nicely documented in a randomized controlled trial (RCT) in 52 nondiabetic patients with nephropathy on an ACE inhibitor (Slagman et al., 2011). A lowering of dietary sodium intake from 186 to 106 mmol/day provided a greater reduction in blood pressure and proteinuria than did addition of an ARB.

Protection from Diuretic-Induced Potassium Loss

High levels of dietary sodium make patients more vulnerable to the major side effect of diuretic therapy, potassium loss. The diuretic inhibits sodium reabsorption proximal to that part of the distal convoluted tubule where secretion of potassium is coupled with

TABLE 6-4

Additional Benefits of Moderate Sodium Reduction

Improvement in large artery compliance (Gates et al., 2004)
Enhancement of efficacy of antihypertensive drugs (Slagman et al., 2011; Aziza et al., 2013)
Reduction of diuretic-induced potassium loss (Ram et al., 1981)
Regression of left ventricular hypertrophy (Rodriguez et al., 2011)
Reduction in proteinuria (Agarwal, 2012)
Reduction in urine calcium excretion (Carbone et al., 2003)
Decrease in osteoporosis (Martini et al., 2000)
Decreased prevalence of stomach cancer (Fock et al., 2008)
Decreased prevalence of stroke (Joossens & Kesteloot, 2008)
Decreased prevalence of asthma (Peat, 1996)
Decreased prevalence of cataract (Cumming et al., 2000)
Protection against onset of hypertension (Whellton PK, 2014)

sodium reabsorption under the influence of aldosterone. When a diuretic is given daily while the patient ingests large amounts of sodium, the initial diuretic-induced sodium depletion shrinks plasma volume, activating renin release and secondarily increasing aldosterone secretion. As the diuretic continues to inhibit sodium reabsorption, more sodium is delivered to this distal site. The increased amounts of aldosterone act to increase sodium reabsorption, thereby increasing potassium secretion; the potassium is swept into the urine.

With modest sodium reduction, less sodium is delivered to the distal exchange site, and therefore, less potassium is swept into the urine. This modest restriction should not further activate the renin–angiotensin–aldosterone mechanism to cause more distal sodium-for-potassium exchange, because that usually occurs only with more rigid sodium restriction.

Dissenting Views

There are a few dissenters to the value of such moderate sodium reduction. Their dissent is based on the possibility that such reduction may cause hazards that outweigh its benefits. These putative dangers include the following:

- ▶ Sodium reduction has not been shown to reduce cardiovascular morbidity or mortality in properly performed, controlled trials even if it lowers blood pressure. This complaint is valid, but it must be understood to pose an impossible burden. It is obvious that it is impossible to perform an RCT in 20,000 free-living subjects over 10 years as would be needed, as projected from studies on treatment of hypertensive patients with drugs. John Snow was correct to close the Broad Street pump on purely observational evidence. There are at least 40 studies showing increased cardiovascular events with higher sodium intake and reduced events with lower sodium intake (Aburto et al., 2013b; He et al., 2013).
- ▶ With severe sodium restriction, down to a level as low as 30 mmol/day, plasma levels of renin, aldosterone, and lipids increase (Graudal et al., 2012). Such rigid reductions are simply impossible for free-living people to maintain, even those on dialysis who are acutely aware of the dangers of sodium intake. Moreover, maintaining a dietary intake of sodium below 66 mmol/day precludes a nutritionally adequate diet in the U.S. (Maillott & Drewnowski, 2012).

- ▶ In patients with end-stage renal disease (Thomas et al., 2011) or type 2 diabetes (Ekinci et al., 2011), an increase in mortality was seen with lower sodium intake, but the contribution of the lower intake contributed to only 7% of the difference.
- ▶ In the ONTARGET trial, the rate of cardiovascular disease showed a U curve, with increases above 8 g/day or below 3 g/day (O'Donnell et al., 2011). However, the estimate of 24-hour levels was based on a single voided specimen, which is known to be inaccurate (Whelton, 2011).
- ▶ In a meta-analysis of seven RCTs on sodium reduction, more cardiovascular events were reported in those on a lower sodium intake (Taylor et al., 2011). In fact, all of the increase came from one trial of patients with severe heart failure who were taking massive doses of diuretic (He & MacGregor, 2011). The other six studies showed a 20% lower risk of cardiovascular disease in those on a lower sodium intake.
- ▶ In a largely normotensive population followed for 7.9 years, those with initially lower sodium excretion had higher cardiovascular mortality (Stolarz-Skrzypek et al., 2011). However, the small number of deaths in the high-sodium tertile (10) was too small for statistical analysis, and only one urine collection at the start of the trial was used to estimate the 7.9-year level of intake.

These five observational studies all have serious faults, which make their conclusions suspect. Nonetheless, even if they were valid, these five (all that were found in a search of the literature from 2000 to 2013) do not come close to countering the data from over 40 studies that have shown a decrease in cardiovascular events with lower sodium intake.

Conclusions

High sodium intake is harmful, and moderate sodium reduction is worthwhile and feasible. The reduction of BP possible with a universal reduction in sodium intake of 50 mmol/day down to the recommended level of 100 mmol/day has been estimated to translate into a decrease of 0.7 to 1.2 million deaths over a 10-year interval (Coxson et al., 2013). Such estimates may be valid: Repeated surveys from 1966 to 1986 in Belgium showed a progressive decrease in average sodium intake from 203 to 144 mmol/day; these falls correlated closely with lesser rises in BP with increasing age and decreased stroke mortality in

the population (Joossens & Kesteloot, 1991). In a 10-year follow-up of 2,657 subjects, a 17% increase in strokes was found with each 500 mg/d increase in sodium intake (Gardener et al., 2012). Therefore, population-wide reductions in sodium intake are likely to both improve health and reduce costs to society. The documented potential for benefit, with the remote possibility of harm, makes moderate sodium reduction a desirable goal both for the individual hypertensive patient and for the population at large (Whelton, 2014).

POTASSIUM SUPPLEMENTATION

Some of the benefits of reduced sodium intake could reflect an increased potassium intake (Aburto et al., 2013a; Yang et al., 2011), although in the TONE study, the antihypertensive effects of the two were independent of each other (Appel et al., 2001).

Clinical Data

Aburto et al. (2013a) identified 22 RCTs and 11 cohort studies on the effects of potassium supplementation on BP, 16 in hypertensive patients. A pooled analysis of the 33 trials showed an overall reduction in BP of 3.5/2.0 mm Hg with greater effects in the 16 trials of hypertensives (5.3/3.1 mm Hg) or when the intake of potassium was as high as 90 to 120 mmol/day (7.2/4.0). In addition, the response was greater when the sodium intake was above 176 mmol/day. No significant adverse effects on blood lipids, catecholamines, or renal function were noted.

Protection Against Strokes

In the analysis of nine cohort studies, Aburto et al. (2013b) found that increased potassium intake was associated with a 24% reduction in the incidence of strokes (Fig. 6-4). In another meta-analysis of data from 15 cohort studies covering over 240,000 subjects,

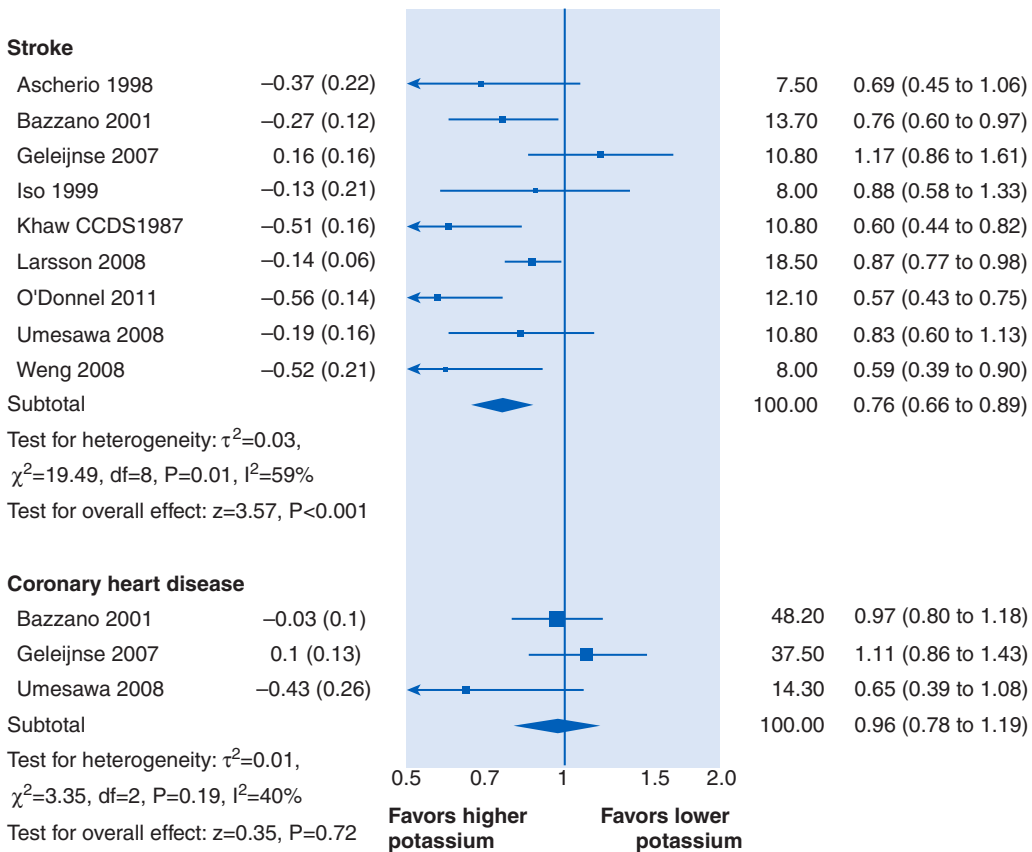


FIGURE 6-4 • Association between higher potassium intake and risk of incident cardiovascular disease, stroke, and coronary heart disease in adults. (Modified from Aburto NJ, Hanson S, Gutierrez H, et al. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. *BMJ* 2013a;346:f1378).

a 42 mmol/day increase in potassium intake was associated with a 21% lower risk of stroke (D'Elia et al., 2011).

Recommendations

Though potassium supplements may lower the BP, they are too costly and potentially hazardous for routine use in the treatment of hypertension in normokalemic patients. They are indicated for diuretic-induced hypokalemia and, in the form of potassium-containing salt substitutes, will add little expense. For the larger population, a reduction of high-sodium/low-potassium processed foods with an increase of low-sodium/high-potassium natural foods is likely all that is needed to achieve the potential benefits (Kelly et al., 2012). Fruits and beans provide the largest quantity of potassium per serving.

CALCIUM SUPPLEMENTATION

More milk or, in blacks, supplements of vitamin D may lower blood pressure, but calcium supplements or even high levels of dietary calcium intake will *increase* the risk of CVD mortality in men (Xiao et al., 2013) and women (Michaelsson et al., 2013). Although the effects of increased calcium on BP were not reported in these two reports, increases in calcium excretion were associated with higher BP in two large cross-sectional studies (Kesteloot et al., 2011). Furthermore, increased calcium intake was directly associated with the risk of stroke in 34,670 women over a 10.4-year follow-up (Larsson et al., 2011).

Recommendations

In the presence of such data showing a significant adverse effect on cardiovascular disease, calcium supplements are not recommended for treatment of hypertension, an example of the critical need for evidence to base recommendations despite repeated claims of a beneficial effect (McCarron & Morris, 1985). The best course is to ensure an adequate dietary calcium intake but not to give calcium supplements to either prevent or treat hypertension.

MAGNESIUM SUPPLEMENTATION

Whereas serum and intracellular magnesium levels are normal in most untreated hypertensives, low muscle magnesium concentration has been found in half

of patients on chronic high-dose diuretic therapy (Drup et al., 1993) and low serum levels in patients on long-term proton pump inhibitors (Furlanetto & Faulhaber, 2011). Moreover, in a 7.6-year follow-up of 5,511 people, low urinary magnesium levels were associated with an increased risk of hypertension (Joosten et al., 2013).

However, in a review of 12 high-quality trials of magnesium supplements covering 545 hypertensives, Dickinson et al. (2006) found that SBP fell by an insignificant -1.3 mm Hg, whereas DBP fell by a significant -2.2 mm Hg. The conclusion was: "In view of the poor quality of included trials and the heterogeneity between trials, the evidence in favor of a causal association between magnesium supplementation and BP reduction is weak and is probably due to bias...."

Therefore, rather than giving magnesium supplements, increasing dietary consumption with fresh fruits and vegetables that provide magnesium seems preferable (Larsson et al., 2008).

INCREASED PHYSICAL ACTIVITY

The evidence for protection from both the development of hypertension and CVD and all-cause mortality by regular physical activity is incontrovertible. Nonetheless, most people in all industrialized societies are becoming less physically active in their daily lives, spending more and more time in sedentary activities (Kohl et al., 2012). Not only will increased physical activity and higher levels of exercise capacity reduce mortality (Wen et al., 2011) but they will also likely prevent the development of hypertension (Shook et al., 2012). In a prospective 4.7-year follow-up of 6,000 people, the incidence of hypertension was reduced by 42% in those who engaged in high levels of physical activity even if they had a parental history of hypertension (Shook et al., 2012). A mortality benefit extends to those with hypertension (Rossi et al., 2012) or even hypertension resistant to medical therapy (Dimeo et al., 2012). In a cohort study covering 400,000 people, as little as 15 minutes of exercise a day was associated with reduced mortality (Wen et al., 2011).

Clinical Data

BP is lowered by exercise whether aerobic (Cornelissen et al., 2013) or resistance (Figuroa et al., 2013), even without weight loss (Lee et al., 2011). The benefit

extends even to children as young as 5 years (Knowles et al., 2013) and the elderly with prevention of cognitive impairment (Verdelho et al., 2012). Moreover, patients with orthostatic hypotension may have less of a postural fall after performing regular exercise (Moraes et al., 2012).

Because the SBP rises during exercise and because the abrupt rise in BP after arising from sleep may be associated with an increased incidence of cardiovascular events, concerns about exercise in the morning have been raised. However, even in patients with known coronary disease, no increase in events was noted with exercise performed in the morning versus the afternoon (Murray et al., 1993). On the other hand, strenuous physical exertion in patients who are habitually sedentary may, on occasion, precipitate an acute myocardial infarction (Dahabreh & Paulus, 2011). Therefore, sedentary patients should be advised to increase their level of activity slowly.

Hypertensives may experience difficulty if they take β -blockers, which blunt exercise-mediated increases in heart rate and cardiac output (Vanhees et al., 2000). Other antihypertensive agents should not interfere with exercise ability.

There may be concerns about another activity that involves exercise—sexual intercourse, which is accompanied by significant rises in pulse and BP that are equivalent to stage II of the standardized Bruce treadmill test for men and stage I for women (Palmieri et al., 2007). Although actually quite rare even among patients with coronary disease, the triggering of myocardial infarction during sexual activity likely can be prevented by regular exercise (Dahabreh & Paulus, 2011). Moreover, erectile dysfunction in obese men may be overcome by a program of physical activity and weight loss (Gupta et al., 2011).

Recommendations

Increased levels of physical activity, either during ordinary life or with structured exercise, may lower BP and prevent the onset of hypertension (Faselis et al., 2012). As little as 15 minutes of walking or its equivalent per day provides a reduction in mortality (Wen et al., 2011), and as little as 30 minutes a day three times a week slows the decline in cognitive function in the elderly (Verdelho et al., 2012). Despite the proven benefits, few physicians counsel their patients about exercise, even though counseling has been shown to be effective in increasing patients' level of physical activity (Hallal & Lee, 2013). Other

than for cessation of smoking, this advice can have the most immediate acceptance and greatest overall benefit.

MODERATION OF ALCOHOL

Alcohol is a two-sided issue: Up to one portion a day for women and two for men are protective against heart attacks and stroke (Ronksley et al., 2011), but consumption of more than one usual portions per day may raise BP (Briasoulis et al., 2012). (A usual portion of alcohol-containing beverage is 12 oz of beer, 4 oz of wine, or 1.5 oz of whiskey, each containing 10 to 12 mL of alcohol.)

Effects on Blood Pressure

Acutely, the drinking of 60 g of ethanol, the amount contained in five usual portions, induces an immediate fall in BP averaging 4/4 mm Hg followed, after 6 hours, by a rise averaging 7/4 mm Hg (Rosito et al., 1999). Three or more portions per day is associated with a significant increased risk of hypertension (Briasoulis et al., 2012), and binge drinking is associated with increased blood pressure and cardiovascular mortality (Sull et al., 2010). When heavy drinkers abstain, their BP usually goes down (Xin et al., 2001). An analysis of the relation between the risk of hypertension and the pattern of drinking found a slightly lower incidence among those who drank daily with meals but a 41% increased incidence in those who drank without food (Stranges et al., 2004).

Studies on the effects of alcohol may be confounded by a number of factors including a healthier lifestyle in those who drink in moderation and the inclusion of former heavy drinkers into current nondrinkers.

Beneficial Effects

Nonetheless, there is impressive evidence for a protective effect of moderate, regular alcohol consumption of one-half to two portions per day on a host of cardiovascular and other diseases when compared to similar outcomes in nondrinkers or heavy drinkers. In an analysis of data from 84 high-quality studies, Ronksley et al. (2011) found a 25% lower risk for cardiovascular mortality and a 29% reduction in the incidence of coronary disease but no effect on stroke. In addition, moderate drinking has been associated with

less heart failure (Djoussé & Gaziano, 2007), the incidence of type 2 diabetes (Wei et al., 2000), osteoporosis (Berg et al., 2008), and cognitive impairment (Stampfer et al., 2005). Beneficial effects have been attributed to improvements in the lipid profile, in hemostatic factors, insulin sensitivity (Avogaro et al., 2002), and antioxidant activity (Vasdev et al., 2006).

However, no mortality benefit is seen in young people, and a 15% increased incidence of breast cancer has been reported in women who drink more than one portion per day (Chen et al., 2011) and of colon cancer in those who drink more than two portions per day (Cho et al., 2004). Beyond the apparently proved association between even small amounts of alcohol and breast cancer, claims have been made for an association with multiple others cancers (Nelson et al., 2013). However, when the data are examined, all of these associations (save for the extremely rare cancer of the larynx) are shown to be *lower* in those who drink >20 to 40 g/day (equivalent to 2 to 3 usual portions) compared to those who drink 0 to 20 g/day (equivalent to none to 1 and a half usual portion). No explanation is offered for this inverse relationship, but it adds to the evidence for the safety of moderate drinking. As of now, the associations of moderate regular alcohol consumption with multiple benefits support current guidelines, which allow for moderate drinking.

Wine may be more protective than beer or whiskey (Renaud et al., 2004), but wine drinkers tend to have a healthier lifestyle, so this apparent benefit may be exaggerated. Although there is some evidence that red wine is more protective than white wine because of its increased levels of polyphenols (Botden et al., 2011), the same investigators later reported no lowering of blood pressure with red wine (Botden et al., 2012). To add to the confusion, red wine with the alcohol removed lowered blood pressure and increased plasma NO (Chiva-Blanch et al., 2012).

Recommendations

The following guidelines seem appropriate:

- Carefully assess alcohol intake, as some people drink well beyond moderate amounts without being aware of their excessive consumption or its deleterious effects.
- If intake is more than one portion per day in women or two per day in men, advise a reduction to that level.
- Strongly advise against binge drinking.

- Drink along with food.
- For most people who consume moderate amounts of alcohol, no change is needed. If middle-aged (45- to 64-year-old) people start to drink, they rarely go beyond recommended amounts while properly benefiting from lower rates of cardiovascular morbidity (King et al., 2008).

OTHER DIETARY FACTORS

The impressive results of the DASH diet shown in Figure 6-2 strongly support an antihypertensive effect of a diet low in saturated fat and high in fiber and minerals from fresh fruits and vegetables (Sacks et al., 2001). Moreover, among 1,710 middle-aged men followed up for 7 years, the rise in SBP was significantly less with diets higher in fruits and vegetables and lower in red meats (Miura et al., 2004). Vegetarians likely have less hypertension than non-vegetarians. Compared to those eating a non-vegetarian diet, those consuming a vegetarian diet under controlled conditions had a lower BP in 7 clinical trials and 32 observational studies (Yokoyama et al., 2014).

Responses of BP to dietary ingredients may be genetically determined: Only the 10% of hypertensives with a specific genotype had a lowering of BP with supplemental riboflavin (Wilson et al., 2013).

Dietary Nitrate

Certain green leafy vegetables, such as spinach, lettuce, and beetroot have high inorganic nitrate (NO₃) content. In an intriguing rediscovery of the antihypertensive effect of nitrate via its endogenous bioconversion to nitrite (NO₂), partially on the tongue, Webb et al. (2008) and Kapil et al. (2010) found a significant acute BP lowering, vasoprotective and antiplatelet effect of dietary nitrate contained in beetroot juice. After bioconversion from nitrate, the nitrite is reduced to NO when ischemia or injury induces a more acidic environment within tissues. The NO generated from nitrite induces vasodilation, thereby lowering BP.

Fiber

One feature of a vegetarian diet is the increased amount of fiber. A meta-analysis of 24 randomized, placebo-controlled clinical trials published from 1966 to 2003 on the effect on BP of supplements of dietary fiber averaging 11.5 g/day found an average fall of

1.1/1.3 mm Hg (Streppel et al., 2005). Greater intake of fiber is associated with a significantly lower incidence of initial stroke (Threapleton et al., 2013) and reduce mortality after a MI (Li et al., 2014).

Dietary Fat

In keeping with the potential contribution of the low saturated fat content of the DASH diet, increased consumption of low-fat dairy food was reported to reduce the incidence of hypertension (Soedamah-Muthu et al., 2012). The type of fat may be important. As a component of the cardiovascularly beneficial Mediterranean diet, olive oil may lower BP because of its high content of monounsaturated fatty acids or antioxidant polyphenols (Moreno-Luna et al., 2012), and increased consumption of monounsaturated fatty acids was associated with lower diastolic BP (Miura et al., 2013). Increased intake of linoleic acid, the main dietary polyunsaturated fatty acid, was associated with a significant fall in BP (Miura et al., 2008). Omega-3 fatty acid in flaxseed has been shown to lower BP significantly (Rodriguez-Levy et al., 2013), but overall, antioxidant supplements have been found to have no effect on cardiovascular events (Myung et al., 2013).

On the other hand, flavonoid-rich dark chocolate may be beneficial: Consumption of 100 g/day provided an improvement in endothelial function (Grassi et al., 2012), and in seven high-quality studies, higher intake of chocolate was associated with a 37% reduction in cardiovascular events and a 29% reduction in strokes (Buitrago-Lopez et al., 2011). Cocoa flavanol was reported to lower BP and improve cognitive function in elderly subjects (Desideri et al., 2012).

Lipid-Lowering Diet and Drugs

Lipid-lowering drugs, in particular statins, improve the endothelial dysfunction associated with dyslipidemia, thereby lowering BP (Kanaki et al., 2012). Protection against atherosclerotic complications, including stroke, has been seen with statins in both normotensives and hypertensives (Taylor et al., 2013).

Uric Acid Reduction

Epidemiologic evidence suggests a link between elevated serum uric acid and both hypertension and cardiovascular diseases (Feig et al., 2008a). In small groups of adolescents with elevated BP, investigators

have conducted RCTs, which show reductions in blood pressure with both allopurinol (Feig et al., 2008b) and probenecid (Soletsky & Feig, 2012). As seen in Chapter 7, most diuretics raise serum uric acid levels which could blunt their effectiveness in reducing blood pressure and cardiovascular events.

Protein Intake

Although high protein intake has been thought to be detrimental, in large part by placing an additional load on the kidney, both INTERSALT (Stamler et al., 1996) and INTERMAP (Elliott et al., 2006) found a lower BP in people who consume a high-vegetable protein diet. Soy protein lowered systolic BP in hypertensive women (Liu et al., 2013). However, increased red meat intake is associated with higher SBP (Tzoulaki et al., 2008).

Antioxidants

Although the antihypertensive effect of a diet rich in fruits and vegetables has been related to the accompanying increase in antioxidant vitamins, trials of antioxidant supplements such as coenzyme Q10 have shown no effect on blood pressure (Young et al., 2012) or prevention of cardiovascular events (Myung et al., 2013).

Coffee and Tea

Even though greater coffee intake has been associated with a steeper age-related increase in blood pressure (Giggey et al., 2011), increased coffee consumption was associated with decreases in both total and cardiovascular mortality in a prospective study involving over 400,000 people (Freedman et al., 2012), and more green tea may reduce the risk of CVD and stroke (Kokubo et al., 2013). Three cups of black tea a day provided a small fall in blood pressure in an RCT of 95 subjects (Hodgson et al., 2012). However, in a meta-analysis of the effects of coffee consumption, no significant effects were found for either BP or the risk of hypertension (Steffen et al., 2012).

MISCELLANEOUS

A large number of complementary and alternative therapies are being used for hypertension among other indications, more in the U.S. than in other countries surveyed (Marshall et al., 2012). When such therapies, including biofeedback (Greenhalgh et al., 2010),

acupuncture (Flachskampf et al., 2007), and device-guided slow breathing (Landman et al., 2014), are subjected to appropriately controlled study, they often are found to be ineffectual (Brook et al., 2013).

Nonetheless, if available and acceptable to the patient, one or another form of relaxation therapy may be tried, as such techniques may provide additional benefits in reducing coronary risk beyond any effect on BP. Patients should be forewarned that short-term effects may not be maintained, so continued surveillance is needed.

Garlic and Herbal Remedies

Garlic, mainly as a deodorized powder, has been found to significantly lower BP in hypertensive subjects by 8.4/7.3 mm Hg in four placebo-controlled RCTs (Ried et al., 2008).

Herbal remedies are being widely used for all sorts of unproved benefits, totally unsupervised in the U.S. because of Senator Orrin Hatch's interference with the Food and Drug Administration's surveillance (Bent, 2008). None has been shown to lower BP (with the obvious exceptions of *Rauwolfia* and *Veratrum*) and some, in fact, will raise BP, including ephedra, bitter orange, Siberian ginseng, and licorice extract (Rasmussen et al., 2012).

Other Modalities

Melatonin, 2.5 mg at bedtime for 3 weeks, was found to reduce nighttime BP by 6/4 mm Hg in a crossover trial in 16 hypertensives (Scheer et al., 2004). *Medications that increase sleep duration* may be helpful since short sleep duration has been said to increase the incidence of hypertension (Wang et al., 2012). Hypertension is incited both by *air pollution* (Dong et al., 2013) and *occupational noise* (Chang et al., 2013), further validating the values of clean air and silence.

Surgical Procedures

From 1935 through the 1950s, surgical sympathectomy, along with a rigid low-salt diet, was about all that was available for treating hypertension. Sympathectomy was shown to be beneficial for those with severe disease (Thorpe et al., 1950), but with current medical therapy, there is no place for the procedure. However, as described in chapter 3, denervation of the sympathetic nerves in the renal artery and activation of the carotid baroreceptor are

being actively studied for relief of hypertension resistant to usual therapy. A much more serious surgical procedure, decompression of the rostral ventrolateral medulla, may have a transient antihypertensive effect (Frank et al., 2009) but has never been properly tested.

Conclusions

Appropriate lifestyle modifications should be assiduously promoted in all patients. Those with mild hypertension may thereby be able to stay off drugs; those with more severe hypertension may need less medication. Hopefully, population-wide adoption of healthier lifestyles will reduce the incidence of hypertension and its complications. Meanwhile, most hypertensive patients will need antihypertensive drugs as described in the next chapter.

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Treatment of Hypertension: Drug Therapy

In the previous two chapters, the evidence for the need for blood pressure (BP) reduction and the use of lifestyle modifications to lower the BP were reviewed. This chapter begins with ways to improve on the management of the disease with drugs. Then each class of drugs currently available is covered. An analysis of initial drug choice and of the subsequent order of additional therapy follows; then comes considerations of the management of special populations and of hypertensives with various other conditions.

Before proceeding, a brief reiteration of an issue covered in Chapters 1 and 5 seems appropriate: Does therapy that brings hypertension to a “controlled” level bring the patient’s cardiovascular mortality down to that seen in normotensive people? The answer may be “No.” Although the data are limited, three prospective long-term follow-up studies have reported that hypertensive patients who were adequately controlled with antihypertensive drugs remained at higher risk (Andersson et al., 1998; Asayama et al., 2014; Lawlor et al., 2011). Perhaps the drugs to be described, although effective in lowering BP and morbidity and mortality in the short time of most trials, do not do so over longer time. If so, the need for prevention becomes even more critical.

CURRENT STATE OF CONTROL OF HYPERTENSION

As reviewed in Chapter 1, hypertension is the most common risk factor for heart attack, stroke, and heart failure and second only to diabetes for renal failure. With a longer life span and increasing obesity, the incidence of hypertension will continue to increase, particularly in developing societies (Chow et al., 2013). Therefore, the use of drugs for the treatment of

hypertension will continue to grow. As will be seen, currently available antihypertensive drugs, preferably in concert with appropriate lifestyle changes and self-monitoring, can control the BP in most hypertensive patients (Calhoun et al., 2014).

Even though the number of well-controlled patients, defined as having a BP below 140/90 mm Hg, is progressively growing, almost half of hypertensives in the United States (U.S.) remain above that level (Go et al., 2014). Higher rates of adequate control have been reported under a well-organized systems of long-term follow-up as provided in the U.S. Veterans Administration medical centers (Fletcher et al., 2012) and health-care organizations (Jaffe et al., 2013). Even in primary care, adherence to intensive management regimens improves control (Stewart et al., 2014). Before considering the drugs that are available, the issue of how to achieve better control of hypertension will be addressed.

Reasons for Poor Control

As will be noted, all components of the management of hypertension contribute to the inadequacies that persist. Despite these concerns, we should be heartened by the reduction in coronary and stroke mortality that have resulted from improved control of hypertension over the past few decades.

Problems with Physicians

Some practitioners are either unaware of the need to more intensively treat hypertension, particularly isolated systolic hypertension in the elderly, or are unwilling to do so. Admittedly, systolic levels are more difficult to bring under control even under the best of circumstances, with fewer than half of patients enrolled in

controlled trials having their systolics brought to 140 mm Hg or lower, whereas 80% of diastolics were brought to 90 mm Hg or lower (Mancia & Grassi, 2002).

However, much of the problem in clinical practice is “clinical inertia,” the unwillingness to push therapy to the desired goal (Redon et al., 2011). This unwillingness may reflect inaccurate perceptions: That systolic elevations “aren’t that bad,” that they can’t be lowered without multiple medications and side effects, and that little benefit will accompany better control.

On the other hand, before blaming practitioners for not more aggressively treating patients with “mild” (stage 1) hypertension or elderly patients with systolic levels from 140 to 160 mm Hg, as noted in Chapter 5, there is no convincing evidence for benefit in treatment of patients with stage 1 hypertension who are otherwise at low risk (Diao et al., 2012) and the best evidence for treatment of those over age 80 comes from the Hypertension in the Very Elderly Trial (HYVET) in which treatment was based on a systolic level above 160 mm Hg (Bulpitt et al., 2013). Whereas multiple trials have shown benefits of active treatment in patients aged 65 to 80 years, the patients in almost all of these trials had initial systolic blood pressures (SBPs) of 160 mm Hg or higher (Blood Pressure Trialists, 2008).

Hypertension “experts” have contributed to practitioners’ problems by promoting conflicting positions even on as fundamental an issue as the level of blood pressure for both the start and the goal of therapy. Based purely on evidence, the level for patients 60 years or older has been recommended to be 150/90 mm Hg (James et al., 2014), thereby considerably reducing the number of patients to be treated (Navar-Boggan et al., 2014). However, most expert guidelines continue to use 140/90 for all patients (Mancia et al., 2013; Weber et al., 2014). Even lower goals may be beneficial (Reboldi et al., 2014). Logically, the decisions should be based on overall risk rather than on a (constantly changing) number (Sussman et al., 2013).

Beyond physician inertia and confusion, problems with the health care delivery system can markedly reduce long-term adherence. Particularly in inner-city clinics that in the U.S. serve a large portion of the elderly and poor, records are often unavailable, little continuity of care is provided, and patients are made to wait long hours for short visits without an opportunity for meaningful interaction with their physician.

As the only developed country without universal health coverage, the U.S. is particularly susceptible to the faults of an erratic health care delivery system and the lack of health insurance by a large part of the

population so that patients are unable to obtain continuity of care or purchase medications (Meneton et al., 2012).

Imaginative programs have been used to improve adherence (Jaffe et al., 2013). These include telemonitoring of BPs taken at home (Bove et al., 2013), self-management (Watson et al., 2012), provision and coordination of care by pharmacists and nurses (Carter et al., 2008a), tailored feedback to physicians (Egan et al., 2011), and monitoring patients at a place which they frequent, i.e., their barbershop (Rader et al., 2013) or church (Ferdinand et al., 2012). All of these have been shown to improve adherence.

Problems with Patients

As many as half of hypertensives prescribed an antihypertensive medication will not be taking it within a year (Naderi et al., 2012). There are many patient-related reasons for poor adherence to antihypertensive therapy. Perhaps the most important is the largely asymptomatic nature of hypertension, making it difficult for patients to forego immediate pleasures (salt, calories, money, etc.) for distant, unrecognized benefits, even more so if therapy makes them feel worse (Trevisol et al., 2012). Moreover, just the attachment of the label “hypertensive” induces a decrease in mental health and increases depressive symptoms, particularly in black subjects (Spruill et al., 2012). Such labeling effects are in keeping with the repeatedly noted association of depression with nonadherence to therapy (Cene et al., 2013).

In a systematic review of qualitative research that included 53 studies from 16 countries, Marshall et al. (2012) found these associations between hypertension and adherence to drug therapy:

- A large proportion thought that hypertension was principally caused by stress and that it produced symptoms such as headache, dizziness, and sweating.
- Patients often intentionally reduced or stopped treatment without consulting their doctor.
- Patients commonly perceived that their BP improved when symptoms abated or when they were not stressed and that treatment was not needed at these times.
- Patients disliked treatment and its side effects and feared addiction.
- Patients reported various external factors that prevented adherence, including insufficient money to pay for treatment, the cost of appointments and healthy food, and a lack of health insurance.

Marshall et al. (2012) concluded that “these beliefs were remarkably similar across ethnic and geographical groups.”

Problems with the Therapy

As noted, hypertension has all the wrong characteristics to ensure adherence to therapy, but these are often compounded by problems of therapy, including

- ▶ Difficulty in changing unhealthy lifestyles, in particular weight gain from too many calories and too little physical activity (see Chapter 6).
- ▶ The high cost of most new, patent-protected medications. When available, generic agents that are equally efficacious are more likely to be taken (Shrank et al., 2006).
- ▶ The prescription of two or more doses per day when long-acting once-a-day options are available (Egan et al., 2012). Even worse is one daily dose of drugs, e.g., atenolol, which lack a 24-hour effect (Neutel et al., 1990).
- ▶ Side effects of antihypertensive drugs, likely the major reason that diuretics and β -blockers have lower rates of adherence than angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) (Naderi et al., 2012).
- ▶ Interactions with other medications and substances, nonsteroidal anti-inflammatory drugs (NSAIDs) the most common, simvastatin likely the least recognizable (Carey et al., 2012), and herbal remedies perhaps the most dangerous (Rasmussen et al., 2012).
- ▶ Difficulty in assessment of adherence. Although there are multiple ways to assess the degree of patients' pill taking, few have been found to be accurate beyond assays of patients' blood (Brinker et al., 2014; Strauch et al., 2013) or urine (Jung et al., 2013).
- ▶ Variable responses to any dose of any medication. The starting and usual doses are determined by trials in only a limited number of usually uncomplicated patients. In practice, many patients respond either more or less to any drug (Law et al., 2003).

Ways to Improve Adherence to Therapy

Although many books and articles have suggested ways to keep more patients on effective therapy of hypertension, the list of those that have been shown to affect clinical outcomes is relatively short (Table 7-1)

(Adams et al., 2013; Egan et al., 2012; Jaffe et al., 2013; Stewart et al., 2012). In the future, genetic typing may provide a way to maximize the response, but as of now, few have been reported to provide clinically useful data (Turner et al., 2013).

Patient Involvement

Involvement of the patient is helpful, not only in making initial decisions which are therefore more likely to be followed but also in monitoring the course of the disease. Home BP readings should always be recommended, preferably taken by the patient or sometimes by other caregivers. Moreover, as noted in Chapter 2, responses to therapy are more closely related to out-of-office measurements than office readings.

Intensity of Therapy

The rapidity of reaching goal is now in question since too fast a course may cause intolerable symptoms, but too slow may expose high-risk patients to immediate dangers. The benefit of more rapid control was graphically shown in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, wherein the quicker response over the first 3 to 6 months to the CCB amlodipine than to the angiotensin II receptor blocker (ARB) valsartan, provided greater protection against heart attacks and strokes (Julius et al., 2004). The patients in VALUE were all at high risk for cardiovascular disease, so it still seems appropriate to “start low and go low” for most, particularly the elderly with systolic hypertension. For those with higher levels of BP and, even more so, with higher overall risk, a “higher and faster” approach may be more appropriate.

Timing of Dosing

The time of day to take one-a-day antihypertensive medications needs to be more carefully considered. Early morning has usually been recommended, but there are two potential problems: First, the pills may not exert a full 24-hour effect; second, an even greater effect may be needed in the early morning, before today's therapy has kicked in, to keep the pressure from surging in the immediate postarising time, thereby contributing to the “morning surge” of cardiovascular catastrophes.

The solution for the first problem is twofold: First, ensure full 24-hour control by having the patient measure early morning BP at home; second, choose

TABLE 7-1

Guidelines to Improve Maintenance of Antihypertensive Therapy

- Involve the patient in decision making to the extent desired
 - Provide individual assessments of current risks and potential benefits of control
 - Inform the patient about the condition and its treatment
 - Encourage home BP monitoring
- Articulate the goal of therapy: to reduce BP to near normotension with few or no side effects
- Be alert for signs of inadequate intake of medications, e.g., absence of BP response or expected effects, e.g., bradycardia with β -blocker
- Encourage lifestyle changes if needed
- Recognize and manage depression
- Maintain contact with the patient
 - Provide appointment reminders
 - Encourage visits and calls to allied health personnel
 - Give feedback to the patient via home BP readings
 - Make contact with patients who do not return
- Keep care inexpensive and simple
 - Do the least workup as needed
 - Obtain follow-up laboratory data only yearly unless indicated more often
 - Use home BP readings
 - Use once-daily doses of long-acting drugs
 - Use generic drugs and break larger doses of scored tablets in half
 - If appropriate, use combination tablets
 - Inspect all pill containers at each visit
 - If medications must be taken separately, provide clear, easily read instructions
 - Use clinical protocols monitored by nurses and assistants
- Prescribe according to pharmacologic principles
 - Add one drug or combination at a time
 - Start with small doses, aiming for 5- to 10-mm Hg reductions at each step, unless more rapid response is indicated
 - Have medication taken immediately on awakening in the morning
 - If morning surge of BP (above 160/100) persists, give at least some drugs at 6 p.m. or at bedtime
- Provide feedback and validation of success

intrinsically long-acting medications, e.g., metoprolol XL rather than atenolol, trandolapril rather than enalapril, and amlodipine rather than felodipine.

The solution for the second problem seems as obvious: i.e., take medications later in the day or even at bedtime. A group of investigators from Vigo, Spain, have published the results of multiple studies in hypertensives, including some with diabetes or chronic kidney disease, that show improved BP control and cardiovascular outcomes with bedtime rather than morning dosing (Hermida et al., 2011).

In a Cochrane Review of the 21 RCTs published between 1978 to 2009 that compared morning versus evening dosing regimens, the authors concluded, “There were no significant differences in overall adverse events and withdrawals due to adverse events among the evening versus morning dosage regimens. In terms of BP lowering efficacy, for 24-hour SBP and diastolic blood pressure (DBP), the data suggest that

better blood pressure control was achieved with bedtime dosing than morning administration of antihypertensive medication, the significance of which is not known” (Zhao et al., 2011).

Dealing with Side Effects

Some medications are easier to take than others, but some patients cannot seem to take any. Such patients with nonspecific intolerance to multiple antihypertensive drugs almost always have underlying psychological morbidity, often manifested as recurrent hyperventilation, panic attacks, generalized anxiety, or depression (Davies et al., 2003). As noted before, the labeling of hypertension can induce adverse psychological effects (Spruill et al., 2012). Fortunately, the use of currently available drugs slows cognitive decline and may prevent dementia (Marpillat et al., 2013), but some aspects of the quality of life (QOL) may be worse in hypertensives

under drug treatment than equally hypertensive patients on no medication (Trevisol et al., 2012).

Follow-Up Visits

To achieve and maintain target BP with the lowest possible dosage of medication requires ongoing patient follow-up, preferably with home blood pressure monitoring (BPM), and may involve multiple dosage adjustments. Most patients should be seen within 1 to 2 months after the initiation of therapy to determine the adequacy of BP control, the degree of patient cooperation in taking pills, the need for more therapy, and the presence of adverse effects. Once the BP is stabilized, follow-up at 3- to 6-month intervals is generally appropriate. In most patients, particularly the elderly and patients with orthostatic symptoms, monitoring should include BP measurement in the supine position and after standing for up to 5 minutes, to recognize postural hypotension.

SPECIFICS ABOUT ANTIHYPERTENSIVE DRUGS

The modern era of antihypertensive therapy began only about 55 years ago with the pioneering work of Ed Freis in the U.S. and Horace Smirk in New Zealand

(Piepho & Beal, 2000). Since then, a large panoply of drugs have been developed, as listed in Table 7-2. We will consider the drugs in the order shown in Table 7-2.

There are 10 ACEIs listed, most of them offering no advantage over the others except for longer durations of action than captopril and enalapril. Why so many of the same classes? The answer is given by Light and Lexchin (2012). They state: “Although the pharmaceutical industry and its analysts measure innovation in terms of new molecular entities as a stand-in for therapeutically superior medications, most have provided only minor clinical advantages over existing treatments The industry’s own report on all internationally marketed new drugs concluded that only 11% were therapeutically and pharmacologically innovative. Since the mid-1990s, independent reviews have also concluded that about 85% to 90% of all new drugs provide few or no clinical advantages for patients.”

To be sure, in a capitalistic, competitive market system, multiple options within the same classes of drugs will remain available. However, better advice can be provided. Attempts are being made; the National Institute for Clinical Excellence (NICE) in the United Kingdom, the Hypertension Education Program in Canada, the National Institutes of Health (NIH) and, in particular, the National High Blood

TABLE 7-2

Antihypertensive Drugs Available in the U.S. (as of 2014)

Diuretics	Adrenergic inhibitors		Vasodilators	
Thiazides	Peripheral	β-Blockers	Direct	ACEIs
Hydrochlorothiazide	Guanadrel	Acebutolol	Hydralazine	Benazepril
Nonthiazides	Guanethidine	Atenolol	Minoxidil	Captopril
Chlorthalidone	Reserpine	Bisoprolol	Calcium Channel Blockers	Enalapril
Indapamide	Central α₂-agonists	Carteolol	Dihydropyridine	Fosinopril
Metolazone	Clonidine	*Carvedilol	Amlodipine	Lisinopril
Loop Diuretics	Guanabenz	*Labetalol	Felodipine	Moexipril
Bumetanide	Guanfacine	Metoprolol	Nicardipine	Perindopril
Furosemide	Methyldopa	Nadolol	Nifedipine	Quinapril
Torsemide	α₁-Blockers	*Nebivolol	Nisoldipine	Ramipril
Nonsulfonamide	Doxazosin	Pindolol	Non-dihydropyridine	Trandolapril
Ethacrynic acid	Prazosin	Penbutolol	Diltiazem	All receptor blockers
Potassium sparingers	Terazosin	Timolol	*Verapamil	Azilsartan
Amiloride				Candesartan
Triamterene				Eprosartan
Aldosterone Blockers				Irbesartan
Eplerenone				Losartan
Spironolactone				Olmесartan
				Telmisartan
				Valsartan

*Vasodilating

Pressure Education Program in the U.S. are trying to bring the best advice to practitioners.

The number of hypertensive subjects taking anti-hypertensive drugs has progressively risen over the past 40 years. Diuretics have continued to be the most commonly prescribed, followed by ACEIs, β -blockers, and CCBs, with ARBs rising the fastest and α -blockers continuing to fall. Logical combinations will be used increasingly (Parati et al., 2014).

Law et al. (2009) suggest that two or three drugs in half usual doses be given, rather than full doses of one or two, both to achieve greater efficacy and to reduce dose-dependent side effects. A “Polypill” containing small doses of a diuretic, ACEI, statin, and aspirin has been shown to be effective (Thom et al., 2013).

The use of drugs in various secondary forms of hypertension (e.g., spironolactone in primary aldosteronism) is considered in the respective chapters on these identifiable causes.

DIURETICS

Among the first orally effective drugs to become available, diuretics are being used even more frequently because their effectiveness has been reiterated and, with lower doses, their side effects minimized.

Diuretics differ in structure and major site of action within the nephron (Fig. 7-1). The site of action determines their relative efficacy, as expressed in the maximal percentage of filtered sodium chloride excreted (Brater, 2000). Agents acting in the proximal tubule (site I) are seldom used to treat hypertension. Treatment is usually initiated with a thiazide-type diuretic (acting at site III, the distal convoluted tubule). Chlorthalidone and indapamide, although

they act at the same site, are structurally different from the thiazides and will be covered separately. If renal function is significantly impaired (i.e., serum creatinine exceeding 1.5 mg/dL), a loop diuretic (acting at site II, the thick ascending limb of the loop of Henle) or metolazone likely will be needed. A potassium-sparing agent (acting at site IV) may be given with the diuretic to reduce the likelihood of hypokalemia. By themselves, potassium-sparing agents are relatively weak antihypertensives.

The diuretics now available in the U.S. are listed in Table 7-3. Aldosterone receptor blockers, though potassium spasers, are considered separately because of their additional effects.

Thiazide Diuretics

Hydrochlorothiazide (HCT) is the most commonly used diuretic for the treatment of hypertension in the U.S. and, if a diuretic is part of a combination product, HCT is almost always chosen (Kaplan, 2011). However, starting in 2004, a group of investigators at the Carver School of Medicine at the University of Iowa have published data showing that chlorthalidone is both stronger and longer-acting than HCT (Carter et al., 2004; Ernst et al., 2011). Their results have been repeatedly confirmed, most impressively with 24-hour ambulatory BP monitoring (Messerli et al., 2011). More importantly, chlorthalidone when used alone has been shown to reduce morbidity and mortality (Roush et al., 2012) whereas HCT when used alone has not been shown to do so (Messerli & Bangalore, 2011). As a consequence of these results, chlorthalidone will likely be used more frequently. One combination of it with an ARB has recently appeared (Cushman et al., 2012a).

Mode of Action

The thiazide diuretics act by inhibiting sodium and chloride cotransport across the luminal membrane of the early segment of the distal convoluted tubule, where 5% to 8% of filtered sodium is normally reabsorbed (Brater, 2000) (see Fig. 7-1, site III). Plasma and extracellular fluid volume are thereby shrunken, and cardiac output falls (Wilson & Freis, 1959). Humoral and intrarenal counterregulatory mechanisms rapidly reestablish the steady state so that sodium intake and excretion are balanced within 3 to 9 days in the presence of a decreased body fluid volume (Sica, 2004a). With chronic use, plasma volume returns partially

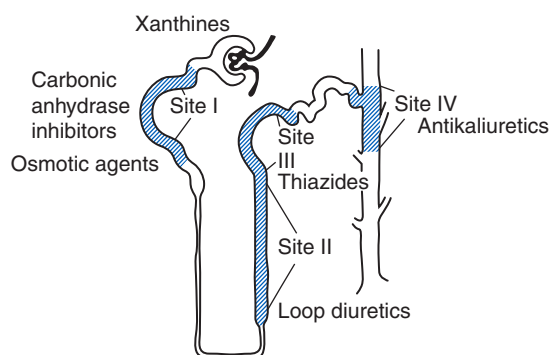


FIGURE 7-1 • Diagrammatic representation of the nephron showing the four main tubular sites where diuretics interfere with sodium reabsorption.

TABLE 7-3

Diuretics and Potassium-Sparing Agents

Drug	Daily Dosage (mg)	Duration of Action (h)
Thiazides		
Bendroflumethiazide	1.25–5.0	18
Benzthiazide	50–200	12–18
Chlorothiazide	250–1,000	6–12
Hydrochlorothiazide	12.5–50	12–18
Hydroflumethiazide	12.5–50	12–18
Trichlormethiazide	1.0–4.0	18–24
Nonthiazide sulfonamides		
Chlorthalidone	12.5–50	24–72
Indapamide	1.25–2.5	24
Metolazone	0.5–1.0	24
Mykrox	2.5–10	24
Loop diuretics		
Bumetanide	0.5–5.0	4–6
Furosemide	20–480	4–6
Torsemide	5–40	12
Nonsulfonamide		
Ethacrynic acid	25–100	12
Potassium-sparing agents		
Amiloride	5–10	24
Triamterene	50–150	12
Aldosterone blockers		
Spirolactone	25–100	8–12
Eplerenone	50–100	12

toward normal, but, at the same time, peripheral resistance decreases (Zhu et al., 2005) (Fig. 7-2).

Determinants of Response

The degree of BP response to diuretics is predicated on their capacity to activate the counterregulatory

defenses to a lower BP and a shrunken fluid volume—in particular, a reactive rise in renin and aldosterone levels. Those who start with low, suppressed plasma renin activity (PRA) and aldosterone levels and who are capable of mounting only a weak rise in these levels after diuretics are initiated have been shown to be more “diuretic responsive” (Chapman et al., 2002).

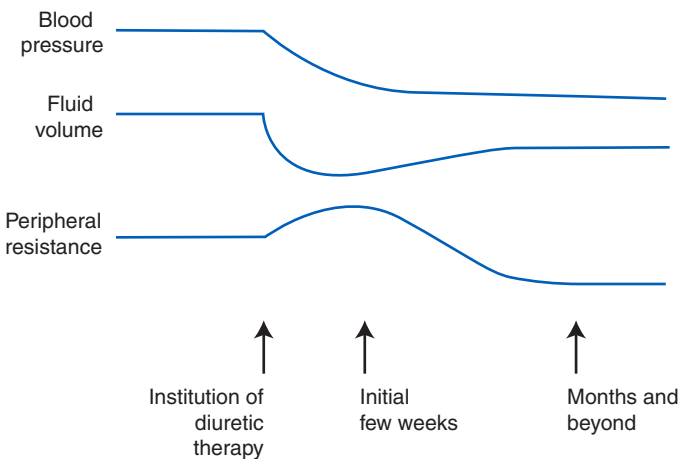


FIGURE 7-2 • Scheme of the hemodynamic changes responsible for the antihypertensive effects of diuretic therapy.

This includes older, black, and hypertensive people, all of whom frequently have lower renin levels (Kaplan, 1977). Those who respond less well, with a fall in mean BP of less than 10%, were found to have a greater degree of plasma volume depletion and greater stimulation of renin and aldosterone, contributing to a persistently high peripheral resistance (van Brummelen et al., 1980). Blockade of the reactive rise in renin–angiotensin–aldosterone, as with the addition of an ACEI or ARB will potentiate the antihypertensive action (McHenry et al., 2013).

Nonthiazide Sulfonamide Diuretics

Chlorthalidone

Although commonly considered a thiazide, chlorthalidone is of a different chemical structure and milligram for milligram is both stronger and longer-acting than is hydrochlorothiazide (HCT), effective even with reduced renal function (Cirillo et al., 2014). In a meta-analysis, Peterzan et al. (2012) found that the estimated dose predicted to reduce SBP by 10 mm Hg was 8.6 mg of chlorthalidone and 26.4 mg of HCT. As noted, although HCT has become by far the most widely used diuretic to treat hypertension in the U.S., chlorthalidone has been used in all trials sponsored by the NIH, with as much or more protection against heart attacks, heart failure, and strokes as seen with other agents (Roush et al., 2012). On the other hand, there are no data showing such benefits of HCT in the currently recommended lower doses of 12.5 to 25 mg/day (Kaplan, 2011).

Indapamide

Indapamide (Lozol) is a chlorobenzene sulfonamide but has a methylindoline moiety, which may provide additional protective actions beyond its diuretic effect (Chillon & Baumbach, 2004). It is as effective in reducing the BP as are thiazides or CCBs (Emeriau et al., 2001); maintains a 24-hour effect; and, in appropriately low doses of 1.25 mg/day, rarely raises serum lipids but in larger doses, hyponatremia and hypokalemia may occur. With 1.5-mg doses, regression of left ventricular hypertrophy (LVH) was better (Gosse et al., 2000) and reduction in microalbuminuria equal to (Marre et al., 2004) that seen with enalapril, 20 mg/day. On the background of an ACEI, indapamide provided a 43% reduction in recurrences of stroke (PROGRESS Collaborative Group, 2001), and it was the diuretic used in the HYVET trial (Beckett et al., 2008).

Metolazone

Metolazone, a long-acting and more potent quinazoline thiazide derivative, maintains its effect in the presence of renal insufficiency (Paton & Kane, 1977). Small doses, 0.5 to 1.0 mg/day, of a new formulation (Mykrox) may be equal to ordinary long-acting thiazide diuretics (Miller et al., 1988); the agent is particularly useful in patients with renal insufficiency and resistant hypertension, but variable absorption may interfere with its efficacy.

Antihypertensive Efficacy

When used alone, diuretics provide efficacy similar to that of other classes of drugs (Law et al., 2009). Blacks and the elderly respond better to diuretics than do nonblacks and younger patients (Brown et al., 2003) presumably because they have lesser renin responsiveness.

Diuretics potentiate the effect of all other antihypertensive agents, including CCBs (Sica, 2004a). This potentiation depends on the contraction of fluid volume by the diuretic (Finnerty et al., 1970a,b) and thereby the prevention of fluid accumulation that frequently follows the use of nondiuretic antihypertensive drugs. Because of the altered pressure–natriuresis curve of primary hypertension (Saito & Kimura, 1996), whenever the BP is lowered, fluid retention is expected (Fig. 7-3). The need for a diuretic may be lessened with ACEIs, ARBs, and DRIs, which inhibit the renin–aldosterone mechanism, and with CCBs, which have some intrinsic natriuretic activity but potentiation persists with all classes.

Duration of Action

The durations of action listed in Table 7-3 relate to the diuretic effect; the full antihypertensive effect may not last beyond the diuretic effect. Even though HCT has only a 12- to 18-hour duration of diuretic action, not until the comparison between HCT and chlorthalidone using ambulatory BP monitoring (ABPM) was there a clear evidence for a lessening of HCT antihypertensive effect during the night (Ernst et al., 2006).

Dosage

Monotherapy

The recommended daily dose of thiazide diuretics has been progressively falling from as high as 200 mg of HCT or equivalent doses of other thiazides in the early 1960s (Cranston et al., 1963) to as little as

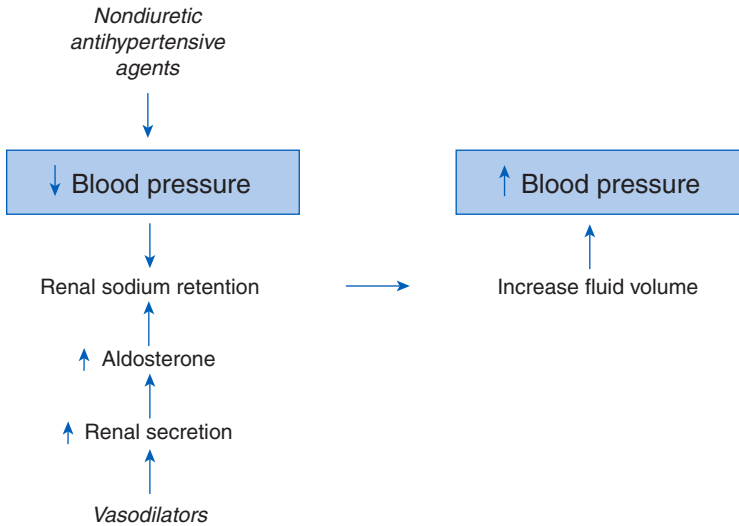


FIGURE 7-3 • Manner by which non-diuretic antihypertensive agents may lose their effectiveness by reactive renal sodium retention.

12.5 mg today. In hypertensives with good renal function, most of the antihypertensive effect will be obtained from such small doses, with less hypokalemia and other side effects. However, as shown by Carlsen et al. (1990), the full antihypertensive effect of low doses of diuretic may not become apparent in 4 weeks, so patience is advised when low doses are prescribed.

Combination Therapy

Thiazides may also be coupled with loop diuretics in those with renal impairment, because they counter the distal nephron hypertrophy that occurs with loop diuretics alone (Brater, 2000). The combination of a thiazide with a loop diuretic usually increases sodium excretion but may induce hypokalemia, hyponatremia, and hypotension (Dussol et al., 2012).

Resistance to Diuretics

Resistance to the natriuretic and antihypertensive action of diuretics may occur for numerous reasons including these:

- ▶ Excessive dietary sodium intake.
- ▶ For those with renal impairment (i.e., serum creatinine >1.5 mg/dL or creatinine clearance <30 mL/minute), thiazides likely will not work. Because these drugs must be secreted into the renal tubules to work and because endogenous organic acids that build up in renal insufficiency compete with diuretics for transport into the proximal tubule, the renal response progressively falls with increasing renal damage.

- ▶ Food affects the absorption and bioavailability of different diuretics to variable degrees (Neuvonen & Kivistö, 1989), so the drugs should be taken in a uniform pattern in terms of the time of day and food ingestion.
- ▶ NSAIDs may blunt the effect of most diuretics (Cheng & Harris, 2004).

Protection Against Cardiovascular Events

Diuretics protect against cardiovascular morbidity and mortality as well as any other class of drug (Cushman et al., 2012b). In a network meta-analysis of RCTs published from 1997 through 2009, diuretics were found to be the most effective class of antihypertensive drugs to prevent heart failure (Sciarretta et al., 2011).

Side Effects

As shown in Figure 7-4, the likely pathogenesis for most of the more common complications related to diuretic use arises from the intrinsic activity of the drugs, and most complications are, therefore, related to the dose and duration of diuretic use. Logically, side effects occur with about the same frequency and severity with equipotent doses of all diuretics, and their occurrence will diminish with lower doses.

Hypokalemia

The degree of hypokalemia is dose dependent. In a meta-analysis that included 26 trials with HCT, 3 of chlorthalidone, and 1 with bendroflumethiazide, Peterzan et al. (2012) showed that the extent of the fall in serum potassium increased with the dose of

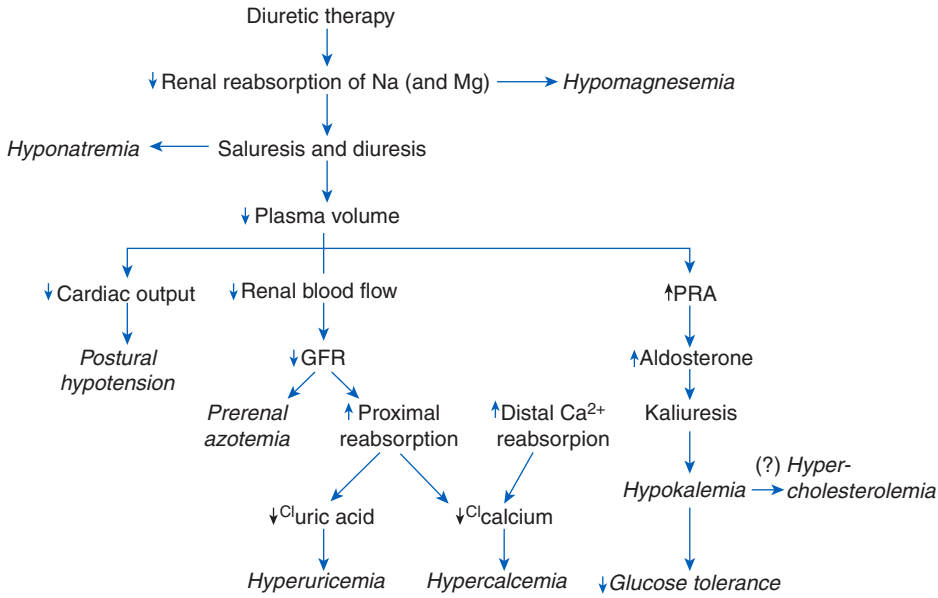


FIGURE 7-4 • Mechanisms by which chronic diuretic therapy may lead to various complications. The mechanism for hypercholesterolemia remains in question, although it is shown as arising via hypokalemia. Ca, calcium; Cl, chlorine; GFR, glomerular filtration rate; Na, sodium; Mg, magnesium; PRA, plasma renin activity.

each drug (Fig. 7-5). The estimated doses to lower serum potassium by 0.4 mmol/L were 11.9 mg for chlorthalidone and 40.5 mg for HCT.

The major potential risks of potassium depletion are to increase the incidence of stroke (Levine & Coull, 2002) and ventricular arrhythmias causing sudden death (Grobbee & Hoes, 1995). Patients on digitalis may develop toxicity, perhaps because both digitalis

and hypokalemia inhibit the Na⁺/K⁺-adenosine triphosphatase (Na⁺/K⁺-ATPase) pump, the activity of which is essential to normal intracellular electrolyte balance and membrane potential (Nørgaard & Kjeldsen, 1991).

VENTRICULAR ARRHYTHMIAS AND SUDDEN DEATH

In two case–control studies, the risk of sudden death was nearly doubled in those on large doses of naked

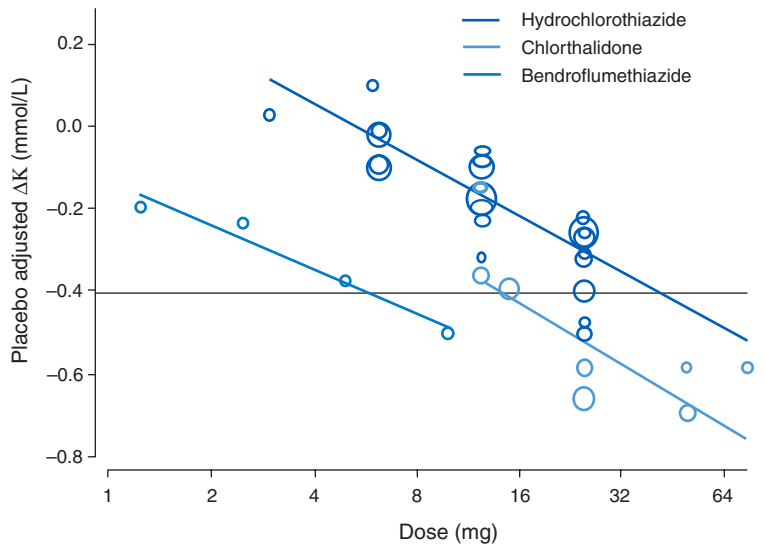


FIGURE 7-5 • Dose–response relations between doses of three diuretics and changes in serum potassium. (Adapted from Peterzan MA, Hardy R, Chaturvedi N, et al. Meta-analysis of dose–response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension* 2012;59:1104–1109.)

diuretics as compared to those on thiazide plus a potassium-sparing agent (Hoes et al., 1995; Siscovick et al., 1994). In the SHEP trial, among those randomly allocated to 12.5 to 25 mg chlorthalidone, the 7.2% who developed hypokalemia had less than half the reduction in major cardiovascular events than did those who remained normokalemic (Franse et al., 2000).

PREVENTION OF DIURETIC-INDUCED HYPOKALEMIA

By lowering dietary sodium, increasing dietary potassium, and using the least amount of diuretic needed, potassium depletion may be avoided. A potassium-sparing agent, β -blocker, ACEI, ARB, or DRI given with the diuretic will reduce the degree of potassium loss but may not prevent the development of hypokalemia. Aldosterone receptor blockers may be more efficient (Coca et al., 2005).

REPLETION OF DIURETIC-INDUCED HYPOKALEMIA

If prevention does not work, the potassium deficiency can be replaced with supplemental K^+ , usually given as the chloride. However, potassium citrate (Sakhae et al., 1991) or bicarbonate (Frassetto et al., 2000) will be more effective in reducing urinary calcium loss in patients with renal stones or osteoporosis. The KCl may be given as a potassium-containing salt substitute; a number of these substitutes are available, and they are less expensive than are potassium supplements.

Caution is advised in giving potassium supplements to patients receiving ACEIs, ARBs, or DRIs since these will suppress aldosterone levels and thereby prevent the excretion of extra potassium. The problem may be compounded in diabetics who may be unable to move potassium rapidly into cells and in those with renal insufficiency who may have a limited ability to excrete potassium.

Hypomagnesemia

Some of the problems attributed to hypokalemia may be caused by hypomagnesemia but conventional doses of diuretics rarely induce magnesium deficiency (Wilcox, 1999).

Clinical features include weakness, nausea, neuromuscular irritability, and the appearance of ventricular arrhythmias, which are resistant to treatment unless both hypomagnesemia and hypokalemia are corrected (Whang et al., 1985). If repletion is needed, oral magnesium oxide, 200 to 400 mg/day (10 to 20 mmol), or potassium–magnesium citrate may be tolerated without gastrointestinal distress (Pak, 2000).

Hyponatremia

By impairing the dilution of the tubular fluid, thiazides reduce the capacity for rapid and effective elimination of free water, and slight, asymptomatic falls in serum sodium concentration are common (Leung et al., 2011). Rarely, severe, symptomatic hyponatremia develops, usually soon after high doses of diuretics are started in thin elderly women who appear to have an expanded fluid volume from increased water intake in the face of a decreased ability to excrete free water (Mann, 2008).

Hyperuricemia

Serum uric acid levels are high in as many as 30% of untreated hypertensives and diuretics increase renal urate reabsorption, raising uric acid levels further, occasionally provoking gout (Choi et al., 2012). Moreover, Richard Johnson and others have provided evidence for a casual role of hyperuricemia in the pathogenesis of hypertension (Feig et al., 2008a) and renal damage (Obermayr et al., 2008).

Beyond diuretics, Choi et al. (2012) found an association between gout and the use of β -blockers, ACEIs, and ARBs except losartan, whereas the use of losartan or CCBs was associated with a lower risk. If therapy is given for hyperuricemia, the logical choice is probenecid to increase renal excretion of uric acid and possibly to lower the BP (Soletsky & Feig, 2012).

Calcium Metabolism Alterations

Renal calcium reabsorption also is increased with chronic thiazide therapy, and urinary calcium excretion is decreased by 40% to 50% (Friedman & Bushinsky, 1999). A slight rise in serum calcium (i.e., 0.1 to 0.2 mg/dL) is usual, and hypercalcemia is often provoked in patients with preexisting hyperparathyroidism or vitamin D–treated hypoparathyroidism. By reducing renal calcium excretion, thiazides are used to treat patients with renal stones caused by hypercalcemia from increased calcium absorption (Quereda et al., 1996). The retention of calcium in bone offers protection from osteoporosis and fractures (Schoofs et al., 2003). However, loop diuretics, which increase urinary calcium excretion, are associated with an increased rate of hip bone loss in older men (Lim et al., 2008).

Glucose Intolerance and Insulin Resistance

Insulin resistance, impairment of glucose tolerance, precipitation of overt diabetes, and worsening of diabetic control have all been observed in patients taking

larger doses of thiazides (Carter et al., 2008b). In a review of data from 83 trials with thiazides, the rise in blood glucose was closely correlated with the fall in serum potassium (Zillich et al., 2006).

As with all the adverse effects of diuretics, the impairment of glucose utilization that connotes insulin resistance is seen more with high doses (McHenry et al., 2013). The incidence of new-onset diabetes among the ALLHAT trial participants who took chlorthalidone (most at a dose of 25 mg) was 11.5% compared to 8.3% in those who started with amlodipine and 7.6% in those who started with lisinopril (Black et al., 2008). It is likely that part of the increases in diabetes in diuretic-treated patients comes from the concomitant use of β -blockers, the “conventional” therapy of older trials.

Effect on Lipids

With low doses, thiazides have little effect on the blood lipid profile (Weir & Moser, 2000). However, higher doses may induce significant effects on fat distribution, which in turn may be associated with insulin resistance. Eriksson et al. (2008) examined the effects of a placebo, the ARB candesartan (16 to 32 mg/day) and HCT (50 mg/day), each given to 26 hypertensives with abdominal obesity for 12 weeks in a randomized crossover design. After the 12 weeks on the diuretic, the subjects had increases in abdominal and hepatic fat, abnormal liver function test, insulin resistance, and increased C-reactive protein levels. None of these effects were seen after placebo or ARB.

Erectile Dysfunction

Impotence may be more common with diuretics than with other drugs. In the large, randomized Medical Research Council (MRC) trial, impotence was reported by 22.6% of the men on bendrofluzide, as compared to a rate of 10.1% among those on placebo and 13.2% among those on propranolol (Medical Research Council Working Party, 1981). In the Treatment of Mild Hypertension Study (TOMHS), the men randomized to chlorthalidone had a 17.1% incidence of erection problems through 24 months, as compared to an 8.1% incidence in those on placebo (Grimm et al., 1997).

Other Side Effects

Fever and chills, blood dyscrasias, cholecystitis, pancreatitis, necrotizing vasculitis, acute interstitial nephritis, and noncardiogenic pulmonary edema have been seen rarely. Allergic skin rashes occur in 0.28%

of patients, and approximately the same percentage develops photosensitivity, which may be involved in the reported increase in lip cancer (Friedman et al., 2012). An increased relative risk of renal cell cancer has been reported with diuretic therapy (Corrao et al., 2007), but the association is much stronger with hypertension per se (Colt et al., 2011).

Conclusion

Strong controlled trial data document the benefits of diuretics in particular chlorthalidone, for the treatment of hypertension. Nonetheless, diuretics can cause multiple metabolic perturbations that could reduce their ability to protect against progressive atherosclerosis as they lower BP, including rises in uric acid, increasing insulin resistance, and deranged fat distribution. These adverse effects are dose dependent and should be much less problematic with appropriately lower doses, doses that will provide most, if not all, of their antihypertensive effects.

Loop Diuretics

Loop diuretics primarily block chloride reabsorption by inhibition of the $\text{Na}^+/\text{K}^+/\text{Cl}^-$ cotransport system of the luminal membrane of the thick ascending limb of Henle loop, the site where 35% to 45% of filtered sodium is reabsorbed (see Fig. 7-1). Therefore, the loop diuretics are more potent and have a more rapid onset of action than do the thiazides. However, they are no more effective in lowering BP or less likely to cause side effects if given in equipotent amounts. Their major use is in patients with renal insufficiency, in whom large enough doses can be given to achieve an effective luminal concentration (see Chapter 9).

Furosemide

The maintenance of a slightly shrunken body fluid volume, which is critical for an antihypertensive action from diuretic therapy, is not met by the short duration of furosemide action (3 to 6 hours for an oral dose); during the remaining hours, sodium is retained, so that net fluid balance over 24 hours is left unaltered (Wilcox et al., 1983). If furosemide is used twice daily, the first dose should be given early in the morning and the second in the late afternoon, both to provide diuretic action at the time of sodium intake and to avoid nocturia.

Bumetanide

Bumetanide, although 40 times more potent and 2 times more bioavailable than furosemide on a weight basis, is identical in its actions when given in an equivalent dose (Brater et al., 1983).

Torsemide

Torsemide differs from the other diuretics in that it is mainly eliminated by hepatic metabolism, with only 20% being excreted unchanged in the urine (Brater, 1993). Therefore, it has a more prolonged duration of action, as long as 12 hours.

In small doses of 2.5 to 5 mg, torsemide may lower BP in uncomplicated hypertension, whereas larger doses are needed for chronic edematous states or with renal insufficiency (Dunn et al., 1995). In patients with chronic renal disease, 40 mg of torsemide once a day provided equal natriuresis and hypertensive effect as 40 mg of furosemide twice a day (Vasavada et al., 2003).

Ethacrynic Acid

Although structurally different from furosemide, ethacrynic acid also works primarily in the ascending limb of Henle loop and has an equal potency. It is used much less than is furosemide, mainly because of its greater propensity to cause permanent hearing loss with high doses. Since it does not contain a sulfonamide moiety, its main use has been in patients with sulfonamide sensitivity.

Potassium-Sparing Agents

Amiloride and triamterene act directly to inhibit sodium reabsorption by the epithelial sodium channels in the renal distal tubule, decreasing the net negative potential in the tubular lumen and thereby reducing potassium and hydrogen secretion and excretion, independent of aldosterone. Since neither are potent natriuretics, they are almost exclusively used in combination with thiazides, which, by delivering more sodium to the K^+ spargers' site of action, increase their K^+ -sparing effect while countering the K^+ -wasting effect of the diuretic. Presumably, by preventing hypokalemia, the use of K^+ -sparing diuretics reduced the risk of death compared to the use of non- K^+ -sparing diuretics (Hebert et al., 2008).

Amiloride

Amiloride is usually used with a thiazide diuretic in tablets containing 50 mg of HCT and 5 mg of amiloride. The drug has been used as medical therapy for hyperaldosteronism in patients intolerant to aldosterone blockers and in patients with mutations of the genes regulating sodium channels that lead to the full-blown Liddle syndrome (see Chapter 11) or to a less severe prototype from the T594M polymorphism (Baker et al., 2002).

Nausea, flatulence, and skin rash have been the most frequent side effects and hyperkalemia the most serious. Moreover, a number of cases of hyponatremia in elderly patients have been reported after its use in combination with HCT (Mathew et al., 1990).

Triamterene

As with amiloride, triamterene (37.5 mg) is usually combined with HCT (25 mg). Triamterene may be excreted into the urine and may find its way into renal stones (Sörgel et al., 1985). Because triamterene is a folic acid antagonist, it should not be used during pregnancy (Hernández-Díaz et al., 2000).

Aldosterone Receptor Blockers

The first of these, spironolactone, has long been available but little used in the U.S. until publication of the Randomized Aldactone Evaluation Study (RALES) which showed a 30% decrease in mortality in patients with severe heart failure given 25 mg of spironolactone in addition to their other medications (Pitt et al., 1999). Since then, a large body of experimental and clinical evidence has revealed a multiorgan profibrotic effect of aldosterone so that blocking the hormone has assumed an important place in clinical medicine. At the same time, the marketing of a more specific aldosterone blocker, eplerenone, has stimulated the use of these agents.

Mode of Action

The primary mineralocorticoid aldosterone causes hypertension when present in large excess, the syndrome of primary aldosteronism covered in Chapter 11. However, even "normal" amounts of aldosterone in the presence of the relatively high sodium intake of modern societies are now known to activate mineralocorticoid receptors in multiple organs including the brain, heart, kidney, and blood vessels (Schiffrin, 2006).

In turn, vasculitis and fibrosis are induced, independent of the traditional renal sodium–retaining effect of the hormone. Moreover, the incidence of hypertension over 4 years was 60% higher in those initially nonhypertensive subjects who were in the highest quartile of serum aldosterone (Vasan et al., 2004).

Eplerenone in a twice higher dose has equivalence to spironolactone in blocking the mineralocorticoid receptor but a much lower blockade of androgen and progesterone receptors, explaining its fewer side effects (Funder, 2002). In 2003, the addition of eplerenone was shown to reduce morbidity and mortality among patients with acute myocardial infarction (MI) complicated by left ventricular (LV) dysfunction in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) (Pitt et al., 2003). Subsequently, the drug was shown to reduce mortality in these subjects whether they had been hypertensive or not (Pitt et al., 2008).

In both the RALES and EPHESUS trials, the aldosterone blocker provided additional benefit to patients receiving full doses of blockers of the renin–angiotensin system (RAS), ACEIs, or ARBs. It is now known that aldosterone synthesis is not completely suppressed with these agents, breaking through to maintain the pretreatment aldosterone levels even if angiotensin II (AII) levels remain suppressed (Bomback et al., 2012).

Antihypertensive Efficacy

Spironolactone has been used alone to treat hypertension for many years, particularly in France (Jeunemaitre et al., 1987), but its major use in the U.S. has been as a K⁺ sparer in combination with a thiazide diuretic, providing an effect equivalent to 32 mmol of KCl (Toner et al., 1991) or to treat aldosteronism caused by bilateral adrenal hyperplasia. More recently, it has been found to effectively control patients with refractory hypertension (Chapman et al., 2007; Oxlund et al., 2013). As expected, the drug lowers BP more in patients with low plasma renin and higher aldosterone levels (Weinberger, 2004). Aldosterone blockers improve diastolic function (Grandi et al., 2002), are antiarrhythmic (Swedberg et al., 2012), reduce proteinuria in patients with diabetic nephropathy (Sato et al., 2003), and prevent diuretic-induced sympathetic nervous system activation and insulin resistance (Raheja et al., 2012). For these reasons, the use of aldosterone blockers will almost certainly expand to initial therapy, usually in combination with a diuretic, for more and more hypertensives.

Side Effects

The less specific spironolactone in doses of 25 to 50 mg/day induced gynecomastia in 6% of patients and biochemical abnormalities (mainly hyperkalemia) in 2% of the patients with resistant hypertension in the ASCOT trial (Chapman et al., 2007). The more specific eplerenone induced gynecomastia in fewer than 1% of men in the EPHESUS trial (Pitt et al., 2005). Hyperkalemia may occur with either agent but is more common in the presence of renal insufficiency; concomitant β -blocker, ACEI, ARB, or DRI therapy; or the use of potassium supplements (Muzzarelli et al., 2012). With appropriate monitoring, eplerenone is both safe and effective in patients with impaired renal function (Eschalier et al., 2013). The antibiotic trimethoprim is similar to the potassium-sparing agent amiloride and reduces potassium excretion by 40%. Therefore, hyperkalemia may occur if the antibiotic is given to patients on an aldosterone blocker (Antoniu et al., 2011).

ADRENERGIC-INHIBITING DRUGS

Of the adrenergic-inhibiting agents currently used to treat hypertension, some act centrally on α_2 -receptors to inhibit sympathetic nerve activity, some inhibit postganglionic sympathetic neurons, and some block the α - or β -adrenoreceptors on target organs (Fig. 7-6). Agents that act by blocking ganglia are no longer used.

Central α -Agonists

Central α -agents stimulate α_{2a} -adrenergic receptors that are involved in depressor sympathoinhibitory mechanisms (Vongpatanasin et al., 2011). Some are selective, whereas clonidine also acts on central imidazoline receptors. These drugs have well-defined effects, including

- A marked decline in sympathetic activity reflected in lower levels of norepinephrine (NE)
- A reduction of the ability of the baroreceptor reflex to compensate for a decrease in BP, accounting for the relative bradycardia and enhanced hypotensive action noted on standing
- A modest decrease in both peripheral resistance and cardiac output
- A fall in plasma renin levels
- Fluid retention

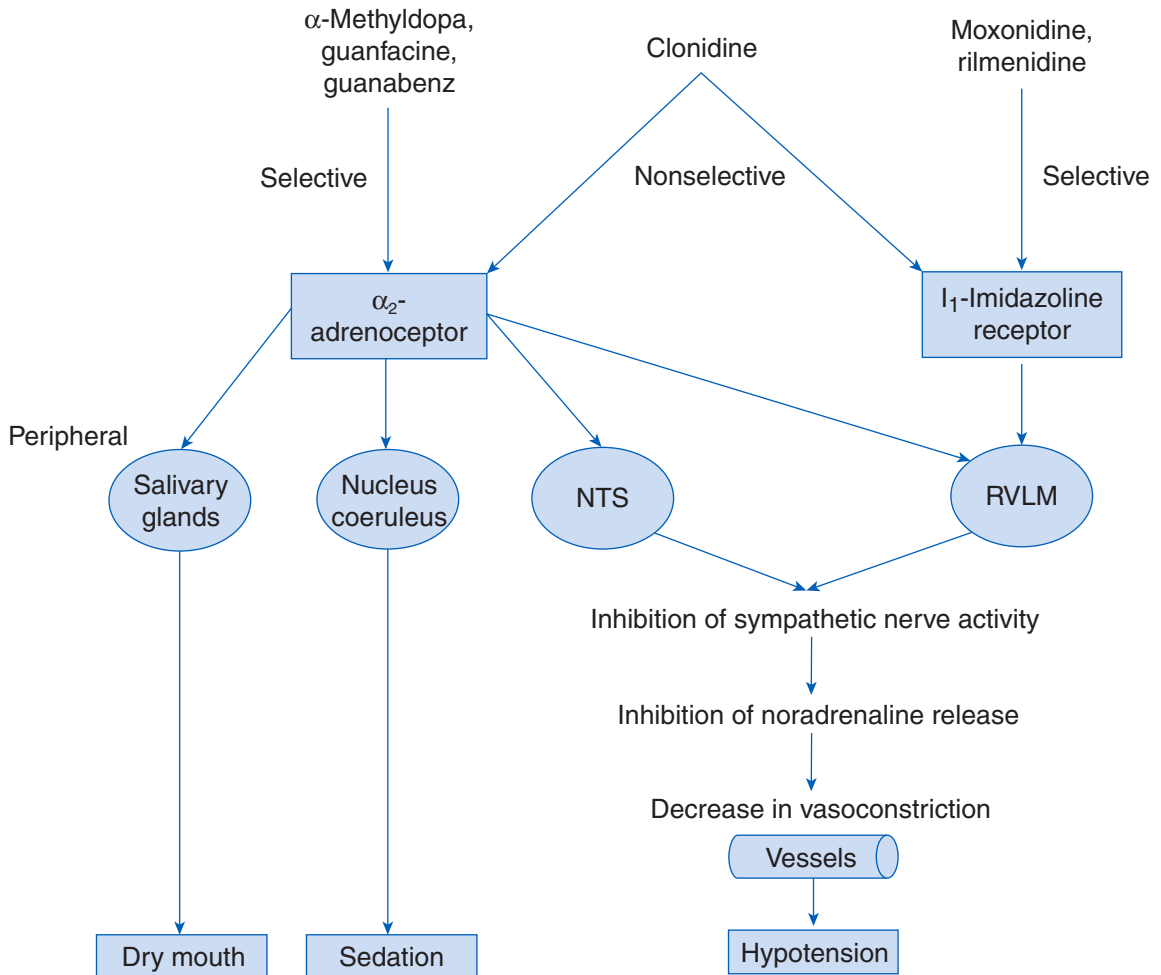


FIGURE 7-6 • Central antihypertensive mechanisms of various types of centrally acting antihypertensive drugs. NTS, nucleus tractus solitarius; RVLM, rostral ventrolateral medulla. (Modified from van Zwieten PA. The renaissance of centrally acting antihypertensive drugs. *J Hyperten* 1999;17(Suppl 3):S15–S21.)

- Maintenance of renal blood flow despite a fall in BP
- Common side effects reflecting their central site of action: Sedation, decreased alertness, and a dry mouth

Methyldopa

From the early 1960s to the late 1970s, when β -blockers became available, methyldopa was the second most popular drug (after diuretics) used to treat hypertension. Now its use is almost exclusively for the treatment of hypertension during pregnancy.

Methyldopa is the α -methylated derivative of dopa, the natural precursor of dopamine and NE. Its mode of action involves the formation of methylnorepinephrine, which acts as a potent agonist at

α -adrenergic receptors within the central nervous system (CNS) (van Zwieten, 1999).

Antihypertensive Efficacy

BP is lowered maximally approximately 4 hours after an oral dose of methyldopa, and some effect persists for up to 24 hours. For most patients, therapy should be started with 250 mg two times per day, and the daily dosage can be increased to a maximum of 3.0 g on a twice-per-day schedule. In patients with renal insufficiency, the dosage should be halved.

Side Effects

A variety of autoimmune side effects, including fever and liver dysfunction, can occur with methyldopa.

Liver dysfunction usually disappears when the drug is stopped, but at least 83 cases of serious hepatotoxicity were reported by 1975 (Rodman et al., 1976), with diffuse parenchymal injury similar to autoimmune chronic active hepatitis (Lee, 1995).

An impairment of psychometric performance (Johnson et al., 1990) and a selective loss of upper airway motor activity (Lahive et al., 1988) may not be obvious until the drug is stopped. Overall, in large surveys, the number and range of the adverse reactions to methyldopa are impressive (Webster & Koch, 1996). In view of its unique and potentially serious side effects, other central α -agonists should be used in place of methyldopa.

Guanabenz

Guanabenz, an aminoguanidine, works like clonidine and methyldopa and causes similar side effects. Therapy should begin with 4 mg twice per day, with increments up to a total of 64 mg/day.

Guanfacine

Another selective central α_2 -agonist, guanfacine appears to enter the brain more slowly and to maintain its antihypertensive effect longer than guanabenz, translating into a once-per-day dosage and perhaps fewer CNS side effects (Lewin et al., 1990). Withdrawal symptoms are less common than with clonidine. These characteristics make it the most attractive of this group of centrally acting α_2 -agonists.

Clonidine

Clonidine acts centrally on both α_2 -receptors and imidazoline receptors (see Fig. 7-6). When taken orally, the BP begins to fall within 30 minutes, with the greatest effect occurring between 2 and 4 hours. The duration of effect is from 8 to 12 hours, so it should be given three times a day. The starting dose may be as little as 0.075 mg (Clobass Study Group, 1990), with a maximum of 1.2 mg/day.

A transdermal preparation that delivers clonidine continuously over a 7-day interval is effective and causes milder side effects than does oral therapy (Giugliano et al., 1998), but it may cause considerable skin irritation and side effects similar to those seen with the oral drug, including rebound hypertension when discontinued. It is available in doses of 0.1, 0.2, and 0.3 mg/day.

Side Effects

Clonidine shares the two most common side effects, sedation and dry mouth with methyldopa but not the autoimmune hepatic and hematologic derangements. Depression of sinus and atrioventricular (AV) nodal function may be common, and a few cases of severe bradycardia have been reported (Byrd et al., 1988).

Rebound and Discontinuation Syndromes

If any antihypertensive therapy is inadvertently stopped abruptly, various discontinuation syndromes may occur: (a) A rapid asymptomatic return of the BP to pretreatment levels, which occurs in the majority of patients; (b) a rebound of the BP plus symptoms and signs of sympathetic overactivity; and (c) an overshoot of the BP above pretreatment levels.

A discontinuation syndrome has been reported, more frequently with clonidine (Neusy & Lowenstein, 1989), likely reflecting a rapid return of catecholamine secretion that had been suppressed during therapy. Those who had been on a combination of a central adrenergic inhibitor, e.g., clonidine, and a β -blocker may be particularly susceptible if the central inhibitor is withdrawn while the β -blocker is continued (Lilja et al., 1982). This leads to a sudden surge in plasma catecholamines in a situation in which peripheral α -receptors are left unopposed to induce vasoconstriction because the β -receptors are blocked and cannot mediate vasodilation.

If a discontinuation syndrome appears, clonidine should be restarted, and the symptoms will likely recede rapidly.

Other Uses

Clonidine has been reported to be useful in numerous conditions that may accompany hypertension, including

- Restless legs syndrome (Wagner et al., 1996)
- Opiate withdrawal (Bond, 1986)
- Menopausal hot flashes (Pandya et al., 2000)
- Diarrhea due to diabetic neuropathy (Fedorak et al., 1985)
- Sympathetic nervous hyperactivity in patients with alcoholic cirrhosis (Esler et al., 1992)
- However, the use of clonidine perioperatively has been found to be dangerous (Devereaux et al., 2014).

Imidazoline Receptor Agonists

Not available in the U.S. but used elsewhere, monoxidine and rilmenidine are two centrally acting drugs

that have as their primary site of action the imidazoline receptor located in the rostral ventrolateral medulla oblongata, wherein α_2 -receptors are less abundant (see Fig. 7-6) (van Zwieten, 1999). They effectively reduce sympathetic activity (Esler et al., 2004) with less of the sedation and dry mouth seen with clonidine and selective α_2 -agonists.

Peripheral Adrenergic Inhibitors

Reserpine

First reported to be an effective antihypertensive in the 1940s (Bhatia, 1942), reserpine became a popular drug in the 1960s and 1970s but has been used less and less because, being an inexpensive generic, it has no constituency pushing for its use, and when used in high doses, it has caused depression, earning it a bad reputation.

Reserpine, one of the many alkaloids of the Indian snakeroot *Rauwolfia serpentina*, is absorbed readily from the gut, is taken up rapidly by lipid-containing tissue, and binds to sites involved with storage of biogenic amines. Its effects start slowly and persist, so only one dose per day is needed.

Reserpine blocks the transport of NE into its storage granules so that less of the neurotransmitter is available when the adrenergic nerves are stimulated, resulting in a decrease of peripheral vascular resistance. Catecholamines also are depleted in the brain, which may account for the sedative and depressant effects of the drug, and in the myocardium, which may decrease cardiac output and induce a slight bradycardia.

Antihypertensive Efficacy

By itself, reserpine has limited antihypertensive potency, resulting in an average decrease of only 3/5 mm Hg; when combined with a thiazide, the reduction averaged 14/11 mm Hg (Veterans Administration Cooperative Study, 1962). With a diuretic, as little as 0.05 mg once daily will provide most of the antihypertensive effect of 0.25 mg and is associated with less lethargy and impotence (Participating VA Medical Centers, 1982).

Side Effects

Side effects, which are relatively infrequent at appropriately low doses include nasal stuffiness, increased gastric acid secretion, and CNS depression, which may simply tranquilize an apprehensive patient and is rarely severe enough to lead to serious depression.

Guanethidine

Guanethidine at one time was frequently used because it requires only one dose per day and has a steep dose–response relationship, thus producing an effect in almost every patient. Because of severe postural hypotension, the use of guanethidine has virtually disappeared.

α -Adrenergic Receptor Blockers

Selective α_1 -blockers have had a relatively small share of the overall market for antihypertensive drugs in the U.S., and as a consequence of the increase in heart failure reported in the ALLHAT trial (ALLHAT Officers, 2000), their use in the U.S. is now almost exclusively for relief of prostatism. Nonetheless, doxazosin was successfully used in the ASCOT trial without an increase in heart failure (Chapman et al., 2008).

Mode of Action

The nonselective α -blockers phenoxybenzamine and phentolamine are used almost exclusively in the medical management of pheochromocytoma, because they are only minimally effective in primary hypertension (see Chapter 12).

Prazosin, doxazosin, and terazosin act as a competitive antagonist of postsynaptic α_2 -receptors (Fig. 7-7). These agents block the activation of postsynaptic α_1 -receptors by circulating or neurally released catecholamines, reducing peripheral resistance without major changes in cardiac output.

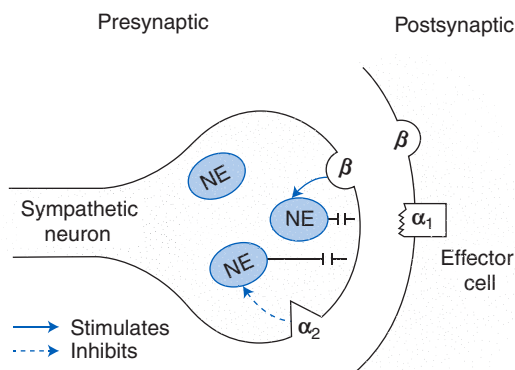


FIGURE 7-7 • Schematic view of the action of selective postsynaptic α_1 -blockers. By blocking the α_1 -adrenergic receptor on the vascular smooth muscle, catecholamine-induced vasoconstriction is inhibited. The α_2 -adrenergic receptor on the neuronal membrane is not blocked; therefore, inhibition of additional NE release by the short feedback mechanism is maintained.

The presynaptic α_2 -receptors remain open, capable of binding neurotransmitter and thereby inhibiting the release of additional NE through a direct negative-feedback mechanism. This inhibition of NE release explains the lesser frequency of tachycardia, increased cardiac output, and rise in renin levels that characterize the response to drugs that block both the presynaptic α_2 -receptor and the postsynaptic α_1 -receptor (e.g., phentolamine). Despite this selective blockade, neurally mediated responses to stress and exercise are unaffected, and the baroreceptor reflex remains active.

Accompanying these desirable attributes may be other actions that lessen the usefulness of α -adrenergic blockers: They relax the venous bed as well and, at least initially, may affect the visceral vascular bed more than the peripheral vascular bed. The subsequent pooling of blood in the viscera may explain the propensity to first-dose hypotension seen with the fast-acting prazosin (Saxena & Bolt, 1986). Volume retention is common, perhaps because renin and aldosterone levels are less suppressed than they are with other adrenergic-inhibiting drugs.

Prazosin is rapidly absorbed, reaches maximal blood levels at 2 hours, and has a plasma half-life of approximately 3 hours. Terazosin and doxazosin are less lipid soluble and have half, or less, of the affinity for α_1 -receptors as compared with prazosin. Therefore, they induce a slower and less profound initial fall in BP, particularly after standing, than does prazosin.

Antihypertensive Efficacy

The antihypertensive efficacy of doxazosin and terazosin is equivalent to that of diuretics, β -blockers, ACEIs, and CCBs (Achari et al., 2000). The addition of doxazosin was shown in the ASCOT trial to control hypertension effectively in patients resistant to two or more other agents (Chapman et al., 2008).

The initial dose should be 1 mg, slowly titrated upward to achieve the desired fall in BP, with a total daily dose of up to 20 mg. α -Blockers can be given at bedtime to provide a greater nocturnal fall in BP in and blunting of the morning surge that is involved in the increased incidence of cardiovascular events at that time (Matsui et al., 2008).

Genitourinary Function

Doxazosin, tamsulosin, and terazosin have been found to provide excellent relief from the obstructive symptoms of benign prostatic hypertrophy. The combination of doxazosin and the 5α -reductase inhibitor

finasteride slowed the clinical progression of benign prostatic hypertrophy (BPH) better than either drug alone (McConnell et al., 2003).

In the TOMHS trial of a representative from each of the five major classes of antihypertensives, only doxazosin reduced the incidence of impotence below that seen with placebo (Grimm et al., 1997).

The ALLHAT experience indicates the need to use a diuretic with an α -blocker for the treatment of hypertension, particularly in those with LVH or other risk factors for congestive heart failure (CHF) (Matsui et al., 2008). α -Blockers are useful as add-on therapy in patients with resistant hypertension and the preferred initial therapy for hypertensives with BPH.

Side Effects

Postural hypotension developing in 30 to 90 minutes may be seen particularly in volume-depleted patients given the shorter-acting prazosin. Urinary incontinence in women may be caused by α -blockers (Marshall & Beevers, 1996).

β -Adrenergic Receptor Blockers

For many years, β -adrenergic blocking agents were the second most popular antihypertensive drugs after diuretics. Although they are no more effective than other antihypertensive agents and may on occasion induce serious side effects, they offer the special advantage of relieving a number of concomitant diseases. In view of their proven ability to provide secondary cardioprotection after an acute MI, it was hoped that they would provide special primary protection against initial coronary events as well. This hope remains unfulfilled. To the contrary, β -blockers have failed to reduce heart attacks better than other classes (Bangalore et al., 2012) while providing less protection against strokes (Law et al., 2009). This is particularly true for the most popular, atenolol (Lindholm et al., 2005).

Nonetheless, the proven benefits of β -blockers in patients with either coronary disease (particularly after an acute MI) or CHF ensure that these drugs will continue to be widely used. Moreover, the use of the vasodilating β -blockers, covered after the traditional ones, will continue to replace the traditional ones.

Mode of Action

These agents are chemically similar to β -agonists and to each other (Fig. 7-8). The competitive inhibition of β -blockers on β -adrenergic receptors produces

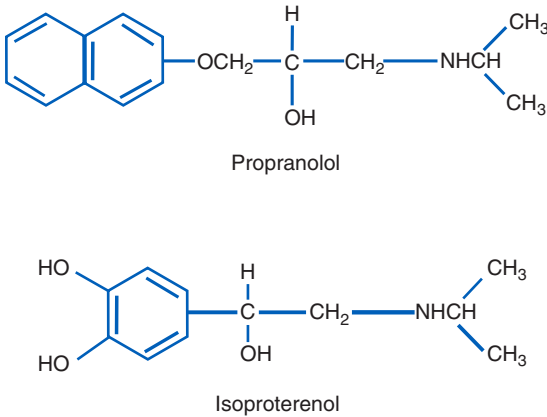


FIGURE 7-8 • Structure of propranolol and the β -agonist isoproterenol.

numerous effects on functions that regulate the BP, including a reduction in cardiac output, a diminution of renin release, perhaps a decrease in central sympathetic nervous outflow, and a presynaptic blockade that inhibits catecholamine release. The hemodynamic effects appear to change over time. Cardiac output usually falls acutely (except with high-ISA [intrinsic sympathomimetic activity] pindolol) and remains lower chronically; peripheral resistance, on the other hand, usually rises acutely but falls toward, if not to, normal with time (Man in't Veld et al., 1988).

Pharmacologic Differences

Since the introduction of propranolol for treatment of hypertension in 1964 (Prichard and Gillam, 1964), a number of similar drugs have been synthesized, approximately 20 being marketed throughout the world, 12 in the U.S. The various β -blockers can be conveniently classified by their relative selectivity for the β_1 -receptors (primarily in the heart) and the presence of ISA, also referred to as *partial agonist activity* and their *lipid solubility* (Table 7-4).

Lipid Solubility

Those that are more lipid soluble (lipophilic) tend to be taken up and metabolized extensively by the liver. As an example, with oral propranolol and metoprolol, up to 70% is removed on the first pass of portal blood through the liver. The bioavailability of these β -blockers is, therefore, less after oral than after intravenous administration.

Those such as nadolol, which is much less lipid soluble (lipophobic), escape hepatic metabolism and

are mainly excreted by the kidneys, unchanged. As a result, its plasma half-life and duration of action is much longer.

β_1 -Receptor Cardioselectivity

All currently available β -blockers antagonize cardiac β_1 -receptors competitively, but they vary in their degree of β_2 -receptor blockade in extracardiac tissues. The assumption that an agent with relative cardioselectivity is automatically less likely to cause side effects must be tempered by these considerations: Recognizing that no β -blocker is purely cardioselective, particularly in large doses, and when high endogenous catechol levels are needed, as during an attack of asthma, even minimal degrees of β_2 -blockade from a cardioselective drug may cause trouble (Haffner et al., 1992). However, more cardioselective β -blockers have been found to be more protective against strokes than less cardioselective ones (Webb et al., 2011).

On the other hand, in the presence of certain concomitant diseases, such as migraine and tremor, a nonselective β_2 -antagonist effect may be preferable.

Intrinsic Sympathomimetic Activity

Of the β -blockers now available in the U.S., pindolol and, to a lesser degree, acebutolol have ISA, implying that even in concentrations that fully occupy the β -receptors, the biologic effect is less than that seen with a full agonist.

Antihypertensive Efficacy

In the usual doses prescribed (Table 7-4), various β -blockers have equal antihypertensive efficacy as other classes of drugs if the BP is measured at the brachial artery (Parker et al., 2012). However, β -blocker-based therapy has been found not to reduce strokes as well as other classes with a 16% shortfall (Lindholm et al., 2005). Three reasons have been proposed. First the less than 24 hours effect of atenolol, the most widely used β -blocker, but given only once daily in all of the trials. The second and third reasons relate to the higher central (aortic) pressure with β -blockers than with vasodilating agents, i.e., all other classes of antihypertensive drugs, despite their equal effect as measured at the periphery. The second culprit is the bradycardia increasing cardiac work to maintain total cardiac output, thereby raising central BP (Bangalore et al., 2008). The third relates to the peripheral

TABLE 7-4

Pharmacologic Properties of Some β -Blockers

Drug	β_1 -Selectivity	Intrinsic Sympathomimetic Activity	α -Blockage	Lipid Solubility	Usual Daily Dosage (Frequency)
Acebutolol	+	+	–	+	200–1,200 mg (1)
Atenolol	++	–	–	–	25–100 mg (2)
Betaxolol	++	–	–	–	5–40 mg (1)
Bisoprolol	+++	–	–	+	2.5–20 mg (1)
Bucindolol	–	–	–	+	50–200 mg
Carteolol	–	+	–	–	2.5–10 mg (1)
Carvedilol ^a	–	–	+	+++	12.5–50 mg (2,1)
Celiprolol	++	+	–	–	200–400 mg (1)
Esmolol	++	–	–	–	25–300 μ g/kg/min iv
Lbetalol ^a	–	–	+	++	200–1200 mg (2)
Metoprolol	++	–	–	++	50–200 mg (2,1)
Nadolol	–	–	–	–	20–240 mg (1)
Nebivolol ^a	++	–	–	++	5–10 mg (1)
Penbutolol	–	+	–	+++	10–20 mg (1)
Pindolol	–	+++	–	++	10–60 (2)
Propranolol	–	–	–	+++	40–240 mg (2,1)
Timolol	–	–	–	++	10–40 mg (2)

Parenthesis (2,1) indicate short- and long-acting formulations.

+, ++, and +++ signs indicate the magnitude of the effect on various properties; – sign indicates no effect.

^aVasodilating.

vasoconstriction induced by the β -2 blocking action, causing the reflected pulse wave to strike the heart during systolic, further increasing cardiac work to overcome the higher central pressure. With vasodilators, the pulse wave returns even slower, bringing higher pressure during diastole, increasing coronary perfusion without increasing cardiac work. This difference was documented in the CAFE substudy of the ASCOT trial (Williams et al., 2006) and has been further validated (Mackenzie et al., 2009).

Other Uses

- Coronary disease (Andersson et al., 2014)
- Postmyocardial infarction (Bangalore et al., 2007)
- Heart failure from LV systolic dysfunction (Chatterjee et al., 2013)
- Hypertrophic cardiomyopathy (Spirito et al., 1997)
- Severe mitral regurgitation (Varadarajan et al., 2008)
- Therapy with direct vasodilators (Zacest et al., 1972)
- Anxiety and stress (Fogari et al., 1992)

β -Blockers have been widely used preoperatively but Bolsin et al. (2013) warn that they should be used only in those needing heart rate or BP control.

Side Effects

These have been reported to be more common in patients receiving β -blockers:

- Fatigue (Ko et al., 2002)
- Diminished exercise ability (Vanhees et al., 2000)
- Weight gain (Messerli et al., 2007)
- Worsening of insulin sensitivity (Ayers et al., 2012)
- New onset of diabetes (Gress et al., 2000)
- Rise in serum triglycerides, fall in HDL cholesterol (Smith et al., 2012)
- Possible increased risk of fetal malformations when used early in pregnancy (Yakoob et al., 2013)
- Worsening of psoriasis (Savola et al., 1987)

Two additional groups of patients may experience special problems: Insulin-taking diabetics who are prone to hypoglycemia and coronary patients. As for diabetics, the responses to hypoglycemia—both the symptoms

and the counterregulatory hormonal changes that raise the blood sugar level—are largely mediated by epinephrine, particularly in those who are insulin dependent because they usually are also deficient in glucagon. If these patients become hypoglycemic, β -blockade delays the return of the blood sugar. The only symptom of hypoglycemia may be sweating, which may be enhanced by the presence of a β -blocker (Molnar et al., 1974).

Patients with coronary disease who discontinue chronic β -blocker therapy may experience a discontinuation syndrome of increasing angina, infarction, or sudden death (Teichert et al., 2007). These ischemic episodes likely reflect the phenomenon of supersensitivity: An increased number of β -receptors appear in response to the functional blockade of receptors by the β -blocker; when the β -blocker is discontinued and no longer occupies the receptors, the increased number of receptors are suddenly exposed to endogenous catecholamines, resulting in a greater α -agonist response for a given level of catechols. Hypertensives, with a high frequency of underlying coronary atherosclerosis, may be particularly susceptible to this type of withdrawal syndrome; thus, when the drugs are discontinued, their dosage should be cut by half every 2 or 3 days, and the drugs stopped after the third reduction.

The following side effects have *not* been consistently or significantly found to be more common with β -blocker use:

- Depression (Ko et al., 2002)
- Sexual dysfunction (Ko et al., 2002)
- Cognitive loss (Pérez-Stable et al., 2000)
- Worsening of peripheral vascular disease (Espinola-Klein et al., 2011)
- Worsening of mild to moderate reactive airway disease or obstructive lung disease (Kazani & Israel, 2011)

Moreover, on the positive side, β -blockers may reduce urine calcium excretion (Lind et al., 1994) and thereby decrease the risk of fractures (Schlienger et al., 2004).

Vasodilating β -Blockers

In this category are one old drug (labetalol) whose vasodilatory properties come from its high level of α -blockade, one newer drug (carvedilol) with some α -blocking activity, but primarily a direct vasodilatory action, and one (nebivolol) that is a highly selective β_1 -blocker that works by generating NO.

Vasodilating β -blockers may be particularly effective in the treatment of elderly patients with isolated systolic hypertension. In addition to reducing aortic stiffness, as do other β -blockers, they also reduce the amplification of central systolic pressure by reducing the rapidity of wave reflection from the periphery (Mahmud and Feely, 2008), thereby reducing cardiac work and LV wall thickness (Kampus et al., 2011).

Labetalol

Labetalol is a nonselective β_1 - and β_2 -receptor blocker combined with α -blocking action in a 4:1 ratio. It is an effective antihypertensive drug when given twice daily, maintaining good 24-hour control and blunting the early morning surges in pressure (Ruilope, 1994). The usual starting doses are 100 mg b.i.d. The maximal daily dose is 1,200 mg.

Labetalol has been used both orally and intravenously to treat hypertensive emergencies, including postoperative hypertension (Lebel et al., 1985) and acute aortic dissection (Grubb et al., 1987). It has been successfully used to treat hypertension during pregnancy (Pickles et al., 1992).

Side Effects

Symptomatic orthostatic hypotension is the most common side effect, seen most often during initial therapy with larger doses. Other side effects include intense scalp itching, ejaculatory failure (Goa et al., 1989), and bronchospasm (George et al., 1985).

Perhaps the most serious side effect of labetalol is hepatotoxicity: At least three deaths have been reported (Clark et al., 1990). As a result, a warning has been added to its label in the U.S., stating, "Hepatic injury may be slowly progressive despite minimal symptomatology. Appropriate laboratory testing should be done at the first symptom or sign of liver dysfunction."

In keeping with its α -blocking effect, labetalol has less adverse effect on lipids as do β -blockers (Lardinois & Neuman, 1988).

Carvedilol

As a nonselective β -blocker with only one-tenth as much α -blocking activity, carvedilol has been used mainly for treatment of heart failure. It is also approved for the treatment of hypertension.

Beyond its slight α -blocking effect, carvedilol vasodilates by increasing generation of endogenous NO from endothelial cells (Kalinowski et al., 2003). As with labetalol, BP falls without a fall in cardiac output but rather a decrease in peripheral resistance.

In doses starting at 6.25 mg twice a day and proceeding up to 25 mg b.i.d., carvedilol is equal to 50 up to 200 mg of metoprolol b.i.d. (Bakris et al., 2004). A once-a-day formulation is now available.

Carvedilol has been found to provide additional survival benefit in patients with varying grades of CHF than do other β -blockers (DiNicolantonio et al., 2013) even in those with low systolic pressure (Rouleau et al., 2004) while better preserving renal function (Di Lenarda et al., 2005).

Unlike traditional β -blockers, carvedilol does not worsen insulin sensitivity or have as much of an adverse effect on lipids (Bakris et al., 2004).

Nebivolol

This drug is the most selective β_1 -blocker of this family of drugs and exerts its effect by generating and releasing NO while having a complimentary antioxidant effect (Ignarro, 2004; Price et al., 2013) and no adverse metabolic effects (Ayers et al., 2012).

DIRECT VASODILATORS

In this category, we have added nitrates to those agents that vasodilate by entering vascular smooth muscle cells (Ghosh et al., 2013). This is in contrast to those that vasodilate in other ways—by inhibiting hormonal vasoconstrictor mechanisms (e.g., ACEIs), by preventing calcium entry into the cells that initiate constriction (e.g., CCBs), or by blocking α -receptor—mediated vasoconstriction (e.g., α_1 -blockers). The various vasodilators differ considerably in their power, mode of action, and relative activities on arteries and veins. The intravenous direct vasodilators are covered in Chapter 8.

Hydralazine

Hydralazine was introduced in the early 1950s (Freis et al., 1953) but was little used because of its activation of the sympathetic nervous system. Its use increased in the 1970s when the rationale for triple therapy—a diuretic, an adrenergic inhibitor, and a

direct vasodilator—was demonstrated (Zacest et al., 1972). However, its use receded again with the advent of the newer vasodilating drugs.

Hydralazine acts directly to relax the smooth muscle in the walls of peripheral arterioles, the resistance vessels more so than the capacitance vessels, thereby decreasing peripheral resistance and BP (Saxena & Bolt, 1986). Coincidental to the peripheral vasodilation, the heart rate, stroke volume, and cardiac output rise, reflecting a baroreceptor-mediated reflex increase in sympathetic discharge (Lin et al., 1983) and direct stimulation of the heart (Khatri et al., 1977). In addition, the sympathetic overactivity and the fall in BP increase renin release, further counteracting the vasodilator's effect and likely adding to the reactive sodium retention that accompanies the fall in BP. Therefore, it is given along with a β -blocker and a diuretic in the treatment of more severe hypertension.

Hydralazine should usually be started at 25 mg two times per day. The maximal dose should be limited to 200 mg/day to lessen the likelihood of a lupus-like syndrome and because higher doses seldom provide additional benefit. Hydralazine is approved for use during pregnancy. It has been combined with isosorbide dinitrate for treatment of heart failure in blacks (Cohn et al., 2011).

The inactivation of hydralazine involves acetylation in the liver by the enzyme *N*-acetyltransferase. The level of this enzyme activity is genetically determined, and rapid acetylators require larger doses than do slow acetylators to achieve an equivalent effect (Ramsay et al., 1984). Perry (1973) showed that patients who develop a lupuslike toxicity tend to be slow acetylators and thus are exposed to the drug longer.

Side Effects

Three kinds of side effects are seen: Those due to reflex sympathetic activation, those due to a lupuslike reaction, and those due to nonspecific problems. Headaches, flushing, and tachycardia should be anticipated and prevented by concomitant use of adrenergic inhibitors. The drug should be given with caution to patients with coronary artery disease (CAD) and should be avoided in patients with a dissecting aortic aneurysm or recent cerebral hemorrhage, in view of its propensity to increase cardiac output and cerebral blood flow (CBF).

The lupuslike reaction was first described by Perry (1973). An early, febrile reaction resembling serum sickness was seen in 11 patients; late toxicity developed in 44 resembling systemic lupus erythematosus or rheumatoid arthritis. These symptoms almost invariably go away when the drug is stopped or the dosage is lowered. The lupuslike syndrome is clearly dose dependent (Cameron & Ramsay, 1984).

Other side effects of hydralazine include anorexia, nausea, vomiting, and diarrhea; less common effects are paresthesias, tremor, and muscle cramps.

Minoxidil

More potent than hydralazine, minoxidil has become a mainstay in the therapy of severe hypertension associated with renal insufficiency (see Chapter 9). Its propensity to grow hair precludes its use in many women, but this effect has led to its use as a topical ointment for male pattern baldness.

Minoxidil induces smooth muscle relaxation by opening cardiovascular ATP-sensitive potassium channels, a mechanism apparently unique among vasodilators currently available in the U.S. but similar to the mode of action of various potassium channel openers (e.g., nicorandil) (Ito et al., 2004).

Because minoxidil is both more potent and longer lasting than hydralazine, it turns on the various reactions to direct arteriolar vasodilation to an even greater degree. Therefore, large doses of potent loop diuretics and adrenergic blockers will be needed in most patients.

When used with diuretics and adrenergic inhibitors, minoxidil controls hypertension in more than 75% of patients whose disease was previously resistant

to multiple drugs (Sica, 2004b). It can be given once daily in a range of 2.5 to 80 mg.

Side Effects

The most common side effect, seen in nearly 80% of patients, is hirsutism, beginning with fairly fine hair on the face and then with coarse hair increasing everywhere. It is apparently related to the vasodilation produced by the drug and not to hormonal effects. The hair gradually disappears when the drug is stopped (Kidwai & George, 1992).

Beyond generalized volume expansion, pericardial effusions appear in approximately 3% of patients who receive minoxidil (Martin et al., 1980).

Nitrates

Nitrates, both nitroglycerin (Willmot et al., 2006) and oral isosorbide nitrate (Stokes et al., 2005), by their vasodilating properties as exogenous endothelium-derived relaxing factor (NO), can also be used as antihypertensives. Stokes et al. (2005) found isosorbide mononitrate to lower SBP by an average of 16 mm Hg without significant effect on diastolic BPM in 16 elderly patients with resistant systolic hypertension. The pulse pressure fell by 13 mm Hg and the augmentation index, a measure of pulse wave reflection, fell by 25%. Tolerance did not seem to develop.

Despite the attractiveness of this approach for treatment of systolic hypertension, the lack of a commercial sponsor for testing a generic drug in a large clinical trial makes it unlikely that a currently available nitrate will be approved as an antihypertensive drug.

TABLE 7-5

Cardiovascular Profile of CCBs

	Nifedipine	Amlodipine	Diltiazem	Verapamil
Heart rate	↑	↑/0	↓	↓
Sinoatrial node conduction	0	0	↓↓	↓
AV node conduction	0	0	↓	↓
Myocardial contractility	↑/0	↑/0	↓	↓↓
Neurohormonal activation	↑	↑/0	↑	↑
Vascular dilatation	↑↑	↑↑	↑	↑
Coronary flow	↑	↑	↑	↑

↓, decrease; 0, no change; ↑, increase.

Adapted from Eisenberg MJ, Brox A, Bestawros AN. Calcium channel blockers: An update. *Am J Med* 2004;116:35-43.

CALCIUM CHANNEL BLOCKERS

CCBs were introduced as antianginal agents in the 1970s and as antihypertensives in the 1980s. Their use grew rapidly so that they became the second most popular group of drugs used by U.S. practitioners for the treatment of hypertension in the early 2000s.

Mode of Action

Three types of CCBs are now available. All interact with the same calcium channel: the L-type voltage-gated plasma membrane channel, but they have major differences in their structure and cardiovascular effects (Eisenberg et al., 2004) (Table 7-5).

Diltiazem, a benzothiazepine, and *verapamil*, a phenylalkylamine, the currently available nondihydropyridine (non-DHP), are rate slowing: At equivalent concentrations, they induce vasodilation, depress cardiac contractility, and inhibit AV conduction.

Dihydropyridines (DHPs) are predominantly vasodilators and improve endothelial function (Sugiura et al., 2008). The first generation, exemplified by nifedipine, had modest effects on cardiac contractility. The second generation, such as amlodipine, felodipine, and nicardipine, has more effect on vascular dilation than on myocardial contractility or cardiac conduction. A number of other DHPs are not yet approved in the U.S. but are being used elsewhere; these include benidipine, cilnidipine, efonidipine, lacidipine, lercanidipine, manidipine, and nitrendipine. Although

the major differences are between non-DHP and the DHP-CCBs, there are enough differences between the multiple DHP-CCBs so that “caution should be exercised in assuming that all DHP CCBs licensed for once-daily administration are equivalent in their durations of action and overall antihypertensive efficacy” (Meredith & Elliott, 2004).

Surprisingly, some CCBs (felodipine, nimodipine, nifedipine, and, to a lesser extent, amlodipine) have been found to provide mineralocorticoid receptor antagonist activity (Dietz et al., 2008). Neither diltiazem nor verapamil had such activity. Most of the data are in vitro and with fairly high doses of the CCBs, so their relevance to the antihypertensive effect of CCBs in clinical practice remains uncertain.

Sympathetic Activation

One pharmacologic feature that may explain some of the initial side effects of CCBs and has been incriminated as a possible contributor to adverse cardiovascular effects of short-acting agent is their activation of the sympathetic nervous system (Lindqvist et al., 2007). Long-acting CCBs may transiently activate the sympathetic system but the effect is soon attenuated (Grassi et al., 2003).

Duration of Action

One of the major differences between CCBs is their duration of action. As shown in Table 7-6, some of these, such as the formulation of verapamil that

TABLE 7-6

CCBs Approved for Use in the Treatment of Hypertension in the U.S.

Drug	Form and Dose	Time to Peak Effect (h)	Elimination Half-Life (h)
Amlodipine	Tablet; 2.5–10 mg	6–12	30–50
Diltiazem ^a	Immediate-release tablet; dose varies	0.5–1.5	2–5
	Sustained-release tablet; 180–480 mg	6–11	2–5
Felodipine	Sustained-release tablet; 2.5–10 mg	2.5–5	11–16
Isradipine	Tablet; 2.5–10 mg	1.5	8–12
Nicardipine ^a	Immediate-release tablet; 20–40 mg	0.5–2.0	8
	Sustained-release tablet; 60–120 mg	Unknown	8
Nifedipine	Immediate-release capsule; dose varies	0.5	2
	Sustained-release tablet; 30–120 mg	6	7
Nisoldipine	Sustained-release tablet; 20–40 mg	6–12	7–12
Verapamil ^a	Immediate-release tablet; dose varies	0.5–1.0	4.5–12
	Sustained-release tablet; 120–480 mg	4–6	4.5–12

^aAlso available in an intravenous formation, with a time to peak effect ranging from 5 to 15 min after administration.

affords 24-hour effectiveness, are provided by special delivery systems; others, such as amlodipine, have intrinsically long durations of action.

Antihypertensive Efficacy

The currently available CCBs seem comparable in their antihypertensive potency (Eisenberg et al., 2004). As shown by Law et al. (2009) CCBs are equally effective as other classes against all-cause cardiovascular mortality and major morbidity. However, they have provided *less* protection against heart failure, but *more* protection against stroke than other classes. Although the data are limited, combinations of non-DHP and DHP-CCBs provide additional antihypertensive efficacy with safety (Alviar et al., 2013).

Determinants of Efficacy

Age

An apparently greater antihypertensive effectiveness of CCBs in the elderly may reflect pharmacokinetic changes that increase the bioavailability of various CCBs, providing more active drug at any given dose than in younger patients (Lernfelt et al., 1998).

Race

In blacks, the response of the BP to monotherapy with CCBs is better than to ACEIs, ARBs, or β -blockers and equal to the response to diuretics (Brewster et al., 2004).

Additive Effect of Diuretic or Low Sodium Intake

Two factors that increase the efficacy of other classes of antihypertensive drugs—dietary sodium reduction and concomitant use of a diuretic—may not add to the efficacy of CCBs.

Numerous studies have examined these relationships. In general, the findings support the view that dietary sodium restriction may reduce (but not abolish) the antihypertensive effect of CCBs, whereas high sodium intake may enhance (or not diminish) their efficacy (Luft et al., 1991). The explanation may be simple: CCBs have a mild natriuretic effect (Krekels et al., 1997); this effect would be more obvious in the presence of a higher sodium diet so that the BP would fall more. With a low sodium intake, this natriuretic effect would not be as pronounced, so the BP would diminish less. On the other hand, the combination of a diuretic with a CCB provided additive effects equal to that seen when a β -blocker or ARB was added to the CCB (Matsuzaki et al., 2011).

Renal Effects

The mild natriuretic action of DHP-CCBs likely reflects their unique ability, unlike other vasodilators, to maintain or increase effective renal blood flow, glomerular filtration rate (GFR), and renal vascular resistance, which has been attributed to their selective vasodilative action on the renal afferent arterioles (Delles et al., 2003). On the surface, this preferential vasodilation of afferent arterioles with increases in GFR, renal blood flow, and natriuresis appears to favor the use of CCBs as a way of maintaining good renal function. However, a large body of experimental data suggests that increased renal plasma flow and GFR may accelerate the progression of glomerulosclerosis by increasing intraglomerular pressure (Griffin et al., 1995).

However, in the ACCOMPLISH trial, the addition of the CCB amlodipine to the ACEI benazepril provided better renal outcomes than did the combination of the diuretic HCT with the ACEI, with equal reduction of BP (Bakris et al., 2010). On the other hand, in those patients with heavy proteinuria non-DHPs reduced proteinuria better than did DHP-CCBs (Hart and Bakris, 2008) and the relation between reduction in proteinuria and subsequent decline in renal function is strong (Levey and Coresh, 2012).

Other Uses

- CAD (Nissen et al., 2004)
- Tachyarrhythmias (non-DHP-CCBs) (Abernethy & Schwartz, 1999)
- Hypertrophic cardiomyopathy (Roberts & Sigwart, 2001)
- Aortic regurgitation (Levine & Gaasch, 1996)
- Vasospasm after subarachnoid hemorrhage (nimodipine) (Rinkel & Klijn, 2009)
- Peripheral vascular disease (Bagger et al., 1997) and Raynaud reaction (Wigley, 2002)
- Prevention of dementia (Staessen et al., 2011) and stroke (Law et al., 2009)

Side Effects

Relatively mild but sometimes bothersome side effects will preclude the use of these drugs in perhaps 10% of patients. Most side effects—headaches, flushing, local ankle edema—are related to the vasodilation for which drugs are given. With slow-release and longer-acting formulations, vasodilative side effects are reduced. The side effects of the three major classes of

CCBs differ considerably (see Table 7-5). Dependent edema is related to localized vasodilation and not generalized fluid retention and is not prevented or relieved by diuretics but may be relieved by addition of an ACEI (Gradman et al., 1997).

Other Side Effects

Gingival hyperplasia may occur with DHPs (Missouris et al., 2000). A wide spectrum of adverse cutaneous reactions has been reported to occur rarely with various CCBs (Garijo et al., 2005).

No adverse effects on glucose, insulin, or lipids have been seen, and fewer cases of new-onset diabetes developed in the INVEST trials among those given verapamil than in those given atenolol (Pepine et al., 2003). Overdoses usually are manifested by hypotension and conduction disturbances and can usually be overcome with parenteral calcium and insulin and glucose (Salhanick & Shannon, 2003).

Drug Interactions

A problem noted with most other classes of antihypertensive drugs—interference from NSAIDs—is usually not seen with CCBs (Celis et al., 2001). Another interaction has been noted with the DHPs felodipine and nifedipine but not with amlodipine (Vincent et al., 2000): An increased plasma level and duration of action when taken along with large amounts of grapefruit juice that decreases intestinal metabolism of these drugs by inhibition of the CYP3A4 enzyme, thereby increasing the drugs' blood levels (Pirmohamed, 2013). Renal injury has been reported with the antibiotic clarithromycin, which also inhibits CYP3A4 (Gandhi et al., 2013).

Perspective on Use

CCBs have been found to reduce the risk of coronary disease equally, stroke more, but heart failure less, than other antihypertensive therapies while having similar effects on overall mortality. They work well and are usually well tolerated across the entire spectrum of hypertensives. They have some particular niches: The elderly, coexisting angina, and concomitant cyclosporine or NSAID use. If chosen, an inherently long-acting, second-generation DHP seems the best choice, because it will maintain better BP control in the critical early morning hours and on through the next day if the patient misses a daily dose. Rate-slowing CCBs, verapamil or diltiazem, may be preferable with concomitant tachyarrhythmias or heavy proteinuria.

DRUGS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM

There are four ways to reduce the activity of the RAS (Fig. 7-9). The first way, the use of β -blockers to reduce renin release from the juxtaglomerular (J-G) cells, has been covered. The second way, direct inhibition of the activity of renin, is provided by aliskerin. The third way is to inhibit the activity of the angiotensin-converting enzyme (ACE), which converts the inactive decapeptide angiotensin I (AI) to the potent hormone AII; i.e., ACEIs. The fourth way is to use a competitive antagonist that attaches to the AII receptors and blocks the attachment of the native hormone, i.e., ARBs.

Multiple studies have documented an equal antihypertensive efficacy between ACEIs and ARBs (ONTARGET Investigators, 2008) and between aliskerin and either ACEIs or ARBs (Gao et al., 2011).

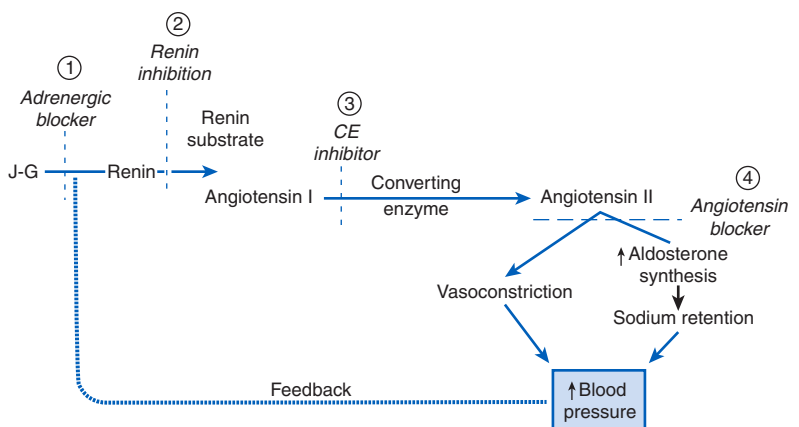


FIGURE 7-9 • The RAS and four sites where its activity may be inhibited. CE, converting enzyme; J-G, juxtaglomerular.

However, multiple adverse effects have been seen with the combination of two RAS blockers (Makani et al., 2013; Mann et al., 2013; Parving et al., 2012). Moreover, acute renal injury has been reported when a RAS blocker is combined with a diuretic and a NSAID (Lapi et al., 2013).

Patients who are younger or nonblack (and tend to have higher levels of renin activity) respond somewhat better to renin-blocking drugs while those who are older or black (and tend to have lower levels of renin activity) respond somewhat better to drugs that do not primarily block renin, i.e., diuretics and CCBs. However, this clinical separation does not require measurements of renin activity and can be based on the age and race of the patient (Canzanello et al., 2008).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Mode of Action

Peptides from the venom of the Brazilian viper *Bothrops jararaca* were discovered to potentiate the effects of bradykinin by inhibiting its degradation (Ferreira, 1965). Soon thereafter, Ng and Vane (1967) recognized that the same enzyme from the carboxypeptidase family could be responsible for both the conversion of AI to AII and the degradation of bradykinin. The nature of this ACE was identified by Erdős and coworkers in 1970 (Yang et al., 1970). Biochemists at the Squibb laboratories fashioned the first inhibitor for the ACE enzyme,

teprotide or SQ20881 (Ondetti et al., 1971), which was shown to lower BP when given intravenously (Gavras et al., 1974). The Squibb group then identified the active site on the ACE and developed the first orally effective ACEI, captopril (Ondetti et al., 1977).

Three chemically different classes of ACEIs have been developed, classified by the ligand of the zinc ion of ACE: Sulfhydryl, carboxyl, and phosphoryl (Table 7-7). In equivalent doses, they are equally effective in lowering the BP (Izzo & Weir, 2011). In one small study, only centrally acting ACEIs, e.g., lisinopril, slowed cognitive decline (Sink et al., 2009).

Pharmacokinetics

As seen in Table 7-7, most ACEIs are prodrugs, esters of the active compounds that are more lipid soluble, so that they are more quickly and completely absorbed. Although there are large differences in bioavailability, these seem to make little difference in their clinical effects. Most ACEIs, except fosinopril and spirapril, are eliminated through the kidneys, having undergone variable degrees of metabolism.

Pharmacodynamics

As seen in Figure 7-9, the most obvious manner by which ACEIs lower the BP is to reduce the circulating levels of AII markedly, thereby removing the direct vasoconstriction induced by this peptide. However, with usual doses of ACEIs, plasma AII levels begin to “escape” after a few hours, in part because of the

TABLE 7-7

Characteristics of ACEIs

Drug	Zinc Ligand	Prodrug	Rate of Elimination	Duration of Action (h)	Dose Range (mg/d)
Benazepril	Carboxyl	Yes	Renal	24	10–40
Captopril	Sulfhydryl	No	Renal	6–12	25–150
Cilazapril	Carboxyl	Yes	Renal	24+	2.5–5.0
Enalapril	Carboxyl	Yes	Renal	18–24	20–40
Fosinopril	Phosphoryl	Yes	Renal-hepatic	24	10–40
Lisinopril	Carboxyl	No	Renal	24	20–40
Moexipril	Carboxyl	Yes	Renal	12–18	15–30
Perindopril	Carboxyl	Yes	Renal	24	4–16
Quinapril	Carboxyl	Yes	Renal	24	20–80
Ramipril	Carboxyl	Yes	Renal	24	5–20
Spirapril	Carboxyl	Yes	Hepatic	24	12.5–50
Trandolapril	Carboxyl	Yes	Renal	24+	4–8

release of more renin, freed from its feedback suppression (Azizi & Menard, 2004).

The complete RAS is present within various tissues, including vessel walls, the heart, and the brain, but its role remains uncertain (Re, 2004). Moreover, nonclassical pathways may be involved in the elaboration of AII, involving either nonrenin effects on angiotensinogen or non-ACE effects on AI (Fig. 7-10). Because ACEIs block only AII production via the classical pathway, there could then be additional effects of both ARBs and DRIs. On the other hand, some of the effects of ACEIs may be mediated via their inhibition of the breakdown of bradykinin.

Effects of ACEIs

Regardless of the contributions of various other mechanisms beyond the reduction in AII levels, the lower AII levels certainly play a major role. In addition to the relief of vasoconstriction, multiple other effects may contribute to their antihypertensive effect, including the following:

- A decrease in aldosterone secretion that may not be persistent (Sato & Saruta, 2003)
- An increase in bradykinin, which in turn increases release of tissue plasminogen activator (tPA) (Labinjoh et al., 2001)
- An increase in the activity of the 11β -hydroxysteroid dehydrogenase-2 enzyme, which could increase renal sodium excretion by protecting the nonselective mineralocorticoid receptor from cortisol (Ricketts & Stewart, 1999)
- Blunting of the expected increase in sympathetic nervous system activity typically seen after vasodilation (Lyons et al., 1997)
- Suppression of endogenous endothelin secretion (Brunner & Kukovetz, 1996)
- Improvement in endothelial dysfunction (Ghiadoni et al., 2003)
- Reduction in oxidative stress by reducing production of reactive oxygen species (Hamilton et al., 2004) and inflammatory factors (Sattler et al., 2005)
- Stimulation of endothelial progenitor cells (Bahlmann et al., 2005)

As a consequence of these multiple effects, ACEI results in a dampening of arterial wave reflections and increased aortic distensibility that provide a greater fall in central aortic pressure (Morgan et al., 2004). These hemodynamic improvements contribute to the reversal of hypertrophy both in the heart and vasculature. As will be noted, ACEIs lower the BP in a manner that tends to protect the function of two vital organs—the heart and the kidneys. In addition, ACEIs may reduce the incidence of new-onset diabetes via multiple mechanisms (Jandeleit-Dahm, 2005). However, in the largest trial to closely examine this effect, the ACEI ramipril did not reduce the incidence of diabetes (Dream Trial Investigators, 2006).

ACEIs are also venodilators, which may be responsible for their ability to reduce the accumulation of ankle edema seen with CCBs when the two agents are combined (Gradman et al., 1997).

Monotherapy

An immediate fall in BP occurs in approximately 70% of patients given captopril, and the decrease is sometimes rather precipitous (Postma et al., 1992). Such a dramatic fall is more likely in those with high renin levels. Black or elderly hypertensives, with lower renin levels as a group, respond less well to ACEIs than do white or younger patients (Brewster et al., 2004).

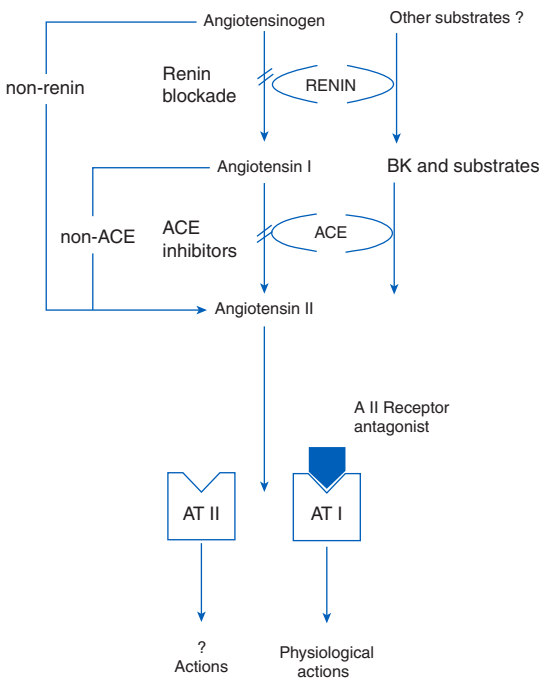


FIGURE 7-10 • Theoretic biochemical and physiologic consequences of blocking the RAS at different steps in the pathway. ACE, angiotensin-converting enzyme; AT, angiotensin; BK, bradykinin. (Modified from Johnston CL, Burrell LM. Evolution of blockade of the renin-angiotensin system. *J Hum Hypertens* 1995;9:375–380.)

As expected, patients with high-renin hypertension from renal artery stenosis may respond particularly well to ACEIs, but the removal of AII's support of perfusion to the ischemic kidney may precipitously reduce renal function, particularly in those with bilateral stenoses (see Chapter 10). If such patients are excluded, ACEIs are usually effective and well tolerated in patients with renal insufficiency (Ahmed et al., 2012). An initial decline of 25% to 30% in renal function after starting ACEI therapy in patients with mild to moderate renal insufficiency has been associated with *better* long-term renoprotection (Apperloo et al., 1997), presumably reflecting a beneficial dilation of efferent arterioles that reduces intraglomerular pressure and filtration (Izzo & Weir, 2011). Although RAS-inhibiting drugs have been said to be no better than other classes of drugs in preventing renal dysfunction (Daïen et al., 2012), they have also been said to be the preferable initial therapy for diabetic hypertensives (Levey and Coresh, 2012).

Combination Therapy

The addition of a diuretic will enhance the efficacy of an ACEI (Cheng & Frishman, 1998), normalizing the BP of another 20% to 25% of patients with mild to moderate hypertension more effectively than would raising the dose of the ACEI (Townsend & Holland, 1990). The marked additive effect of a diuretic likely reflects the ACEI blunting of the reactive rise of AII that usually occurs with diuretic use and that opposes the antihypertensive effect of the diuretic. However, in the ACCOMPLISH trial, the combination of an ACEI and a CCB provided greater benefit than an ACEI plus diuretic (Jamerson et al., 2008).

As noted, the combination of an ACEI with either an ARB or DRI is now considered inappropriate.

Effectiveness in Reducing Morbidity and Mortality

In their analysis of 147 RCTs published by 2007, Law et al. (2009) reported an equal efficacy of ACEIs with other classes of drugs for preventing heart attacks and strokes. In an analysis of trials examining the prevention of dementia, Staessen et al. (2011) reported that in four placebo-controlled trials including 15,076 patients given either an ACEI or an ARB, there was an insignificant 5% reduction but a significant 18% reduction in the 5 trials including 12,269 subjects with the use of either diuretics or CCBs. These data have been disputed (Chiu et al., 2014).

Other Uses

Heart Diseases

An ACEI is indicated for patients with CHD, post-MI, or CHF including those with a preserved ejection fraction (EF) (Lund et al., 2012). The first large trial that documented the benefit of an ACEI in patients with known coronary disease, the HOPE trial (Heart Outcomes, 2000), used ramipril as the ACEI. For treatment of CHF, an ACEI, often a shorter-acting one such as captopril, is started in a low dose to minimize hypotension and azotemia. ACEIs, not ARBs, have protected type 2 diabetics from cardiovascular diseases (Cheng et al., 2014).

Cerebrovascular Diseases

In the meta-analysis of Law et al. (2009), ACEI therapy provided a statistically insignificant 6% lesser protection against stroke as compared to other classes of antihypertensive drugs. The PROGRESS trial (PROGRESS Collaborative Group, 2001) tested the efficacy of the ACEI perindopril for secondary stroke prevention, i.e., in patients who had survived a stroke. By itself, the ACEI had no benefit, but when a diuretic, indapamide, was added, the BP fell further and excellent protection, a 43% relative risk reduction, was noted.

Renal Diseases

Renin-angiotensin inhibitors preferentially dilate the renal efferent arteriole, reducing intraglomerular pressure and restraining glomerulosclerosis, podocyte damage, and proteinuria (Lassila et al., 2004). The clinical consequences of the use of ACEIs in patients with kidney diseases have been examined using four end points:

- ▶ The incidence of proteinuria in diabetic patients has been reduced by 40% (Strippoli et al., 2006), most impressively in a study of 1204 type 2 diabetics free of proteinuria who took one of four regimens for 3 or more years (Remuzzi et al., 2006).
- ▶ Reduction of existing proteinuria has been documented both in diabetics and in nondiabetics (Kunz et al., 2008) and is associated with a significant reduction in mortality (Estacio et al., 2012).
- ▶ Slowing of the progress of renal damage has been noted both in diabetic (Sarafidis et al., 2008) and nondiabetic (Kent et al., 2007) nephropathies.

However, no benefit has been reported in non-diabetic nephropathy with proteinuria less than 500 mg/day (Kent et al., 2007) nor in normoalbuminuria type 1 diabetics (Mauer et al., 2009).

- Overall mortality has not been reduced in 20 trials of patients with diabetic nephropathy despite a significant reduction in the incidence of ESRD.

These data have been used to support the use of an ACEI (or an ARB) in those prone to develop nephropathy, i.e., diabetics, and in those who have proteinuria alone or in concert with reduced renal function (Berl, 2008). However, some believe that the renoprotective effects of ACEIs are provided simply by their lowering of BP (Casas et al., 2005; Griffin and Bidani, 2006).

Nonetheless, the guidelines of expert groups recommend the use of ACEIs and ARBs for both prevention and relief of progressive kidney disease (Fink et al., 2012; Levey and Coresh, 2012).

Other Uses

ACEI therapy is associated with a reduced risk of rupture of abdominal aortic aneurysms, an effect not seen in patients taking diuretics, β -blockers, α -blockers, CCBs, or ARBs (Hackam et al., 2006).

ACEIs have been found to ameliorate altitude polycythemia (Plata et al., 2002), diminish hypertriglyceridemia in nephrotic patients (Ruggenenti et al., 2003), ameliorate migraine (Schrader et al., 2001), and improve walking time in patients with peripheral vascular disease (Ahimastos et al., 2013). The use of an ACEI reduces the risk of pneumonia, particularly in Asians (Caldeira et al., 2012) and in patients after a stroke (Liu et al., 2012) unless they have an ACEI-induced cough (Barnes, 2012). All of this good is only partly countered by an increased sensitivity to pain (Guasti et al., 2002).

Side Effects

Cough and Bronchospasm

A dry, hacking, nonproductive, and sometimes intolerable cough is the most frequent side effect of ACEI therapy; bronchospasm may be the second most frequent. In a review of 125 published series, a cough was described in 11.5% of patients, causing withdrawal of the ACEI in 2.6% (Bangalore et al., 2010).

An increase in bradykinin has been assumed to be the mechanism for the cough, and a genetic polymorphism of the bradykinin β -receptor has been found in a higher proportion of patients who have an ACEI-related cough (Mukae et al., 2000).

Cough is more common in older patients, women, and blacks (Morimoto et al., 2004) and was reported in almost half of Chinese patients (Woo & Nicholls, 1995). It usually goes away in a few weeks after the drug is withdrawn and usually recurs with reexposure to an ACEI. The easiest way to resolve the problem is to replace the ACEI with an ARB.

Hyperkalemia

Hyperkalemia occurs in about 10% of patients taking an ACEI (Palmer, 2004). There are multiple reasons mostly reflecting diminished renal perfusion, decreased aldosterone, and reduced renal tubular function (Palmer, 2004). If recognized, the problem can usually be managed by deleting drugs that further increase potassium load or interfere with its excretion.

Hypoglycemia

Perhaps as a reflection of increased insulin sensitivity, ACEI use has been accompanied by hypoglycemia both in insulin-dependent and non-insulin-dependent diabetics (Herings et al., 1995).

Interference with Erythropoietin

All enhances erythrocytosis, and ACEIs may interfere with the action of erythropoietin in correcting the anemia of CKD patients but also to reduce secondary erythrocytosis as after transplantation (Fakhouri et al., 2004).

Deterioration of Renal Function

Most reports of acute loss of renal function involve preexisting renal hypoperfusion: Patients with CHF, volume depletion, or renal artery stenoses, either bilaterally or to a solitary kidney. Rarely, acute renal failure may occur, usually associated with vomiting-and/or diarrhea-induced marked volume depletion (Stirling et al., 2003). However, acute increases of serum creatinine of up to 30% that stabilize within the first 2 months of ACEI therapy are associated with

better long-term renoprotection (Bakris & Weir, 2000), and so such rises need not lead to withdrawal of ACEI therapy.

Pregnancy

ACEIs are contraindicated during pregnancy, including the first trimester, because they may cause fetal injury and death (Bullo et al., 2012). If a RAS-inhibiting drug is given to a woman with childbearing potential, she should be warned to contact a practitioner if there is any indication of a pregnancy.

Angioedema

Angioedema occurs in 0.2% (Toh et al., 2012) to 0.3% (Makani et al., 2012) of patients given an ACEI, usually within days but sometimes after prolonged use (Miller et al., 2008). It is 4-fold higher in blacks (Brown et al., 1996), 5-fold higher with glitin drugs (Brown et al., 2009), and 50% higher in women. Fatal airway obstruction has been reported (Roberts et al., 2012), so that it is mandatory that patients with angioedema on an ACEI never be given an ACEI again. In a follow-up of 111 patients who had experienced angioedema while on an ACEI, 51 had recurrent angioedema after the ACEI was discontinued, suggesting an underlying propensity that had been exposed by the ACEI (Beltrami et al., 2011). Two patients with localized penile angioedema have been reported (McCabe et al., 2008).

Other Side Effects

ACE activity is present in intestinal brush border, and adverse GI effects have been reported with ACEI use (Jacobs et al., 1994). Other rare effects include pancreatitis (Roush et al., 1991) and cholestatic jaundice (Nissan et al., 1996).

ACEIs that cross the blood–brain barrier have been claimed to slow decline of cognitive function; those that do not (benazepril, enalapril, moexipril, quinapril) may hasten decline (Sink et al., 2009). ACEIs are “lipid neutral” (Kasiske et al., 1995). Headache, dizziness, fatigue, diarrhea, and nausea are listed in reviews but are seldom problems. Sudden withdrawal does not usually lead to a rebound. Overdose causes hypotension that should be easily

managed with fluids and, if needed, dopamine (Lip & Ferner, 1995).

ACEIs do not increase the incidence of cancer (Bangalore et al., 2011a; Sipahi et al., 2011) and may decrease the incidence of breast cancer (Lee et al., 2012).

Perspective on Use

Captopril, when first introduced for use in severe hypertensives and in high doses, earned a bad reputation that was quickly overcome. As appropriately lower doses were used and found to be as effective as other drugs, often with fewer side effects, captopril and then enalapril became increasingly popular. Over the last few years, many more ACEIs have been marketed, most with the added advantage of longer duration of action, allowing for once-daily dosing.

As ACEIs have been used in various situations, three places have been recognized wherein they provide special benefits beyond those provided by other agents: Relief of acute and chronic heart failure, prevention of remodeling and progressive ventricular dysfunction after MI, and slowing of glomerular sclerosis in diabetic and other nephropathies. Even as ACEIs became increasingly popular, their popularity was threatened by the introduction of ARBs, agents that act at a more distal site of the RAS (see Fig. 7-9).

ANGIOTENSIN II RECEPTOR BLOCKERS

Even before ACEIs were available, a peptidic antagonist of AII receptors, saralasin, was shown to lower BP. However, its use was limited by the need for intravenous administration and its pressor effect in low-renin patients resulting from its partial agonist effects. Subsequently, the AII receptor was found to have at least two major subtypes, with the type 1 (AT₁) receptor mediating most of the physiologic roles of AII. The signaling mechanisms and functions of these receptor subtypes are different, and they may exert opposite effects on cell growth and BP regulation (Nickenig, 2004) (Fig. 7-11). Agents that selectively block the AT₁ receptor have been synthesized and marketed for the treatment of hypertension. Losartan was the first,

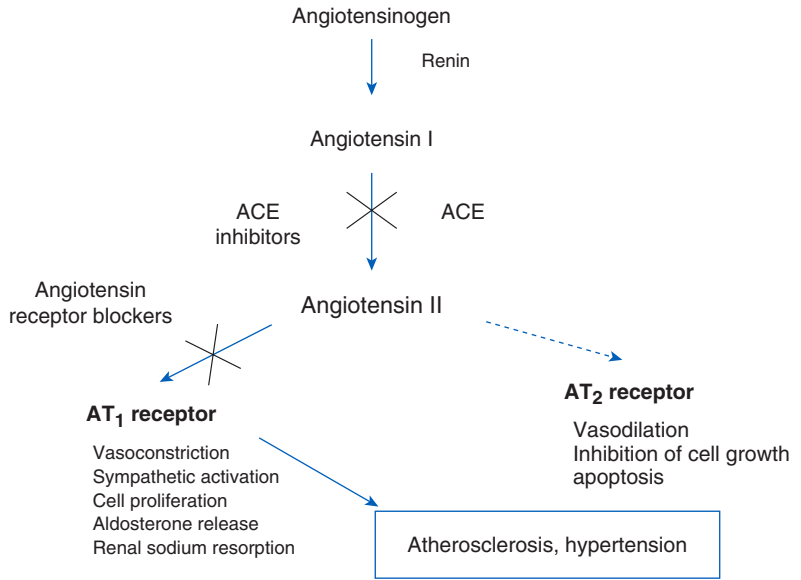


FIGURE 7-11 • The RAS with the major effects of stimulation at AT₁ and AT₂ receptors and the sites of action of ACEIs and ARBs. (Modified from Nickenig G. Should angiotensin II receptor blockers and statins be combined? *Circulation* 2004;110:1013–1020.)

and now seven more have been approved for use in the U.S. (Table 7-8).

Mode of Action

ARBs displace AII from its specific AT₁ receptor, antagonizing all of its known effects and resulting in a dose-dependent fall in peripheral resistance and little change in heart rate or cardiac output (Burnier, 2001). As a consequence of the competitive displacement, circulating levels of AII increase while at the same time, the blockade of the renin–angiotensin mechanism is more complete, including any AII that is generated through pathways that do not involve the ACE (see Fig. 7-11). No obvious good or bad effects of the

increased AII levels have been proven. However, in experimental animals, chronic stimulation of AT₂ receptors has been found to protect the heart, brain, and blood vessels from hypertension-induced damages (Rehman et al., 2012).

Differences Between Angiotensin Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors

The major obvious difference between ARBs and ACEIs is the absence of an increase in kinin levels with the ARB, increases that may be responsible for some of the beneficial effects of ACEIs and likely even more of their side effects, such as cough and angioedema

TABLE 7-8

Angiotensin II Receptor Blockers

Drug	Trade Name	Half-Life (h)	Active Metabolite	Daily Dosage (mg)
Azilsartan	Edarbi (Takeda)	11	Yes	40–80 in 1 dose
Candesartan	Atacand (Astra)	3–11	Yes	8–32 in 1 dose
Eprosartan	Tevetan (Smith Kline)	5–7	No	400–800 in 1–2 doses
Irbesartan	Avapro (BMS, Sanofi)	11–15	No	150–300 in 1 dose
Losartan	Cozaar (Merck)	2 (6–9)	Yes	50–100 in 1–2 doses
Olmесartan	Benicar (Sankyo)	13	Yes	20–40 in 1 dose
Telmisartan	Micardis (BI)	24	No	40–80 in 1 dose
Valsartan	Diovan (Novartis)	9	No	80–320 in 1 dose

(Makani et al., 2012). In the TRANSEND trial, the ARB telmisartan was well tolerated in patients who had been intolerant to an ACEI (Yusuf et al., 2008).

Direct comparisons between ACEIs and ARBs show little difference in antihypertensive efficacy (Taylor et al., 2011), but only ACEIs protected diabetics against cardiovascular diseases (Cheng et al., 2014). Angioedema has been seen but at a much lower rate than with ACEIs (Makani et al., 2012).

Differences Between Angiotensin Receptor Blockers

Three differences have been described. First, losartan has a uricosuric effect (Dang et al., 2006); second, the most recently introduced ARB, azilsartan, is reported to have a greater antihypertensive effect (Cushman et al., 2012a). Third, telmisartan and, to a lesser extent, irbesartan but not the other ARBs act as partial peroxisome proliferator-activated receptor- γ (PPAR γ) agonists, and this effect has been claimed to be of clinical benefit (Takagi et al., 2013). However, telmisartan was no more effective in preventing new-onset diabetes than the ACEI ramipril in the ONTARGET trial (ONTARGET Investigators, 2008), so proof of special benefits of telmisartan beyond its long duration of action remains elusive (Kusunoki et al., 2012).

Antihypertensive Efficacy

In the recommended doses (Table 7-8), all eight currently available ARBs have comparable antihypertensive efficacy with the possible exception of azilsartan. The dose-response curve is fairly flat for all, although increasing doses of valsartan provided more rapid reductions in albuminuria (Weir et al., 2011). In an analysis of 36 publications wherein 24-hour ABPM was performed, most of the ARBs were found to maintain good antihypertensive efficacy at the end of the 24-hour interval (Fabia et al., 2007), although a longer duration of effect has been noted with telmisartan than valsartan (McInnes, 2008).

Other Uses

Renal Diseases

ARBs have been shown to be renoprotective in three placebo-controlled trials in type II diabetics with nephropathy (Brenner et al., 2001; Lewis et al., 2001; Parving et al., 2001), two using irbesartan, the third

losartan, all three showing 20% to 30% reductions in progression of renal damage. As with ACEIs, a transient fall in GFR has been associated with better long-range renal protection (Holtkamp et al., 2011).

Cerebrovascular Disease

As previously noted, numerous trials have shown protective effects of ARBs on stroke, CHD, and heart failure, all appearing to be mostly dependent on BP lowering (Bangalore et al., 2011b). ARBs are of no apparent benefit either in treatment of acute stroke (Sandset et al., 2011) or in prevention of recurrent stroke (Yusuf et al., 2008). As previously noted, Staessen et al. (2011) reported lesser prevention of dementia with ARBs than with either diuretics or CCBs. On the other hand, a prospective cohort analysis of data on 819,491 patients treated over 4 years in U.S. Veterans Administration medical centers with an ARB reported a 24% reduction in the incidence of dementia and a 49% decrease in admissions to nursing homes in those patients with preexisting Alzheimer disease (Li et al., 2010). Similar protection against dementia was reported in a large cohort study (Chiu et al., 2014).

Cardiac Diseases

In their 2009 meta-analysis, Law et al. found a statistically insignificant 4% lesser protection against coronary disease and a 10% better protection against strokes than with other classes of antihypertensive drugs. In a later meta-analysis, Bangalore et al. (2011b) reported that ARB therapy reduced the risk of heart failure as well as stroke and new-onset diabetes when compared either to placebo or other classes including ACEIs.

ARBs have been extensively studied in patients with chronic heart failure or post-MI and found to be equally effective as ACEIs (Lee et al., 2004). However, in an RCT of 341 patients with diastolic dysfunction, valsartan was not significantly better than placebo in improving diastolic function (Solomon et al., 2007).

A reduced incidence of atrial fibrillation (AF) with ARB-based therapy was claimed (Aksnes et al., 2007) but not seen in a large RCT with valsartan (G1551-AF, 2009). In a small cohort study of 18 patients with Marfan syndrome, ARB therapy significantly slowed the rate of progression of aortic root dilation (Brooke et al., 2008).

Side Effects

In virtually every trial of ARBs given to hypertensive patients, they have been better tolerated than other classes of antihypertensives, usually causing no more symptoms than placebo with no increase in cough as seen with ACEIs although angioedema may still occur (Makani et al., 2012). Such tolerability is likely responsible for the higher maintenance of therapy with ARBs than with other antihypertensives (Naderi et al., 2012). No association with cancer has been documented (ARB Trialists Collaboration, 2011; Bangalore et al., 2011a; Bhaskaran et al., 2012).

ARBs, like ACEIs, are contraindicated in pregnancy. In a systematic review of 118 cases, Bullo et al. (2012) found a more frequent association of neonatal complications among the mothers who had taken an ARB during pregnancy than in those who had taken an ACEI.

Perspective on Use

ARBs have rapidly taken their place as excellent drugs for the treatment of hypertension, proteinuric renal diseases, and heart failure, in general equal to but no better than the effects of ACEIs, but failed to protect diabetics from cardiovascular events (Cheng et al., 2014). Their major advantage is the absence of cough seen in about 10% of ACEI users.

DIRECT RENIN INHIBITORS

A DRI, aliskerin (Texturna) has been approved for treatment of hypertension. Despite its limited absorption and bioavailability (3%), aliskerin works because of its high aqueous solubility, high specificity for the enzymatically active site of human renin, and long half-life (40 hours) and because it is minimally metabolized (Brown, 2008). Other DRIs are under investigation (Krop et al., 2013).

Mechanism of Action

As detailed in Chapter 3, the renal J-G apparatus secretes prorenin, which is enzymatically converted to the active renin, largely in the kidney. Renin cleaves the 10 amino acid AI from the protein substrate angiotensinogen. Aliskerin blocks renin's catalytic site, reducing the formation of AI and its generation of AII, resulting in a fall of BP. The lower

levels of AI and AII remove the normal inhibition of prorenin secretion from the J-G apparatus so that levels of prorenin and renin are markedly increased. According to conventional wisdom, as long as aliskerin blocks the catalytic action of prorenin and renin, the BP will fall.

However, prorenin is now recognized to attach to its own receptor in various tissues where it exerts profibrotic effects, without interference from aliskerin (Scheffé et al., 2008).

Antihypertensive Efficacy

Aliskerin lowers BP as well as an ARB (Gao et al., 2011) and has been shown to reduce proteinuria in patients with diabetic nephropathy (Persson et al., 2011).

It should be noted that diabetics have high levels of prorenin, as observed by Luetscher et al. (1985). So there may be a particular advantage for DRIs in the treatment of diabetic patients.

Adverse Effects

Save for transient (and not unexpected) rises in serum potassium, aliskerin has been as benign as ARBs (Gao et al., 2011). As with ACEIs and ARBs, DRIs are contraindicated during pregnancy.

Place in Therapy of Hypertension

There was great enthusiasm over aliskerin, the only new antihypertensive agent introduced in over a decade. But the enthusiasm remains cautious. In the words of two (old) wise hypertensive experts, "No new class of antihypertensive agents should make it to routine use without hard outcome data. That necessity applies even more to dual inhibition of the renin system, which exposes patients to hyperkalemia and renal insufficiency" (Birkenhager & Staessen, 2007).

DRUGS UNDER INVESTIGATION

Angiotensin II Immunization

An antibody conjugated with bacteriophage virus-like particles has been shown to lower BP of hypertensive rats (Chen et al., 2013), but no data in humans have been published.

Vasopeptidase Inhibitors

Vasopeptidase inhibitors are single molecules that simultaneously inhibit the ACE and the neutral endopeptidase (NEP) enzymes, which normally degrade a number of endogenous natriuretic peptides so that decreases in AII and increases in bradykinin are combined with increases in natriuretic peptides (Burnett, 1999). The most widely studied of these agents was omapatrilat (Vanlev), but it caused a disturbing incidence of angioedema (Kostis et al., 2004).

Endothelin Antagonists

As noted in Chapter 3, endothelin may have a role in the pathogenesis of hypertension. Drugs to block one or both endothelin receptors, ET_A and ET_B, have been developed and one, bosentan, has been approved for treatment of pulmonary hypertension.

Possible Drugs for the Future

- ▶ Agents that reduce uric acid levels (Soletsky and Feig, 2012)
- ▶ Inhibitors of aldosterone synthase (Colussi et al., 2013)
- ▶ Stimulation of angiotensin type II receptors (McCarthy et al., 2012)

Conclusion

A number of different drugs are under investigation. Time—and, in the U.S., the U.S. Food and Drug Administration (FDA)—will tell which of them will be available for clinical use. More drugs will be available, probably in rate-controlled forms, so that a single capsule or a patch may provide smooth control over many days. In the meantime, proper use of what is available will control BP in virtually every hypertensive patient and whether new drugs will necessarily improve our ability to do so remains uncertain.

GENERAL GUIDELINES FOR DRUG CHOICES

We will put our current knowledge about the drugs available to treat hypertension into a useful clinical context, proceeding to considerations of the appropriate choices for multiple types of hypertensive patients.

As will become apparent, our past and current obsession of choosing the “best” drug for initial therapy is rapidly giving way to the realization that most patients require two or more drugs for adequate control. Now the search is for the “best” combinations.

Comparisons Between Drugs: Efficacy

The individual practitioner's choice of drug is often based on perceived differences in efficacy in lowering BP and the likelihood of side effects. In fact, overall antihypertensive efficacy varies little between the various available drugs. To gain FDA approval for marketing in the U.S., the drug must have been shown to be effective in reducing the BP in a large portion of the 1,500 or more patients given the drug during its clinical investigation and to have equal efficacy as currently available drugs. Moreover, the dose and formulation of drug are chosen so as not to lower the BP too much or too fast, to avoid hypotensive side effects. Virtually, all oral drugs are designed to do the same thing: Lower the BP at least 10% in the majority of patients with mild to moderate hypertension and overall antihypertensive efficacy varies little between available drugs (Czernichow et al., 2011).

When comparisons between various drugs are made, they almost always come out close to one another. The best such comparison was performed in the TOMHS study (Neaton et al., 1993) with random allocation of five drugs (chlorthalidone, acebutolol, doxazosin, amlodipine, and enalapril), each given to almost 200 mild hypertensives, while another group took a placebo and all patients remained on a nutritional hygienic program. The overall antihypertensive efficacy of the five drugs over 4 years was virtually equal (Neaton et al., 1993).

Despite the fairly equal overall efficacy of various antihypertensive drugs, individual patients may vary considerably in their response to different drugs, often for no obvious reason (Senn, 2004). However, some of this variability can be accounted for by patient characteristics, including age and race. This was seen in a VA cooperative 1-year trial in which 1292 men were randomly given 1 of 6 drugs from each major class: Overall, the CCB was most effective, but the ACEI was best in younger whites, and the β -blocker was best in older whites (Materson et al., 1993; 1995). Similarly, in a randomized crossover trial of elderly patients with isolated systolic hypertension given a representative of four major classes—ACEI, β -blocker,

CCB, and diuretic—each for 1 month, the diuretics and CCB were more effective than the β -blocker or ACEI (Morgan et al., 2001). In similarly designed trials of younger patients with combined systolic and diastolic hypertension, the ACEI and β -blocker were more effective than the CCB or diuretic (Deary et al., 2002; Dickerson et al., 1999). These different effects, which are at least partly related to the level of renin–angiotensin activity, resulted in the AB/CD concept used in the British NICE guidelines (Fig. 7-12).

Comparisons Between Drugs: Reductions in Morbidity and Mortality

The critical issue is not efficacy in lowering BP but rather effectiveness in reducing morbidity and mortality. In virtually every large RCTs, the benefits reflect not the type of drug, but its efficacy in lowering BP. Confirmation of this conclusion was shown in an analysis of data from 32 RCTs examining the relationship between BP change and the risk ratio according to various levels of SBP (Czernichow et al., 2012) (Fig. 7-13). Nonetheless, there are some differences in the ability of certain drugs to protect against certain outcomes. These include the following:

- Traditional β -blockers, in particular atenolol, have provided 16% less protection against stroke than other classes despite equal antihypertensive effects (Lindholm et al., 2005).

- β -Blockers are 14% more effective in preventing recurrent coronary events for a few years after an MI (Law et al., 2009).
- CCBs have an 9% greater protection against stroke (Law et al., 2009) (Fig. 7-14).

Prevention of dementia has been claimed to be better with either diuretics or CCBs than with ACEIs or ARBs (Staessen et al., 2011), but not by others (Li et al., 2010; Chiu et al., 2014).

Which drug is best is less relevant as the need to use more than one drug in the majority of hypertensives has also become obvious. Therefore, the best combination of agents has become the object of most recent trials.

Comparisons Between Drugs: Adverse Effects

As to the issue of differences in adverse effects among different agents, two points are obvious: First, no drug that causes dangerous adverse effects beyond a rare idiosyncratic reaction when given in usual doses will remain on the market, even if it slips by the approval process, as witnessed by the CCB mibefradil. Second, drugs that cause frequent bothersome although not dangerous adverse effects, such as guanethidine, will likely no longer be used now that so many other choices are available.

The various antihypertensive agents vary significantly, both in the frequency of adverse effects and, to an

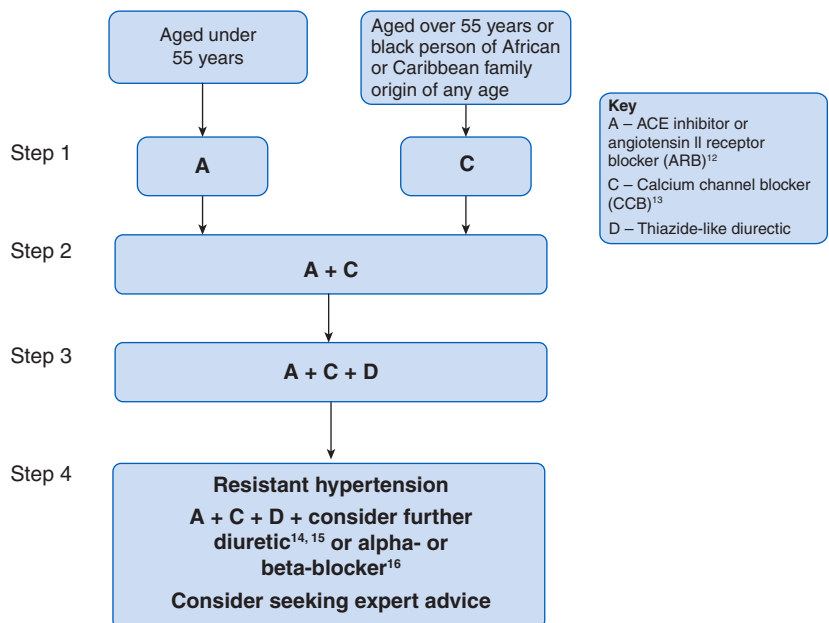


FIGURE 7-12 • The algorithm for antihypertensive drug therapy of the U.K. National Institute for Clinical Excellence. (From National Institute for Clinical Excellence (NICE). *Hypertension: Clinical Management of Primary Hypertension in Adults*. London: National Clinical Guideline Centre (NCGC): (clinical guidelines 127); 2011.)

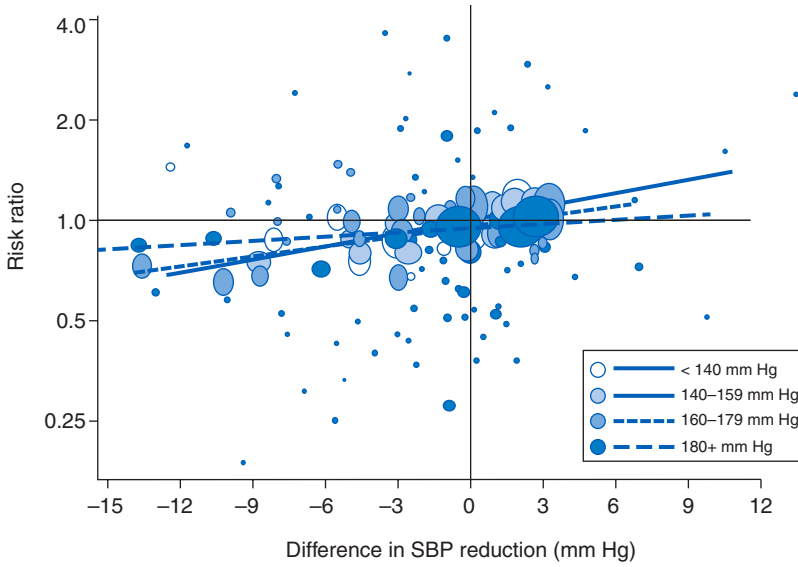
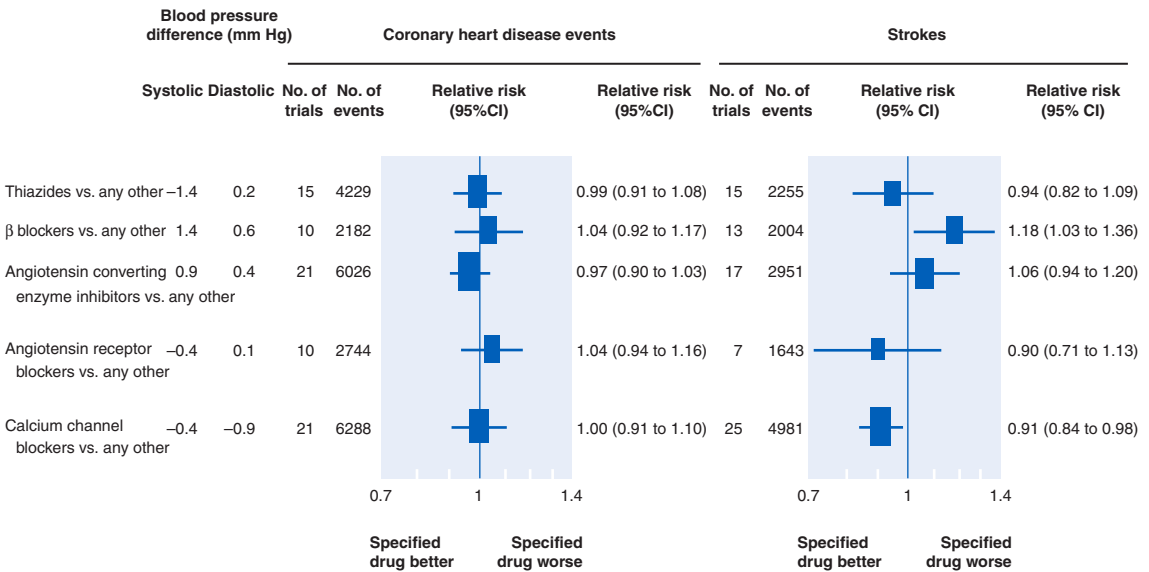


FIGURE 7-13 • Association between changes in SBP and reduction of risk ratio of total cardiovascular events. The area of circle is proportional to the inverse variance of the log odds ratio. (Adapted from Czernichow S, Zanchetti A, Turnbull F, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: Meta-analysis of randomized trials. *J Hypertens* 2011;29:4-16.)

even greater degree, in their nature. The only currently available comparisons of a representative drug from all major classes given as monotherapy to sizable numbers of patients are TOMHS (Neaton et al., 1993) and the VA Cooperative Study (Materson et al., 1993; 1995). Side

effects differed between the drugs, but no one drug was markedly more or less acceptable than the others. The differences may include sexual dysfunction. Impotence was twice as common in men in the TOMHS study given the diuretic chlorthalidone than in those given a



Relative risk estimates of coronary heart disease events and stroke in 46 drug comparison trials comparing each of the five classes of blood pressure lowering drug with any other class of drug (excluding CHD events in trials of β blockers in people with a history of coronary heart disease; see web extra figures 4a-j for individual trial results and summary estimates)

FIGURE 7-14 • Relative risk estimate of coronary heart disease and stroke in 46 drug comparison trials comparing each of the 5 major classes of antihypertensive drug with any other class. (Adapted from Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: Metaanalysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009;338:b1665.)

placebo, whereas less impotence was seen among those given the α -blocker doxazosin (Grimm et al., 1997).

Neither ARBs nor DRIs were available for those previous trials, but equivalence in antihypertensive effect has been seen when one of them was compared against another (Oparil et al., 2007).

Quality of Life

A number of studies have examined the side effects of antihypertensive agents on QOL using various questionnaires and scales. The results show that, although 10% to 20% of patients will experience bothersome adverse effects from most antihypertensive drug (ARBs and DRIs not included), the overall impact of therapies on QOL over 2 to 6 months of observation is positive (Weir et al., 1996; Wiklund et al., 1999). However, in a cross-sectional observational study of 1,858 subjects, 34% hypertensive and 38% on no antihypertensive drug, Trevisol et al. (2012) found a reduced QOL among the treated subjects using a short-form survey with 8 components.

The most important component of QOL is cognitive function. The best available evidence for the ability to delay dementia remains the Syst-Eur trial, which found that CCB-based therapy reduced the incidence by 55% over a mean follow-up of 3.9 years (Forette et al., 2002).

Apparent Intolerance to All Drugs

Some patients have adverse effects from every drug they take, often bringing to the office a long list of what they have been unable to tolerate. In a few, this may reflect successful reduction in BP below the threshold of cerebral autoregulation by usual doses of drugs so that the

patient appears to be intolerant to all medications. Some of these highly susceptible patients can be treated with very small doses of an appropriate agent, because they may be to the far left of the curve of responsiveness. More likely, such patients have psychological morbidity that sometimes can respond to behavioral cognitive therapy or antidepressants (Davies et al., 2003).

Serious Side Effects

In addition to these QOL issues, more serious problems have been blamed on various classes of antihypertensive drugs. Virtually, all these claims have come from noncontrolled, often retrospective, observational case-control studies, and all of them have been subsequently proved to be wrong (Table 7-9).

On the other hand, there may be an association between diuretic use and cancers arising in renal cells (Corrao et al., 2007), but these claims must all be balanced against the multiple observations that the rates of renal cell cancer are increased among untreated hypertensives as well (Colt et al., 2011).

Dose-Response Relationships

Need to Avoid Overdosing

Beyond the individual variabilities in response to drugs, there is a more generalized problem with the use of antihypertensive agents: They often are prescribed in doses that are too high. The problem of overdosing has been obvious with virtually every new drug introduced, wherein the initial recommended doses have been gradually reduced because, after widespread clinical experience, they proved to be too high. The obvious solution to this problem is for practitioners to start patients with doses that will not be

TABLE 7-9

Associations of Serious Adverse Effects with Antihypertensive Drugs

Drug	Adverse Effect	Claim	Refutation
Reserpine CCBs	Breast cancer MI	Armstrong et al. (1974) Furberg et al. (1995)	Horwitz and Feinstein (1985) Blood Pressure Lowering Treatment Trialists' Collaboration (2003)
CCBs ARBs ARBs	Cancer MI Cancer	Pahor et al. (1996) Verma and Strauss (2004) Sipahi et al. (2010)	Kizer and Kimmel (2001) Bangalore et al. (2011b) Bangalore et al. (2011a)

fully effective and to titrate the dose gradually to the desired response.

Need to Lower the Pressure Gradually

While it may be true that more rapid reduction in BP is needed to protect high-risk hypertensives as seen in the VALUE trial (Julius et al., 2004), the “quick fix” is inappropriate for most patients, who are at low to moderate risk. In a large trial with an ACEI, slower dose escalation (every 6 weeks) was shown to provide higher BP control rates and fewer serious adverse events than more rapid escalation (every 2 weeks) (Flack et al., 2000). These results are in keeping with what is known about the autoregulation of CBF supporting the need for a slow and gradual fall in BP to maintain blood flow to the brain. Normally, CBF remains relatively constant at approximately 50 mL/min/100 g of the brain (Strandgaard & Paulson, 1996). When the systemic BP falls, the vessels dilate; when the BP rises, the vessels constrict. The limits of cerebral autoregulation in normal people are between mean arterial BPs of about 60 and 120 mm Hg (e.g., 80/50 to 160/100 mm Hg) (Strandgaard & Haunsø, 1987).

In hypertensives without neurologic deficits, the CBF is not different from that found in normotensives (Eames et al., 2003). This constancy of the CBF reflects a shift in the range of autoregulation to the right to a range of mean BP from approximately 100 to 180 mm Hg (e.g., 130/85 to 240/150 mm Hg). As seen in Figure 7-15, this shift maintains a normal CBF despite the higher BP but makes the hypertensive vulnerable to cerebral ischemia when the BP falls to a level that is well tolerated by normotensives.

Note that the lower limit of autoregulation capable of preserving CBF in hypertensive patients shown in Figure 7-15 is at a mean BP of nearly 110 mm Hg. Thus, acutely lowering the BP from 160/100 mm Hg (mean, 127 mm Hg) to 140/85 mm Hg (mean, 102 mm Hg) may induce cerebral hypoperfusion, although hypotension in the usual sense has not been induced. This likely explains why many elderly patients experience manifestations of cerebral hypoperfusion (weakness, easy fatigability, and postural dizziness) at the start of antihypertensive therapy, even though BP levels do not seem inordinately low (Muller et al., 2014).

Fortunately, with slow and effective control of the BP by medication, the curve drifts back toward normal, explaining the eventual ability of hypertensive patients to tolerate falls in BP to levels that initially produced symptoms of cerebral ischemia. In a study of hypertensives over age 70 treated for 12 weeks, reduction of SBP to less than 140 mm Hg resulted in increases of CBF determined by 3-T arterial spin labeling MRI (Tryambake et al., 2013).

Need for 24-Hour Coverage

As noted in Chapter 2, self-recorded measurements and ambulatory automatic BPM are being increasingly used to ensure the 24-hour duration of action of anti-hypertensive agents. This is particularly critical with the increasing use of once-a-day medications that often do not provide 24-hour efficacy (Lacourcière et al., 2000). Therefore, the patient is exposed to the full impact of the early morning, abrupt rise in BP that is almost certainly involved in the increased incidence of various cardiovascular events immediately after arising (Munger & Kenney, 2000).

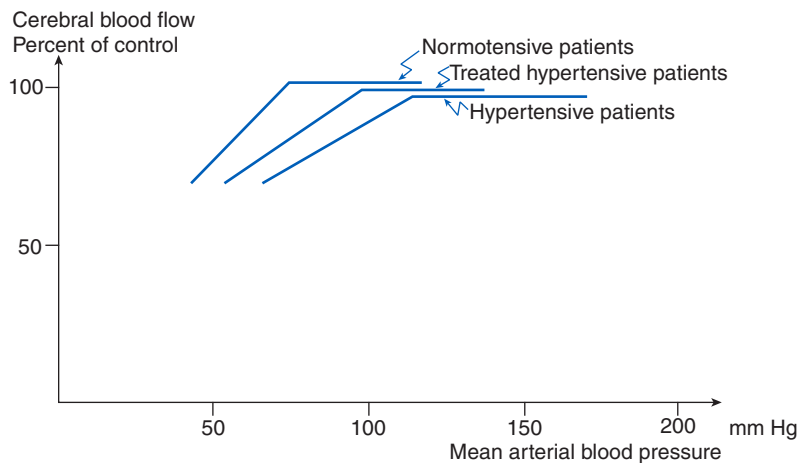


FIGURE 7-15 • Autoregulation of CBF. Mean CBF autoregulation curves from normotensive, severely hypertensive, and effectively treated hypertensive patients are shown. (Modified from Strandgaard S, Haunsø S. Why does antihypertensive treatment prevent stroke but not myocardial infarction? *Lancet* 1987;2:658–661.)

Although ambulatory automatic BPM is not available for most patients, self-recorded measurements with inexpensive semiautomatic devices should be possible for most, thereby ensuring the adequacy of control throughout the waking hours—particularly the early morning hours. As noted earlier, this may require taking medications in the evening or bedtime rather than the usually recommended early a.m.

Value of Greater than 24-Hour Efficacy

Drugs that continue to work beyond 24 hours are even more attractive to prevent loss of control in the considerable number of patients who skip a dose at least once weekly, as documented in 30% or more of patients with hypertension (Rudd, 1995). Among those currently available drugs that likely will maintain good efficacy on a missed day are the diuretic chlorthalidone, the CCB amlodipine, the ACEIs perindopril and trandolapril, and the ARB telmisartan (Lacourcière et al., 2004). In the study shown in Figure 7-16, when the daily doses of the two ARBs were purposely missed, telmisartan maintained its full effect for the 24 hours, valsartan did not.

CHOICE OF DRUGS: FIRST, SECOND, AND BEYOND

Now that the effectiveness and safety of various anti-hypertensive agents have been compared and important pharmacologic considerations have been emphasized, we will turn to the practical issue of which of the many drugs now available (Table 7-10) should be the first, second, or subsequent choices in

individual patients. As noted previously, the need for two or more drugs for most patients has made the choice of first drug less relevant.

Choice of First Drug

Comparative Trials

As noted earlier in this chapter, multiple RCTs have compared the long-term ability of six classes of antihypertensive drugs—diuretics, β -blockers, α -blockers, ACEIs, ARBs, and CCBs—to protect patients from overall and cardiovascular morbidity and mortality, the only meaningful criterion. Only in a few trials are the differences in outcome significant and, for the most of these, the differences are attributed to differences in BP reduction (Law et al., 2009) (see Fig. 7-14).

Expert Committee Recommendations

In the 2003 JNC-7 algorithm, a diuretic was recommended if there were no specific indications for another type of drug (Chobanian et al., 2003). Until now, HCT in doses of 12.5 to 25 mg has been the overwhelming choice and in the U.S. is the diuretic combined with various other classes with the exceptions of atenolol and azilsartan, which are available with chlorthalidone. However, HCT in these doses has not been shown to reduce morbidity or mortality whereas chlorthalidone, 12.5 to 25 mg, has been the diuretic in the NIH-sponsored trials (MRFIT, SHEP, ALLHAT) that have shown benefit so chlorthalidone is increasingly being recommended to be the appropriate diuretic (Ernst et al., 2009; Messerli & Bangalore, 2009).

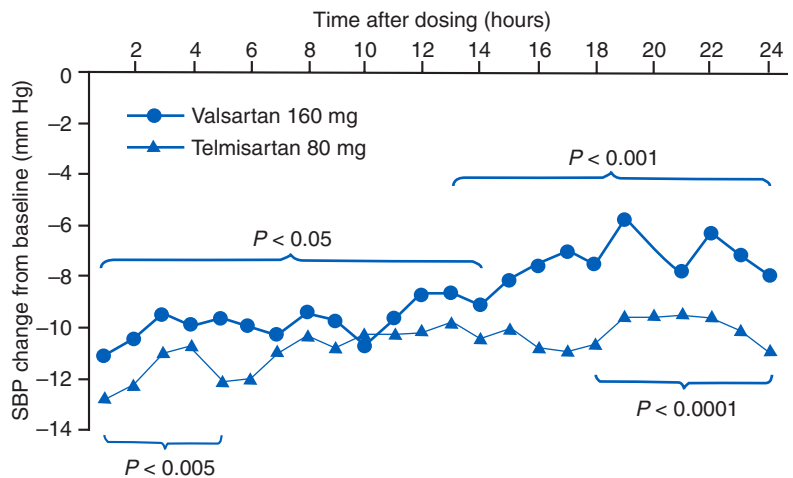


FIGURE 7-16 • Changes in SBP control in the 24 hours after a missed dose of telmisartan 80 mg or valsartan 160 mg in patients with mild-to-moderate hypertension. SBP, systolic blood pressure. (Reproduced from McInnes G. 24-Hour powerful blood pressure-lowering: Is there a clinical need? *J Am Soc Hypertens* 2008;2:S16–S22.)

P values are for telmisartan versus valsartan comparison

TABLE 7-10

Oral Antihypertensive Drugs Available in the U.S. (as of 2013)

Diuretics	Adrenergic Inhibitors		Vasodilators	
Thiazides	Peripheral	β-Blockers	Direct	ACEIs
Hydrochlorothiazide	Guanadrel	Acebutolol	Hydralazine	Benazepril
Nonthiazides	Guanethidine	Atenolol	Minoxidil	Captopril
Chlorthalidone	Reserpine	Bisoprolol	Calcium Channel Blockers	Enalapril
Indapamide	Central α_2-agonists	*Carvedilol	Dihydropyridine	Fosinopril
Metolazone	Clonidine	Carteolol	Amlodipine	Moexipril
Loop diuretics	Guanabenz	*Labetalol	Felodipine	Lisinopril
Bumetanide	Guanfacine	Metoprolol	Nicardipine	Perindopril
Furosemide	Methyldopa	Nadolol	Nifedipine	Quinapril
Torsemide	α_1-Blockers	*Nebivolol	Nisoldipine	Ramipril
Nonsulfonamide	Doxazosin	Pindolol	Non-dihydropyridine	Trandolapril
Ethacrynic acid	Prazosin	Penbutolol	Diltiazem	All receptor blockers
Potassium sparingers	Terazosin	Timolol	Verapamil	Azilsartan
Amiloride				Candesartan
Triamterene				Eprosartan
Aldosterone blockers				Irbesartan
Eplerenone				Losartan
Spironolactone				Olmesartan
				Telmisartan
				Valsartan

*Vasodilating

Other recent expert guidelines take different approaches:

- The British National Institute for Clinical Excellence (2011) recommends that the choice be based on age and race, the A/CD algorithm shown in Figure 7-12.
- The 2013 guidelines of the European Society of Hypertension and European Society of Cardiology (ESH/ESC) give no specific choices for initial or subsequent use, stating “It is obvious that any all-purpose ranking of drugs for general usage is not evidence-based” (Mancia et al., 2013). However, the ESH/ESC guidelines indicate different preferences for various specific indications (Table 7-11) and either compelling or possible contraindications for the use of various classes (Table 7-12).
- The 2014 American Society of Hypertension and International Society of Hypertension (ASH/ISH) guidelines recommend an ACEI or ARB for nonblack patients under age 60 and either a diuretic or CCB for blacks and nonblacks over age 60 (Weber et al., 2014).

Once-Daily Therapy

One point agreed upon by all expert guidelines is the need for long-acting, once-a-day therapy. Choices that are either inherently or artificially long acting are

available in every category. Some may reduce the early morning surge of BP if taken in the evening or at bedtime. That requires home BP monitoring which, hopefully, will be done by more and more patients.

Compelling Indications and Contraindications

Another point of agreement is the need for certain drugs for those compelling indications which have shown to respond better to them as listed in Table 7-11. In addition, a number of certain and possible contraindications are listed in Table 7-12.

Other Factors

Characteristics of the Patient

Individual patient's characteristics may affect the likelihood of a good response to various classes of drugs. As shown in crossover rotations of the four major classes (Deary et al., 2002; Dickerson et al., 1999; Morgan et al., 2001), younger, white patients will usually respond better to either an ACEI/ARB or a β -blocker, perhaps because they tend to have higher renin levels, whereas older and black patients will respond better to diuretics and CCBs, perhaps because they have lower

TABLE 7-11

Drugs to be Preferred in Specific Conditions

Condition	Drug
<i>Asymptomatic organ damage</i>	
LVH	ACE inhibitor, calcium antagonist, ARB
Asymptomatic atherosclerosis	Calcium antagonist, ACE inhibitor
Microalbuminuria	ACE inhibitor, ARB
Renal dysfunction	ACE inhibitor, ARB
<i>Clinical CV event</i>	
Previous stroke	Any agent effectively lowering BP
Previous MI	BB, ACE inhibitor, ARB
Angina pectoris	BB, calcium antagonist
Heart failure	Diuretic, BB, ACE inhibitor, ARB, mineralocorticoid receptor antagonists
Aortic aneurysm	BB
AF, prevention	Consider ARB, ACE inhibitor, BB, or mineralocorticoid receptor antagonist
AF, ventricular rate control	BB, non-DHP calcium antagonist
ESRD/proteinuria	ACE inhibitor, ARB
Peripheral artery disease	ACE inhibitor, calcium antagonist
<i>Other</i>	
ISH (elderly)	Diuretic, calcium antagonist
Metabolic syndrome	ACE inhibitor, ARB, calcium antagonist
Diabetes mellitus	ACE inhibitor, ARB
Pregnancy	Methyldopa, BB, calcium antagonist
Blacks	Diuretic, calcium antagonist

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, β -blocker; BP, blood pressure; CV, cardiovascular; ESRD, end-stage renal disease; ISH, isolated systolic hypertension; LVH, left ventricular hypertrophy.

renin levels. These differences are the basis for the formulations in the guidelines of both the NICE (NICE, 2011) and ASH/ISH (Weber et al., 2014).

Characteristics of the Drug

The six major classes differ in their characteristics that play a role in their advantages and disadvantages. Some agents—such as the direct-acting smooth muscle vasodilators, central α_2 -agonists, and peripheral-acting adrenergic antagonists—are not well suited for initial

monotherapy because they produce annoying adverse effects in a large number of patients. However, as repeatedly documented, if they effectively lower BP, all drugs provide protection from cardiovascular events.

Cost of the Drug

There is clear evidence of an overall cost-effectiveness of the treatment of hypertension, as reviewed in Chapter 1. Fortunately, there is now at least one member of each class available as a low-cost generic.

Combinations as Initial Therapy

Another possible way to reduce the costs of antihypertensive care is to use those combination tablets that cost less than their separate ingredients.

All recent guidelines recognize that most patients will end up on two or more drugs to achieve adequate control, and they recommend two drugs for initial therapy of patients with BP greater than 160/100 mm Hg. Therefore, the idea of starting with two drugs in all patients is gaining currency (Gradman et al., 2013; Thom et al., 2013). A number of combination tablets are available, mostly of a low dose of the diuretic HCT with a β -blocker or RAS blocker. More and more combinations of one of these RAS-suppressing drugs with a CCB are appearing, particularly with amlodipine that is now generic.

One combination particularly favored by nephrologists to reduce proteinuria has been an ACEI + ARB. This advantage, however, was negated by the results of multiple trials where an ACEI + ARB was associated with more hypotension and worse major renal outcomes than seen with either the ACEI or ARB alone (Mann et al., 2008; Rajagopalan et al., 2013).

Choice of Second Drug

If a moderate dose of the first choice is well tolerated and effective but not enough to bring the BP down to the desired level, a second drug can be added, and thereby control will likely be better achieved than by increasing the dose of the first drug (Kim-Mitsuyama et al., 2013; Wald et al., 2009).

Choice of Third or Fourth Drug

Various combinations usually work. The key, as with two drugs, is to combine agents with different mechanisms of action. The most rational is a diuretic, an ACEI or ARB, and a CCB.

TABLE 7-12

Compelling Contraindications and Possible Contraindications

Drugs	Compelling	Possible
Diuretics (thiazides)	Gout	Metabolic syndrome Glucose intolerance Pregnancy Hypercalcemia Hypokalaemia
β -Blockers	Asthma A-V block (grade 2 or 3)	Metabolic syndrome Glucose intolerance Physically active patients Chronic obstructive pulmonary disease (except for vasodilating β -blockers) Tachyarrhythmia, heart failure
CCBs (DHPs) CCBs (verapamil, diltiazem)	A-V block (grade 2 or 3) Severe LV dysfunction Heart failure	
ACE inhibitors	Pregnancy, angioneurotic edema hyperkalaemia bilateral renal artery stenosis	Women with childbearing potential
ARBs	Pregnancy, hyperkalaemia bilateral renal artery stenosis	Women with childbearing potential
Mineralocorticoid receptor blockers	Acute or severe renal failure (eGFR <30 mL/min) hyperkalaemia	

Few patients should need more than three drugs, particularly if the various reasons for resistance to therapy are considered. In the ASCOT trial, either an α -blocker or spironolactone was chosen (Chapman et al., 2007; 2008).

Reduction or Discontinuation of Therapy

Once a good response has occurred and has been maintained for a year or longer, medications may be reduced or discontinued. However, in a closely monitored group of over 6,200 hypertensives who had been successfully controlled, only 18% were able to remain normotensive after stopping therapy (Nelson et al., 2003). The characteristics that make withdrawal more likely to be successful were lower levels of BP before and after therapy, fewer and lower doses of medication needed to control hypertension, and patient's willingness to follow lifestyle modifications.

Whether it is worth the trouble to stop successful drug therapy completely is questionable. The more sensible approach in well-controlled patients would be first to decrease the dose of whatever is being used.

If this succeeds, withdrawal may be attempted with continued close surveillance of the BP.

RESISTANT HYPERTENSION

Causes

As many as 15% of adult hypertensives will not be controlled to a BP less than 140/90 mm Hg with three drugs, i.e., they are resistant (Vemulapalli et al., 2014). The reasons are numerous (Table 7-13). The first need is to establish the presence of resistance by out-of-office BP readings, since as many as half above 140/90 mm Hg in the office may actually be controlled by home or ambulatory BP readings (Fadal Elmula et al., 2013; Verloop et al., 2013).

An appropriate diagnostic and therapeutic approach to resistant hypertension is shown in Figure 7-17 as published by Calhoun et al. (2008). The most likely cause of true resistance is volume overload caused by excessive sodium intake, inadequate diuretic (Graves, 2000), or higher-than-expected aldosterone levels (Gaddam et al., 2008). Resistance is found more often in those who are elderly, obese,

TABLE 7-13

Causes of Inadequate Responsiveness to Therapy

Pseudoresistance
White coat or office elevations
Pseudohypertension in the elderly
Nonadherence to therapy
Drug-related causes
Doses too low
Inappropriate combinations
Rapid inactivation (e.g., hydralazine)
Drug actions and interactions
NSAIDs
Sympathomimetics
Nasal decongestants
Appetite suppressants
Cocaine and other street drugs
Caffeine
Oral contraceptives
Adrenal steroids
Licorice (as may be found in chewing tobacco)
Cyclosporine, tacrolimus
Erythropoietin
Associated conditions
Smoking
Obesity
Sleep apnea
Insulin resistance or hyperinsulinemia
Ethanol intake >1 oz a day
Anxiety-induced hyperventilation or panic attacks
Chronic pain
Intense vasoconstriction (Raynaud phenomenon, arteritis)
Identifiable causes of hypertension
Volume overload
Excess sodium intake
Progressive renal damage (nephrosclerosis)
Fluid retention from reduction of BP
Inadequate diuretic therapy

diabetic, black, or women and those with renal dysfunction (Egan et al., 2013).

Nonadherence to Therapy

Often patients do not take their medications because they cannot afford them and because they have no access to consistent and continuous primary care. As noted earlier in this chapter, there are ways to simplify the regimen and improve access. Recall as well the evidence that patients may appear to be resistant only because their physicians simply do not keep increasing their therapy (Daugherty et al., 2012).

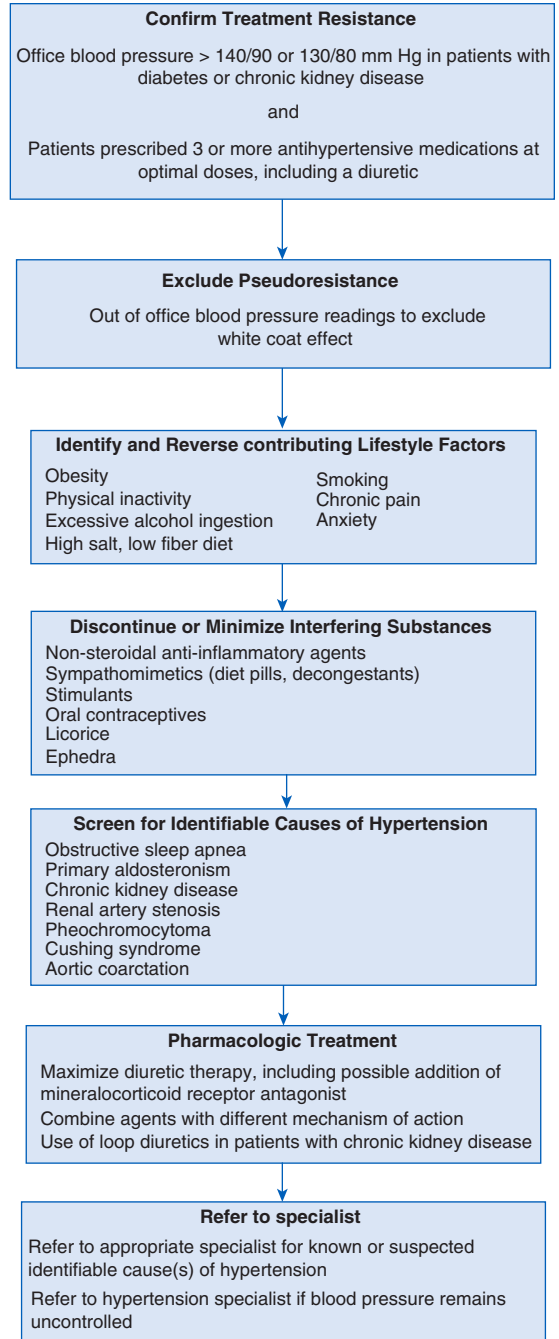


FIGURE 7-17 • Diagnosis and management of patients with resistant hypertension. (Adapted from Calhoun DA, Jones C, Textor S, et al. Resistant hypertension: Diagnosis, evaluation, and treatment. *Hypertension* 2008;51:1403–1419.)

Nonadherence may require assays of the prescribed drugs in blood (Brinker et al., 2014; Strauch et al., 2013) or urine (Jung et al., 2013).

Drug-Related Causes

In a survey of 1,377 hypertensives over 9 months, 75% had some potential interaction with their antihypertensive drugs, and in 35%, the interaction was considered highly significant (Carter et al., 2004).

The most common of these in the U.S. is likely the interference with the antihypertensive effect of virtually all agents save CCBs by NSAIDs. This effect likely involves inhibition of the cyclooxygenase-2 (COX-2) enzyme in the kidneys, thereby reducing sodium excretion and increasing intravascular volume (White, 2007). All NSAIDs must block COX-2 to reduce inflammation and pain and therefore all may raise BP (Warner & Mitchell, 2008). Large doses of aspirin also pose a problem but 80 mg a day does not (Zanchetti et al., 2002).

With the widespread use of herbal remedies, which in the U.S. are totally unregulated, a number of herb–drug interactions are seen. More about such interactions that can raise BP is provided in Chapter 14.

Associated Conditions

Nicotine transiently raises BP, but the effect is often not recognized because the BP is almost always taken in a no-smoking environment. The combination of abdominal and generalized obesity, insulin resistance, and sleep apnea is an increasingly common cause of resistant hypertension (Vongpatanasin, 2014).

Identifiable Causes of Hypertension

These are covered in Chapters 9 through 15. Recently, a possibly much higher prevalence of primary aldosteronism than previously recognized has been reported, and the presence of a low plasma renin level in a resistant hypertensive can be the tip-off for the condition (Calhoun et al., 2008).

Treatment

The need for adequate diuretic is obvious and may require the sequential addition of a loop diuretic or amiloride (Bobrie et al., 2012). The need for blockade of high or even “normal” levels of aldosterone, whether or not associated with autonomous hypersecretion, has become increasingly documented by impressive relief of resistance with even low doses of spironolactone (Chapman et al., 2007) or eplerenone (Jansen et al., 2013) even in patients with renal impairment

(Pisoni et al., 2012). The potent vasodilator, minoxidil, may work when nothing else does (Black et al., 2007).

Two invasive procedures are being tested: An implantable electric activation of the carotid baroreflex (Scheffers et al., 2008) and catheter-based renal sympathetic nerve denervation (Krum et al., 2009). The widely expected success of renal nerve denervation was not documented in the large SYMPPLICITY HTN-3 trial (Bhatt et al., 2014). However, Krum et al. (2014) reported excellent control of 88 patients with resistant hypertension at 3 years follow-up with a mean fall in office BP of 32/14 mm Hg and the only serious adverse effect of renal artery stenosis in one patient. Therefore, some patients appear to respond to renal nerve denervation, but there is no way now known to ascertain their responsiveness. Carotid baroreflex activation works (Bisognano et al., 2011) but remains unapproved.

A careful search of the cause(s) and appropriate antihypertensive therapy can usually correct resistance (Fadl Elmula et al., 2014) but 9.5% of resistant hypertensive patients managed in a specialist clinic remained resistant despite the prescription of six or more drugs (Acelajado et al., 2012).

SPECIAL CONSIDERATIONS IN THE CHOICE OF THERAPY

Children are covered in Chapter 16; women who are pregnant or on estrogens are covered in Chapter 15.

Women

After menopause, hypertension becomes more common in women, likely related to increased sympathetic nervous activity (Barnes et al., 2014), and with longer life span, more women develop isolated systolic hypertension. In the U.S., women who are hypertensive are more likely to be treated and more likely to achieve good control (Go et al., 2014). Compared to men, women have been found to have less regression of LVH on equivalent antihypertensive therapy (Okin et al., 2008) and more chronic renal disease (Muesan et al., 2012). Moreover in the Second Australian National Blood Pressure Study, women randomly assigned to an ACEI derived no reduction in the hazard ratio for cardiovascular events or mortality, whereas the men on an ACEI had a 17% reduction in hazard despite equal and substantial reductions of BP

in both groups (Wing et al., 2003) whereas in the ALLHAT trial, women achieved equal benefit from chlorthalidone-based therapy as did men (Oparil et al., 2013).

Blacks and Other Ethnic Groups

As noted in Chapter 4, black hypertensives have many distinguishing characteristics, some of which could affect their responses to antihypertensive therapy. As a consequence of these factors, blacks in the U.S. have higher rates of hypertension and are less well controlled than other racial groups. However, when they achieve adequate control, blacks usually respond as whites do and experience similar reductions in the incidences of cardiovascular disease as do whites (Brewster et al., 2004).

Blacks respond less well to monotherapy with drugs that suppress the angiotensin–renin system, i.e., β -blockers, ARBs, ACEIs, and DRIs perhaps because they tend to have lower renin levels (Nguyen et al., 2014), and equally as well to diuretics and CCBs (Wright Jr et al., 2005).

Nonetheless, blacks should not be denied β -blockers, ARBs, or ACEIs if special indications for their use are present. Moreover, their response to these drugs is equalized by addition of a diuretic (Libhaber et al., 2004).

There is no good evidence that Hispanics, Asians, or other ethnic groups differ from Whites in their responses to various antihypertensive agents. There are ethnic differences in side effects: Asians have a higher incidence of ACEI-induced cough, and Blacks more ACEI-induced angioedema (Makani et al., 2012).

Elderly Patients

The majority of people over age 65 have hypertension; in most, the hypertension is predominantly or purely systolic because of arterial stiffness. As described in Chapter 4, the risks for such patients are significant. As detailed in Chapter 5, the benefits of treating hypertension in the elderly have been documented. Now that such evidence is available, many more elderly hypertensives will be brought into active therapy with the hope that debilitating morbidities will be reduced, possibly including dementia (Gorelick and Nyenhuis, 2012). At present, only a minority of elderly patients with systolic hypertension are being adequately treated (Go et al., 2014).

The heightened enthusiasm for treating the elderly comes in large part from the results of the HYVET (Beckett et al., 2008). In HYVET, 3,845 subjects over age 80 (mean age 84) were allocated to placebo on therapy starting with the diuretic indapamide and adding the ACEI perindopril if the target BP of less than 150/80 mm Hg was not reached. It should be noted that only 33% of these subjects had isolated systolic hypertension, with the overall mean BP of 173/91 mm Hg. Moreover, they were healthier than most 80-plus-year-old hypertensives with only 12% having had a prior cardiovascular event. Therefore, application of the HYVET results to the overall elderly hypertensive population may be inappropriate.

Nonetheless, the results of HYVET are impressive. After only 2 years, total mortality was reduced by 21%, stroke by 30%, and heart failure by 64% in those on active therapy.

Before beginning drug therapy, the evidence described in Chapter 2 showing that white-coat hypertension is even more common in the elderly than in younger patients should be remembered (Franklin et al., 2012; Pickering, 2004). Therefore, before making the diagnosis, out-of-office readings should be obtained, if possible.

Regardless of age, as long as the patient appears to have a reasonable life expectancy, active therapy is appropriate for all who have a systolic level above 160 mm Hg, with or without an elevated diastolic pressure. No published RCTs have involved elderly patients with SBP between 140 and 160 mm Hg so the decision to treat should be based on overall risk. Those at high risk (e.g., diabetics or smokers) should be started on therapy at systolic levels above 140 mm Hg.

Table 7-14 lists factors often present in the elderly that may complicate their therapy. Because the elderly may have sluggish baroreceptor and sympathetic nervous responsiveness as well as impaired cerebral autoregulation, therapy should be gentle and gradual, avoiding drugs that are likely to cause postural hypotension. Nonetheless, treatment should not be delayed if it is indicated, since the elderly are inherently at greater risk for cardiovascular diseases (Odden et al., 2011).

Lifestyle Modifications

Before beginning drug therapy, the multiple benefits of nondrug therapies that were described in Chapter 6 should also be remembered. The ability of lifestyle changes to lower BP in the elderly has been well documented (Pickering, 2004). In particular, dietary

TABLE 7-14

Factors that Might Contribute to Complications from Pharmacologic Treatment of Hypertension in the Elderly

Factors	Potential Complications
Diminished baroreceptor activity	Orthostatic hypotension
Impaired cerebral autoregulation	Cerebral ischemia with small falls in systolic pressure
Decreased intravascular volume	Orthostatic hypotension
Sensitivity to hypokalemia	Volume depletion, hyponatremia
Decreased renal and hepatic function	Arrhythmia, muscular weakness
Polypharmacy	Drug accumulation
CNS changes	Drug interaction
	Depression, confusion

sodium should be moderately restricted down to 100 to 120 mmol/day because the pressor effect of sodium excess and the antihypertensive efficacy of sodium restriction progressively increase with age (Geleijnse et al., 1994; Weinberger & Fineberg, 1991). However, the elderly may have at least two additional hurdles to overcome in achieving this goal: First, their taste sensitivity may be lessened, so they may ingest more sodium to compensate; and second, they may depend more on processed, prepackaged foods that are high in sodium rather than fresh foods that are low in sodium.

Postural and Postprandial Hypotension

Defined as a fall in BP of either 20 mm Hg systolic or 10 mm Hg diastolic upon unsupported standing from the supine position, postural or orthostatic hypotension is found in 10% to 30% of ambulatory hypertensives over age 60 and as many as 60% of those hospitalized (Feldstein & Weder, 2012). It is often associated with postprandial hypotension by splanchnic pooling, best documented by home BP monitoring (Barochiner et al., 2014). It is more common in diabetics and is a marker of increased mortality. As noted in Figure 7-18, numerous causes may be responsible, including arterial stiffness and baroreceptor insensitivity (Mattace-Rasso et al., 2007). Postural hypotension is often accompanied with supine hypertension, may be delayed beyond 10 minutes on standing, and is a component of more severe syndromes of autonomic failure (Shibao et al., 2013).

Postural hypotension must be recognized before antihypertensive therapy is begun to avoid traumatic falls when the BP is lowered further (Butt et al., 2012).

Fortunately, the physical therapies listed in Figure 7-18 can usually manage the problem but various medications have been tried with limited success, including the sodium-retaining fludrocortisone and the sympathomimetic midodrine (Freeman, 2008). Okamoto et al. (2012) have shown benefit with a combination of a NE transport blocker and yohimbine, an α -2 antagonist.

Choice of Drugs for the Elderly

Most recent guidelines recommend a diuretic or CCB as initial therapy of the elderly. However, a meta-analysis of the results of 31 RCTs including over 190,000 patients showed equal and significant benefit from diuretics, CCBs, ACEIs, and ARBs in those younger than or in those older than age 65 (Blood Pressure Trialists, 2008). In an observational study, those elderly hypertensives given either HCT or chlorthalidone had equal reductions in both morbidity and mortality but those on chlorthalidone had more hypokalemia (Dhalla et al., 2013). Nitrates may lower SBP significantly (Stokes et al., 2005), but since they are generic, it is unlikely that a controlled trial of them will be done.

Therapy should begin with small doses and then should be slowly increased: Start low and go slow. Small doses may be fully effective. Even more so than in younger patients, the elderly do better with long-acting (once-daily), smoothly working agents since they may have trouble following complicated dosage schedules, reading the labels, and opening bottles with safety caps. Home BP recording may be particularly useful, first in overcoming the white-coat effect, which is quantitatively greater in the elderly, and

CAUSAL FACTOR	PATHOPHYSIOLOGY	THERAPY
Rapid rising	Pooling of blood in lower body	Slow rising, particularly from sleep
Vasodilation	Venous pooling Splanchnic pooling Sympatholytic drugs	Supportive panty hose Avoid large meals Avoid such agents
Volume depletion	Low cardiac output - diuretic - very low sodium intake	Maintain intravascular volume by avoiding over-diuresis and sleeping with head of bed elevated
Baroreflex dysfunction	Loss of normal vasoconstriction by sympathetic stimulation	Drinking 16 oz water before arising Various drugs: - sympathomimetics - volume expanders Isometric exercise
Cerebrovascular disease	Low cerebral perfusion	Avoid overtreatment of hypertension Correct dyslipidemia Stop smoking

FIGURE 7-18 • Summary of the pathophysiologic events that occur during the development of symptoms of postural hypotension (**middle column**) and the interaction of exacerbating factors (**left column**) and remedial measures (**right column**) with these events.

second, in ensuring that therapy is enough but not too much. The white-coat effect in the doctor's office may conceal considerable overtreatment.

Another feature of the effect of antihypertensive drugs—variability of the BP seen with their use—has been examined (Webb & Rothwell, 2011). In a prospective cohort study involving 5,461 patients with a mean age of 75.3 years, *greater* visit-to-visit variability of BP measured every 3 months in the office over an average 3.2 years was associated with *decreased* performance in a battery of tests of cognitive function (Sabayan et al., 2013). In a substudy of 553 of these patients, MRIs of the brain showed an association between greater BP variation and lower hippocampal volume and more cortical infarcts.

As noted in Chapter 2, CCBS and diuretics provide less variability of BP than other classes of drugs. Therefore, the lower risk of strokes seen in the meta-analysis of Law et al. (2009) shown in Figure 7-14 with diuretics and CCBs may reflect the less variability of the BP seen with their use (Wang et al., 2014).

Goal of Therapy

The question of how far to lower BP is covered in Chapter 5. Based on the limited evidence from properly performed RCTs, a goal of a SBP less than 150 mm Hg

was recommended for patients over age 60 in the report of members of the JNC-8 committee (James et al., 2014), but other recent guidelines recommend that goal only for patients over age 80, in large part because 150 mm Hg was the goal in the HYVET trial (Beckett et al., 2008).

Effect on Cognitive Decline and Dementia

There is evidence that lowering of BP with diuretic or CCB-based antihypertensive therapy will reduce the incidence of cognitive decline and dementia (Gorelick and Nyenhuis, 2012). However, no such benefit was seen in the HYVET trial over 2 years in patients 80 years or older (Peters et al., 2008).

Most of these trials, in particular HYVET, may have been too little, too late. There are experimental data supporting a neuroprotective effect of lowering BP in rats (Elewa et al., 2007) and data in humans showing plasticity of cerebral hemodynamics to preserve or improve CBF when BP is lowered (Tzeng et al., 2010). Therefore, the least that can now be said is that appropriate antihypertensive therapy will do no harm and may provide protection from cognitive decline.

Obesity and the Metabolic Syndrome

Visceral or abdominal obesity, easily identified by tape measurement of waist circumference, is associated with the metabolic syndrome, in particular with hypertension (Redon et al., 2008). With the marked increase in obesity worldwide, the syndrome will increase in prevalence, reaching down into childhood (Ogden et al., 2014) and up into the elderly (Sloan et al., 2008). In managing the hypertension, care must be taken not to worsen the other components of the syndrome.

Lifestyle Modifications

The major focus must be prevention of obesity. Failing that, weight loss and increased physical activity may work but, as noted in Chapter 6, significant long-term weight loss is very difficult to achieve so bariatric surgery is being increasingly used. Unfortunately, even with marked weight loss with such surgery, hypertension may not be relieved.

Antihypertensive Drug Therapy

High doses of diuretics and, even more, β -blockers should be avoided in those who are prone to develop or who have the metabolic syndrome (Messerli et al., 2008). The incidence of new-onset diabetes in multiple RCTs has been reduced significantly with therapy based on ACEIs, ARBs, and CCBs compared to therapy based on diuretics, β -blockers, or their combination (Aksnes et al., 2008). Unfortunately, even with intensive antihypertensive therapy, more obese subjects remain uncontrolled than nonobese subjects (Czernichow et al., 2012).

Diabetes

Diabetes markedly increases cardiovascular risk partly as a consequence of concomitant hypertension, and few hypertensive diabetics have both conditions adequately treated (Cummings et al., 2013).

Antihypertensive Drug Therapy

In an analysis of antihypertensive therapy in patients with type-2 diabetes, Reboldi et al. (2011) examined 31 trials including 73,913 patients. They found protection against stroke but not against heart attacks. One of the studies included in this meta-analysis was

the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (ACCORD Study Group, 2010). In this trial, 4733 type-2 diabetics were randomly assigned to either intensive therapy to reach a goal of SBP of less than 120 mm Hg or to standard therapy to reach a goal of less than 140 mm Hg. After 1 year, the intensively treated group had a mean BP of 119.3 mm Hg, the standard group, 133.5 mm Hg. Overall, there were no differences in mortality or cardiovascular events. The intensively treated had fewer strokes but no protection against dementia (Williamson et al., 2014). However, more serious adverse effects were seen among the intensively treated: 3.3% versus 1.3% in the standard group.

On the basis of these and other data (Sundstrom et al., 2013), the goal has been changed from less than 130/80 mm Hg to less than 140/85 in the ESH/ESC guidelines (Mancia et al., 2013) and to less than 140/90 in the AHA/ASH (Weber et al., 2014). All recent guidelines recommend an ACEI or ARB for initial therapy based on their superior effectiveness. In the ADVANCE trial, addition of a CCB to a combination of indapamide and perindopril reduced the relative risk of death from 5% down to 28% (Chalmers et al., 2014).

Lipid-Lowering Therapy

Diabetics have more atherogenic lipid patterns than nondiabetics (Sam et al., 2008), and a strong argument has been made for routine use of a statin in all diabetics regardless of lipid levels (Howard et al., 2008). In the Anglo-Scandinavian Outcomes Trial (ASCOT), a synergy was found between amlodipine and atorvastatin on reduction of nonfatal heart attacks and fatal cardiovascular diseases (Sever, 2012). Some of the benefit may have come from the small but statistically significant fall in BP seen with statin drugs (Briasoulis et al., 2013).

Patients with Existing Cardiovascular–Renal Disease

Left Ventricular Hypertrophy

Whether detected by electrocardiography or more sensitive echocardiography, LVH is a significant risk factor. There is now convincing evidence that the risks are reduced by regression of LVH provided by antihypertensive therapy (Burns et al., 2012). Any drug that reduces BP will regress LVH except for naked direct vasodilators.

Coronary Artery Disease

The recent guidelines recommend the target for BP of less than 140/90 mm Hg for patients with CAD. In the high-risk older stage 2 hypertensives in the ACCOMPLISH trial, the combination of amlodipine with benazepril provided better protection against CAD than did the combination of HCT with benazepril despite equal reductions of BP (Bakris et al., 2013).

Heart Failure

In a review of data from 26 trials including 223,313 patients, Sciarretta et al. (2011) found that diuretics were best for preventing HF, followed by RAS blockers. Aldosterone blockade is particularly indicated for post-MI patients with LV dysfunction (Pitt et al., 2008). Once HF has developed, distinction between reduced or preserved EF is useful (Schwartzberg et al., 2012). There are limited data on the benefits of treating those with preserved EF beyond diuretics if edema is present (Edelmann et al., 2013) but unequivocal evidence for the benefits of β -blockers and RAS blockers for those with reduced EF (Yancy et al., 2013).

Atrial Fibrillation

The most common cardiac arrhythmia, AF, is even more common in hypertensive patients (Alonso et al., 2009). Valsartan was found to be ineffective for prevention of recurrent AF (GISSI-AF Investigators, 2009).

Cerebrovascular Disease

Stroke and transient ischemic attacks (TIAs) are becoming more common as people live longer and develop systolic hypertension, as noted in Chapter 4. Even minimally elevated BP in middle-aged people is associated with subtle brain damage (Maillard et al., 2012) that may progress to dementia (Celle et al., 2012). Fortunately, antihypertensive therapy has been repeatedly shown to prevent strokes as covered in Chapter 5.

Prevention

Adoption of a healthy lifestyle is beneficial. In a large observational study, those who adhered to a healthy lifestyle, composed of five features—not smoking, nonobese, physically active, moderate alcohol

consumption, and a lower fat, higher fruit and vegetable diet—had a phenomenally lower risk of stroke, 79% lower for women, 69% lower for men, compared to those who had none of these features (Chiuve et al., 2008).

Acute Stroke

Once a stroke begins, outcomes are improved with rapid hospitalization in a facility with brain-imaging equipment and a stroke unit, where thrombolysis with intra-arterial or intravenous tPA is available (Rothwell et al., 2011).

More than 60% of stroke patients have an acute hypertensive response within the first 24 hours (Sandset et al., 2012). Guidelines for treatment to lower this acutely elevated pressure have been very conservative because of concern that immediate lowering of BP may increase the extent of brain damage (Feldstein, 2014; Grise et al., 2012). However, persistence of BP above 185/110 mm Hg has been a contraindication to thrombolysis (Qureshi, 2008) (Fig. 7-19).

In controlled trials on the treatment of patients with acute stroke and hypertension, careful reduction of BP with the ARBs valsartan (Hornslie et al., 2013) and candesartan (Sandset et al., 2011) were of no benefit and may have been harmful. Moreover, in patients with an intracranial hemorrhage, lowering of BP to 140 mm Hg or lower was not beneficial (Anderson et al., 2013b).

Poststroke Management

The evidence for secondary prevention of recurrent stroke by antihypertensive therapy is strong although the appropriate goal of therapy remains uncertain (Ovbiagele et al., 2011; SPS3 Study Group, 2013; Wang et al., 2013). The HYVET trial found that such protection extends to those over age 80 (Beckett et al., 2008). In addition, aspirin, statins, and control of other risk factors are needed (Rothwell and Markus, 2014).

Peripheral Vascular Disease

Because ACEIs, ARBs, and CCBs have been shown to normalize endothelial dysfunction and vascular remodeling in arteries from hypertensive patients, they are the logical choices in patients with concomitant peripheral vascular disease (Anderson et al., 2013a).

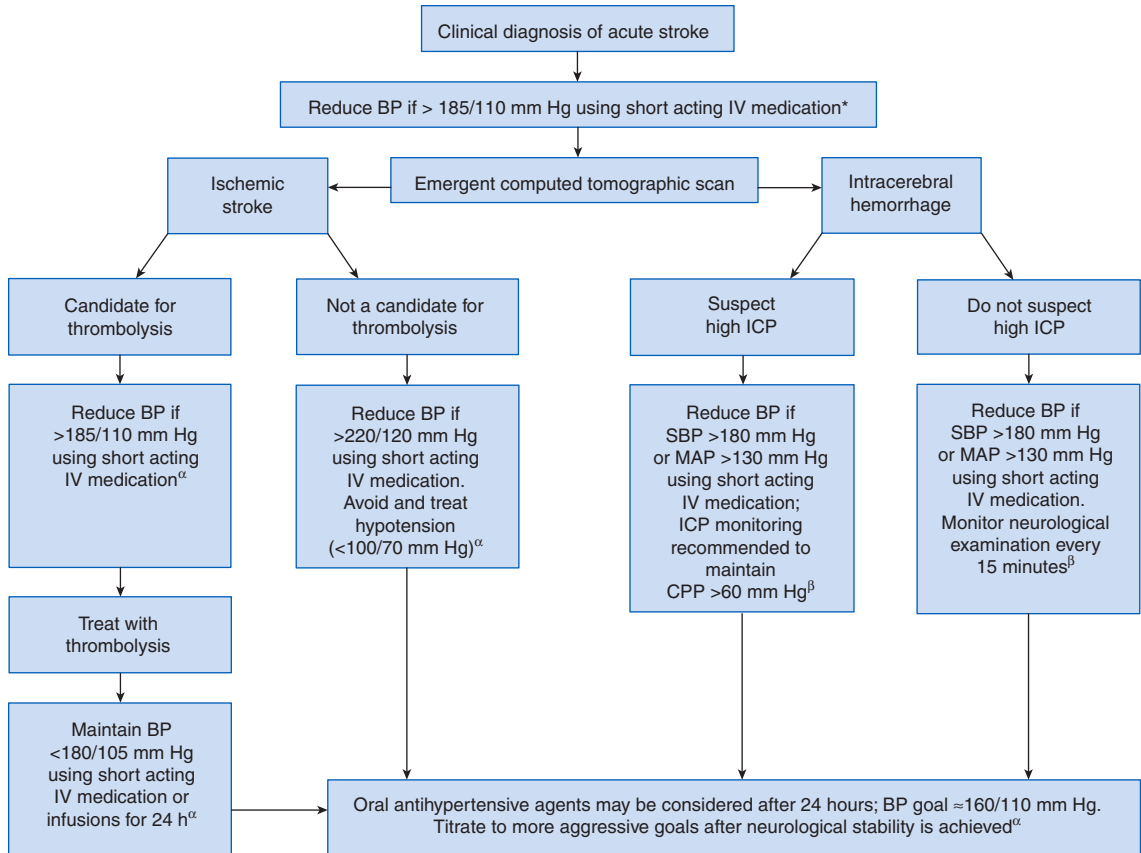


FIGURE 7-19 • Algorithm for treatment of acute hypertensive response among patients with stroke and stroke subtypes. IV, intravenous; SBP, systolic BP; DBP, diastolic BP; CPP, cerebral perfusion pressure. (Reproduced from Quershi AI. Acute hypertensive responses in patients with stroke. *Circulation* 2008;118:176–187, with permission.)

Renal Disease

Because there are so many facets to hypertension in renal disease, Chapter 9 covers that combination in depth. Two points seem worth mentioning here: First, even prehypertension is a risk factor for chronic renal disease (Kanno et al., 2012) and second, microalbuminuria is a serious risk factor and should be looked for in every new hypertensive; if present, reduction in the level of proteinuria may serve as a useful marker of successful therapy (Mahmoodi et al., 2012).

Sexual Dysfunction

Hypertension and its treatment are widely believed to be commonly associated and causally connected to sexual dysfunction, in particular with what was formerly referred to as impotence, but now called the less threatening “erectile dysfunction (ED).”

Incidence

Despite statements such as “erectile dysfunction is one of the major obstacles for noncompliance in antihypertensive treatment” (Della Chiesa et al., 2003), most data do not firmly indicate a close relation between ED and hypertension beyond what is expected in elderly men with an increased number of comorbid conditions (Spatz et al., 2013).

Treatment

If an antihypertensive drug is thought to induce ED (perhaps by further lowering arterial pressure into the sclerotic genital vessels), that drug should be stopped and another from a different class given in small dose to gradually lower BP.

If no reversible cause is found, a phosphodiesterase-5 inhibitor can be safely given with an expectation of return of erectile function in 50% to 70%

(Kloner, 2004). Caution about hypotension is needed if nitrates or α -blockers are being used.

Competitive Athletes

Competitive athletes may be anxious during their pre-competition exam and therefore may have “white-coat hypertension.” If found to be hypertensive, they should obtain out-of-office readings. Those with persistent stage 1 hypertension should have a more complete workup perhaps to include an echocardiogram, but need not be limited in their training or competition (Kaplan et al., 2005). Those with stage 2 hypertension likely should be limited, at least until lifestyle changes (including cessation of androgens, sympathomimetics, growth hormones, etc.), and medication has brought the BP under control. The only drugs that may limit physical performance are β -blockers.

Hypertensive Pilots

The U.S. Federal Aviation Administration has changed the regulations considerably as to the limits of BP and the types of antihypertensive medications that can be taken by people who wish to be certified as pilots. The maximum permitted seated BP is 155/95 mm Hg. Most antihypertensive drugs can be used, with the exceptions of those that act centrally, including reserpine, guanethidine, guanadrel, methyl dopa, and guanabenz.

Hypertension with Anesthesia and Surgery

BP should be well controlled before elective surgery. Patients should continue their antihypertensive medications up to the morning of surgery and resume them, either orally or intravenously, as soon as possible postoperative. β -Blockers are often given preoperatively to patients at high risk for atherosclerotic disease but Bolsin et al. (2013) strongly recommend they be given only for rate or BP control. Clonidine should not be used.

Caution is advised in patients taking an ACEI or ARB. Arora et al. (2008) found a 27.6% increased risk of acute kidney failure in a retrospective cohort study of 1,358 patients who underwent cardiac surgery soon after being on these drugs.

If hypertension needs to be treated during surgery, intravenous labetalol, nitroprusside, nicardipine, or esmolol can be used (see Chapter 8).

Postoperative hypertension is usually precipitated by volume overload, pain, or agitation. For those in need of postoperative BP reduction, parenteral forms of various agents, including the short-acting β -blocker esmolol, labetalol, or nicardipine, can be used. Special problems in postoperative patients after coronary bypass surgery, trauma, and burns are covered in Chapter 14. Anesthetic considerations in patients with pheochromocytoma are covered in Chapter 12.

Postoperatively, significant lowering of BP may occur as a nonspecific response to surgery and may persist for months (Volini & Flaxman, 1939). Do not be deceived by what appears to be an improvement in the patient's hypertension: Anticipate a gradual return to preoperative levels.

PREVENTION OF HYPERTENSION

Two trials have examined the ability to prevent progression of high-normal BP (130 to 139/85 to 89 mm Hg) to above 140/90 mm Hg (Julius et al., 2006; Luders et al., 2008). In these trials, the BP was lowered with an ARB (candesartan) by Julius et al. and an ACEI (ramipril) by Luders et al. In both trials, the BP remained below 140/90 mm Hg during the time of drug intake, but in most subjects followed after the drug was stopped, it rose to above 140/90 mm Hg.

Prevention of future hypertension has been shown in spontaneously hypertensive rats (who all become hypertensive after 20 weeks of age) by giving them an ACEI for as short a time of 2 weeks but only if they were treated before 20 weeks of age (Smallegange et al., 2004). That would translate into treating humans during adolescence to prevent future hypertension. Waiting until the subjects are in their 40s to 70s as done by Julius et al. and Luders et al. may be much too late. Such a study in humans young enough to be protected may not be feasible.

CONCLUSION

The large numbers of drugs now available can be used to treat virtually every hypertensive patient successfully under most any circumstance. Perhaps of even greater eventual value will be the treatment of prehypertensives to prevent the onset of hypertension, only now being examined. Meanwhile, even those at highest

risk—the few who develop a hypertensive emergency—can be effectively treated, as is described in the next chapter.

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Hypertensive Emergencies

Hypertensive emergencies represent, on one hand, the most immediate danger to those afflicted and, on the other, the most dramatic proof of the lifesaving potential of antihypertensive therapy. Such emergencies are now less likely to be the end result of chronic primary hypertension and may occur at any age, representing the manifestations of rapidly rising blood pressure from diverse causes. A recent addition to the causes of malignant hypertension is therapy with vascular endothelial growth factor inhibitors (Caro et al, 2013).

Previous editions of this book included coverage of hypertensive *urgencies*. However the authors are now convinced that this category simply represents blood pressure above some arbitrary level (such as >180/120 mm Hg) that is not accompanied by impending or existing target organ damage and therefore should be called “uncontrolled severe hypertension.” In addition we have deleted the term “*crises*,” leaving hypertensive *emergencies* to represent any condition where elevated blood pressure is accompanied by either target organ damage or some other circumstance that requires immediate lowering of blood pressure such as severe epistaxis, almost always by parenteral antihypertensive drugs (Table 8-1). The list includes some circumstances wherein immediate reduction of blood pressure may be either hazardous, as in the immediate time after an atherosclerotic stroke, or unnecessary, as when postoperative pain is responsible.

One other change is the substitution of “*Hypertension with retinal hemorrhages or papilledema*” for “*Accelerated-malignant hypertension with Grade 3 or 4 retinopathy*,” as suggested by van den Born et al. (2011).

HYPERTENSION WITH RETINAL HEMORRHAGES AND/OR PAPPILLEDEMA

Mechanisms

When BP reaches some critical level—in experimental animals at a mean arterial pressure (MAP) of 150 mm Hg—fibrinoid necrosis appears in arterial walls, likely to be a nonspecific consequence of very high BP (Beilin & Goldby, 1977). In humans, fibrinoid necrosis is relatively rare, perhaps because those who die from an acute episode have not had time to develop the lesion and those who live with therapy are able to repair it. The typical lesions, best seen in the kidney, are hyperplastic arteriosclerosis and accelerated glomerular obsolescence (Kitiyakara & Guzman, 1998).

Clinical Features

Hypertension with retinal hemorrhages or papilledema may be accompanied by various symptoms and complications, the most characteristic being microangiopathic hemolysis (Caro et al, 2013) or renal dysfunction (Table 8-2).

Less common clinical presentations include

- ▶ Aortic dissection with giant cell arteritis (Smulders & Verhagen, 2008)
- ▶ Intramural hematoma of the aorta (Marfatia et al., 2012)
- ▶ Fibrinoid necrosis within abdominal arteries producing major gastrointestinal tract infarction with an acute abdomen (Padfield, 1975)

TABLE 8-1

Hypertensive Emergencies

- Hypertension with retinal hemorrhages and /or papilledema
- Cerebrovascular conditions with hypertension**
- Hypertensive encephalopathy
- Atherothrombotic brain infarction with severe hypertension
- Intracerebral hemorrhage
- Subarachnoid hemorrhage
- Head trauma
- Cardiac conditions with hypertension**
- Acute aortic dissection
- Acute left ventricular failure
- Acute or impending myocardial infarction
- After coronary bypass surgery
- Renal conditions**
- Acute glomerulonephritis
- Renovascular hypertension
- Collagen vascular diseases
- After kidney transplantation
- Treatment with vascular endothelial growth factor
- Excess circulating catecholamines with hypertension**
- Pheochromocytoma crisis
- Food or drug interactions with monoamine oxidase inhibitors
- Sympathomimetic drug use (cocaine)
- Rebound hypertension after sudden cessation of antihypertensive drugs
- Automatic hyperreflexia after spinal cord injury
- Eclampsia**
- Surgical conditions**
- Severe hypertension in patients requiring immediate surgery
- Postoperative hypertension
- Postoperative bleeding from vascular suture lines
- Severe body burns
- Severe epistaxis

- Necrotizing vasculitis as a feature of lupus (Mitchell, 1994), polyarteritis nodosa (Blaustein et al., 2004), or Takayasu arteritis (Kettritz & Luft, 2012)
- Hematospermia or hematuria (Fleming et al., 2008)

Fundusoscopic Findings

The effects of the markedly elevated BP are displayed in the optic fundi (Fig. 8-1). Acute changes may include arteriolar spasm, either segmental or diffuse; retinal edema, with a sheen or ripples; retinal hemorrhages, either superficial and flame shaped or deep and dot shaped; retinal exudates, either hard and waxy from resorption of edema or with a raw cotton appearance

TABLE 8-2

Presenting Symptoms and Associated Complications in Patients with Hypertensive Crisis and Advanced Retinopathy

	Percentage
Headache	63
Visual disturbances	59
Gastrointestinal symptoms (nausea, vomiting, weight loss)	49
Heart failure	30
Neurologic sequelae (encephalopathy)	17
Left ventricular hypertrophy	86
Severe renal impairment (creatinine >300 mmol/L)	33
Mild to moderate renal impairment (115–300 mmol/L)	46
Microangiopathic hemolytic anemia	28

Adapted from van den Born BJ, Beutler JJ, Gaillard CA, et al. Dutch guideline for the management of hypertensive crisis—2010 revision. *Neth J Med* 2011;69:248–255.

from ischemia; and papilledema and engorged retinal veins (Bruce et al., 2012; Foguet et al., 2008).

Similar retinopathy with hemorrhages and even papilledema rarely occurs with severe anemia or subacute bacterial endocarditis. Some patients have pseudopapilledema associated with congenital anomalies, hyaline bodies (drusen) in the disc, or severe farsightedness. Fluorescein fundus photography will

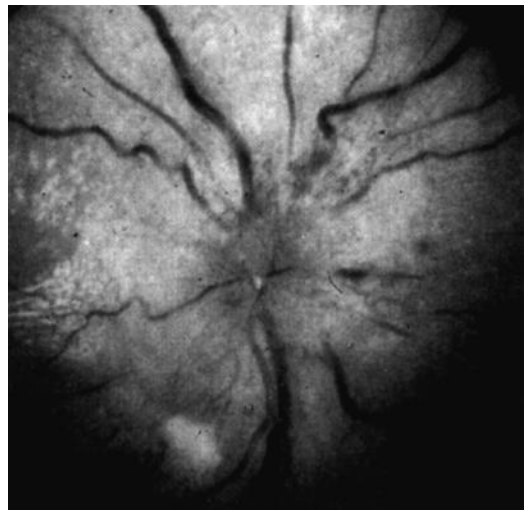


FIGURE 8-1 • Fundusoscopic photography showing typical features of accelerated-malignant hypertension.

distinguish between the true and the pseudo states. In addition, benign intracranial hypertension may produce real papilledema but is usually a minimally symptomatic and self-limited process (Jain & Rosner, 1992).

Evaluation

In addition to an adequate history and physical examination, a few laboratory tests should be done immediately to assess the patient's status (Table 8-3).

Laboratory Findings

In 28% of patients with hypertension and retinal hemorrhages and/or papilledema, van den Born et al. (2011) found thrombotic microangiopathy, characterized by thromboses of small vessels, intravascular hemolysis with fragmented red blood cells, elevated lactic dehydrogenase, and consumption of platelets.

The urine contains protein and red cells. In a few patients, acute oliguric renal failure may be the presenting manifestation (Lip et al., 1997).

Various features of renal dysfunction including proteinuria may be present. Approximately half of patients

have hypokalemia, reflecting secondary aldosteronism from increased renin secretion induced by intrarenal ischemia (Kawazoe et al., 1987). Hyponatremia is usual and can be extreme (Trivelli et al., 2005).

Multiple markers of inflammation, coagulation, platelet activation, and fibrinolysis were found in the blood from 20 patients with various types of hypertensive emergencies compared to the levels seen in hypertensive patients without target organ damage and normotensive subjects (Derhaschnig et al., 2012).

Cardiac troponin I levels were elevated in one-third of patients with a hypertensive emergency, in one series predictive of future cardiovascular events (Pattanshetty et al., 2012) and in another, not predictive (Afonso et al., 2011).

The electrocardiogram usually displays evidence of left ventricular hypertrophy, strain, and lateral ischemia. Echocardiography may show incoordinate contractions with impaired systolic and diastolic function and delayed mitral valve opening. Regression of these abnormalities usually occurs after lowering of BP by antihypertensive therapy (Gosse et al, 2011).

Evaluation for Identifiable Causes

Once causes for the presenting picture other than severe hypertension are excluded and necessary immediate therapy is provided, an appropriate evaluation for identifiable causes of the hypertension should be performed as quickly as possible. It is preferable to obtain necessary blood and urine samples for required laboratory studies before institution of therapies that may markedly complicate subsequent evaluation. None of these procedures should delay effective therapy.

Renovascular hypertension is the most likely secondary cause and, unfortunately, the one that may be least obvious by history, physical examination, and routine laboratory tests. It should be particularly looked for in older patients with extensive atherosclerosis (see Chapter 10).

If there are suggestive symptoms of pheochromocytoma, blood for a plasma metanephrine assay should be collected (see Chapter 12).

Primary aldosteronism should be considered, particularly if significant hypokalemia is noted in the initial blood sample. Plasma renin activity and aldosterone levels should be obtained. In most cases of primary aldosteronism presenting with a hypertension emergency, plasma renin activity levels have been very low despite the intrarenal necrotizing process (Prejbisz et al., 2013).

TABLE 8-3

Initial Evaluation of Patients with a Hypertensive Emergency

History

Prior diagnosis and treatment of hypertension

Intake of pressor agents: street drugs, sympathomimetics

Symptoms of cerebral, cardiac, and visual dysfunction

Physical examination

Blood pressure

Funduscopy

Neurologic status

Cardiopulmonary status

Body fluid volume assessment

Peripheral pulses

Laboratory evaluation

Hematocrit and blood smear

Urine analysis

Automated chemistry: creatinine, glucose, electrolytes

Electrocardiogram and echocardiogram

Plasma renin activity and aldosterone (if primary aldosteronism is suspected)

Plasma for metanephrine (if pheochromocytoma is suspected)

Chest radiograph (if heart failure or aortic dissection is suspected)

Prognosis

If untreated, most patients with hypertension and retinal hemorrhages and/or papilledema will die within 6 months. The 1-year survival rate was only 10% to 20% without therapy (Dustan et al., 1958). With current therapy, 5-year survival rates as high as 91% have been reported (Lane et al., 2009) showing the major protection provided by antihypertensive therapy.

Many patients when first seen have significant renal damage, which markedly worsens their prognosis (Szczech et al., 2010). In one series of 100 consecutive patients, the 5-year survival rate of those without renal impairment (serum creatinine <1.5 mg/dL) was 96%, no different from that of the general population (Bing et al., 2004). However, among those with renal impairment, 5-year survival fell to 65%. In another series of 120 patients followed for a mean of 5.6 years, end-stage renal disease developed in 31%, with the major predictors being an initial serum creatinine >1.9 mg/dL and uncontrolled hypertension (Amraoui et al., 2012).

When vigorous antihypertensive therapy is begun, renal function often worsens transiently, but in nearly half of those with initial renal insufficiency, function remains invariant or improves (Lip et al., 1997). In one series of 54 patients requiring dialysis, 12 recovered sufficient renal function to allow withdrawal of dialysis (James et al., 1995).

HYPERTENSIVE ENCEPHALOPATHY

With or without the structural defects of hypertension with retinal hemorrhages and/or papilledema, progressively higher BP can lead to hypertensive encephalopathy, reported in 10% to 15% of patients with the retinopathy. Conversely, one-third of patients with hypertensive encephalopathy do not have the fundoscopic findings (van den Born et al., 2011).

Pathophysiology

Breakthrough Vasodilation

With changes in BP, cerebral vessels dilate or constrict to maintain a relatively constant level of cerebral blood flow (CBF), the process of autoregulation. Figure 8-2 shows direct measurements taken in cats, with progressive vasodilation as pressures are lowered and progressive vasoconstriction as pressures rise (MacKenzie et al., 1976). Note, however, that when MAPs reach a critical level, approximately 180 mm Hg, the previously constricted vessels, unable to withstand such high pressures, are stretched and dilated—first in areas with less muscular tone, producing irregular sausage-string patterns, and later diffusely, producing generalized vasodilation. This vasodilation allows a breakthrough of CBF, hyperperfusing the brain under high pressure, causing leakage of fluid into the perivascular tissue, leading to

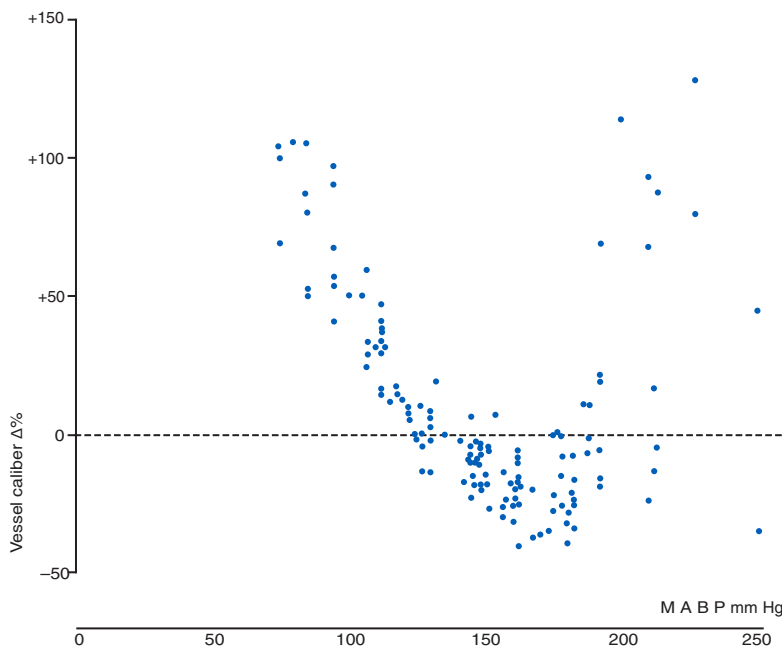


FIGURE 8-2 • Observed change in the caliber of pial arterioles with a caliber of less than 50 μ m in eight cats, calculated as a percentage of change from the caliber at a mean arterial blood pressure (MABP) of 135 mm Hg. The BP was raised by intravenous infusion of angiotensin II. (Reprinted from MacKenzie ET, Strandgaard S, Graham DI, et al. Effects of acutely induced hypertension in cats on pial arteriolar caliber, local cerebral blood flow, and the blood-brain barrier. *Circ Res* 1976;39:33, with permission.)

cerebral edema and the clinical syndrome of hypertensive encephalopathy (Strandgaard & Paulson, 1989).

Breakthrough vasodilation has also been demonstrated in humans (Strandgaard et al., 1973). Figure 8-3 shows curves of autoregulation constructed by measuring CBF repetitively, while arterial BP was lowered by vasodilators or raised by vasoconstrictors. CBF is constant between MAPs of 60 and 120 mm Hg in normotensive subjects. However, when pressure was raised beyond the limit of autoregulation, breakthrough hyperperfusion occurred.

Pressures such as these are handled without obvious trouble in chronic hypertensives, whose blood vessels adapt to the chronically elevated BP with structural thickening and stiffness (Iadecola & Davisson, 2008). Thereby, the entire curve of autoregulation is shifted to the right (see Fig. 8-3). Even with this shift, breakthrough will occur if MAPs are markedly raised to levels beyond 180 mm Hg.

These findings explain a number of clinical observations. Previously normotensive people who suddenly become hypertensive may develop encephalopathy at relatively low levels of hypertension, which are nonetheless beyond their upper limit of autoregulation. These include children with acute glomerulonephritis and young women with eclampsia. On the other hand, chronically hypertensive patients less commonly develop encephalopathy and only at much higher pressures.

In regard to the lower portion of the curve, when the BP is lowered by antihypertensive drugs too quickly, chronic hypertensives often are unable to tolerate the reduction without experiencing cerebral hypoperfusion,

manifested by weakness and dizziness. These symptoms may appear at levels of BP that are still well within the normal range of autoregulation and well tolerated by normotensives. The reason is that the entire curve of autoregulation shifts, so that the lower end also is moved, with a falloff of CBF at levels of 100 to 120 mm Hg MAP (see Fig. 8-3). Moreover, patients with severe hypertension may lose their ability to autoregulate, increasing their risk of cerebral ischemia when BP is lowered acutely (Immink et al., 2004).

As detailed in Chapter 7, if the BP is lowered gradually, the curve can shift back toward normal so that greater reductions in pressure can eventually be tolerated. However, maneuvers that increase CBF further and thereby increase intracranial pressure, such as drugs that induce cerebral vasodilation, e.g., hydralazine, nitroglycerin, and nitroprusside, may be harmful in patients with encephalopathy (Sheta et al., 2011).

Central Nervous System Changes

Symptoms in encephalopathic patients include severe headaches, vomiting, confusion, seizures, visual changes, and, if untreated, coma (Table 8-2). The cerebrospinal fluid rarely shows pleocytosis (McDonald et al., 1993) but is usually under increased pressure. Computed tomography or magnetic resonance imaging usually shows a characteristic posterior leukoencephalopathy predominantly affecting the parietooccipital white matter, often the cerebellum and brainstem (Karampekios et al., 2004), and occasionally other areas as well (Vaughan & Delanty, 2000).

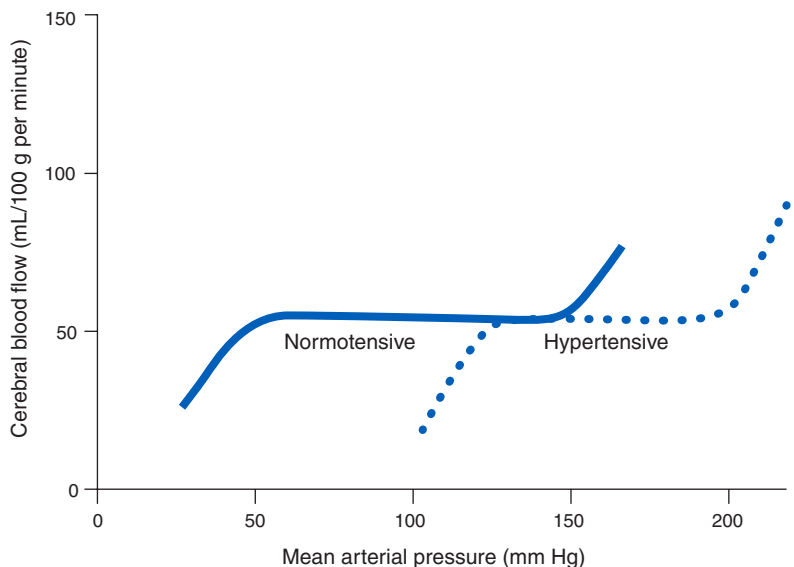


FIGURE 8-3 • Idealized curves of CBF at varying levels of systemic BP in normotensive and hypertensive subjects. Rightward shift in autoregulation is shown with chronic hypertension. (Adapted from Strandgaard S, Olesen J, Skinhøj E, et al. Autoregulation of brain circulation in severe arterial hypertension. *Br Med J* 1973;1:507-510.)

Differential Diagnosis

There are clinical situations in which the BP is elevated and the patient has findings that suggest hypertension-induced target organ damage wherein the findings are unrelated to the elevated BP. Table 8-4 lists conditions that may mimic a hypertensive emergency. A less aggressive approach to lowering of the BP is indicated in such patients. Particular caution is warranted after a thrombotic stroke, when a rapid decrease in BP may shunt blood away from the ischemic area and extend the lesion (Grise et al., 2012).

In addition to these two specific presentations, hypertension may be life threatening when it accompanies other acute conditions wherein a markedly elevated BP contributes to the ongoing tissue damage (see Table 8-1). The role of hypertension in most of these conditions is covered in Chapter 4, and some of the other specific circumstances (e.g., pheochromocytoma crises, eclampsia) are covered in their respective chapters.

THERAPY FOR HYPERTENSIVE EMERGENCIES

The majority of patients with the conditions shown in Table 8-1 require immediate reduction in BP. In those patients with hypertensive encephalopathy, if the pressure is not reduced, cerebral edema will worsen and the lack of autoregulation in ischemic brain tissue

TABLE 8-4

Conditions that May Mimic a Hypertensive Emergency

- Acute left ventricular failure
- End-stage renal disease
- Cerebrovascular accident
- Subarachnoid hemorrhage
- Brain tumor
- Head injury
- Reversible cerebral vasoconstriction syndromes
- Epilepsy (postictal)
- Collagen diseases, particularly systemic lupus, with cerebral vasculitis
- Encephalitis
- Drug ingestion: sympathomimetics (e.g., cocaine)
- Acute intermittent porphyria
- Hypercalcemia
- Acute anxiety with hyperventilation syndrome or panic attack

may result in further increases in the volume of the ischemic tissue, which may cause either acute herniation or more gradual compression of normal brain.

On the other hand, the shift to the right of the curve of cerebral autoregulation in most patients who develop encephalopathy exposes them to the hazards of a fall in CBF when systemic pressure is lowered abruptly by more than approximately 25%, even though these levels are not truly hypotensive (Immink et al., 2004; Strandgaard & Paulson, 1996) (see Fig. 8-3).

Initiating Therapy

With encephalopathy or evidence of progressive myocardial ischemia, no more than a very few minutes should be taken to admit a patient to an intensive care unit, set up intravenous access, and begin frequent monitoring of the BP, usually with an intra-arterial line. The initial blood and urine samples should be obtained, and antihypertensive therapy should begin immediately thereafter.

Monitoring Therapy

Abrupt falls in pressure should be avoided, and the goal of immediate therapy should be to lower the diastolic pressure only to approximately 110 mm Hg. The reductions may need to be even less if signs of tissue ischemia develop as the pressure is lowered. Most of the catastrophes seen with treatment of hypertensive emergencies were related to overly aggressive reduction of the BP (Jansen et al., 1987). On the other hand, careful reduction of elevated BP is usually beneficial in those with an intracranial hemorrhage (Anderson et al, 2013; Koga et al, 2012).

Particular care should be taken in elderly patients and in patients with known cerebrovascular disease, who are even more vulnerable to sudden falls in systemic BP (Fischberg et al., 2000). In patients with recent ischemic stroke, the American Stroke Association recommends cautious reduction of BP by 10% to 15% if systolic levels are above 220 mm Hg or diastolic above 120 mm Hg (Adams et al., 2007). Adverse effects have been seen even with gradual reduction of BP in those with an ischemic stroke (Sandset et al, 2012).

If the neurologic status worsens as treatment proceeds, urgent computed tomography of the brain should be obtained, and, if potentially life-threatening cerebral edema is identified, osmotic diuresis with mannitol, often plus intravenous furosemide, can be effective.

Parenteral Drugs

Table 8-5 lists the choices of parenteral therapy now available. All are capable of inducing hypotension, a risk that mandates careful monitoring of BP. They are covered in the order shown in Table 8-5.

Before examining the various parenteral agents, an important fact must be recognized: There are no data to document which of these drugs is best or, more importantly, whether their use is followed by decrease in morbidity or mortality. As described by Perez and Musini (2008) in their Cochrane systematic review of 5,413 identified citations, only 15 were acceptable as a randomized controlled trial (RCT), and only one of these was of good quality. Perez and Musini (2008) could find no adequate evidence to answer the question, “Does antihypertensive therapy, as compared to placebo or no treatment, change mortality and morbidity in patients with hypertensive emergencies? We feel it is important for physicians to know that this is one of the clinical settings where treatment is not supported by RCT evidence.”

The authors further note the absence of data to inform clinicians as to which drug class provides more benefit than harm. They state: “Neither did we find RCTs that compared different strategies to reduce blood pressure. Thus, how fast or how much blood pressure should be lowered in hypertensive emergencies remains unknown.”

Little has changed since the 2008 analysis by Perez and Musini. However, a group of Dutch investigators have performed another search of Medline and the Cochrane database (van den Born et al., 2011). Despite the continued sparsity of RCTs, they propose recommendations for therapy of patients with various types of hypertensive emergencies (Table 8-6). Two agents listed in their table, urapidil and ketanserin, are not available in the United States (U.S.).

More recently, a systematic review of 10 studies comparing nicardipine versus labetalol has been published (Peacock et al., 2012). Although only 2 of these 10 are RCTs, the authors conclude that the two drugs are “comparable in efficacy and safety... although nicardipine appears to provide more predictable and consistent BP control than labetalol.” Despite Peacock et al.’s analysis, labetalol is more frequently listed as the choice for initial therapy by the Dutch experts, with nicardipine a common alternative (see Table 8-6).

In the absence of definitive evidence, clinicians must continue to administer parenteral drugs to lower markedly elevated BP in patients with a hypertensive

emergency. However, we must do so carefully, with close supervision, choosing drugs that allow for gradual reduction of BP, that have no inherent toxicity, and that provide the ability to back down if target organ functions deteriorate.

With current knowledge, the use of nitroprusside seems hard to defend, but it is the first choice by van den Born et al. in two conditions and is an alternative in seven others.

Nitroprusside

The BP always falls when nitroprusside is given, although it occasionally takes much more than the usual starting dose of 0.25 $\mu\text{g}/\text{kg}/\text{min}$ for a response. The antihypertensive effect disappears within minutes after the drug is stopped. Obviously, the drug should be used only with constant monitoring of the BP.

The nitric oxide that is part of the nitroprusside structure induces immediate arteriolar and venous dilation with no effects on the autonomic or central nervous system (Mansoor & Frishman, 2002). Nitroprusside is metabolized to cyanide by sulfhydryl groups in red cells, and the cyanide is rapidly metabolized to thiocyanate in the liver. If high levels of thiocyanate (>10 mg/dL) remain for days, toxicity may be manifested as fatigue, nausea, disorientation, and psychosis. If cyanide toxicity is suspected because of metabolic acidosis and venous hyperoxemia, nitroprusside should be discontinued and 4 to 6 mg of 3% sodium nitrite given intravenously over 2 to 4 minutes, followed by an infusion of 50 mL of 25% sodium thiosulfate (Friederich & Butterworth, 1995).

Beyond its inherent potential toxicity and the need for constant surveillance with its use, nitroprusside poses an even greater hazard: It reduces CBF while increasing intracranial pressure (Immink et al., 2008). These effects are potentially detrimental in patients with hypertensive encephalopathy or after a stroke. As noted by Varon (2008): “considering the potential for severe toxicity with nitroprusside, this drug should be used only when other intravenous antihypertensive agents are not available and then, only in specific clinical circumstances in patients with normal renal and hepatic function.”

Nitroglycerin

Nitroglycerin as a potent venodilator reduces BP, decreasing preload and cardiac output, both undesirable effects in patients with compromised cerebral

TABLE 8-5

Parenteral Drugs for Treatment of Hypertensive Emergency

Drug ^a	Dose	Onset of Action	Duration of Action	Adverse Effects ^b	Special Indications
<i>Vasodilators</i>					
Nitroprusside	0.25–10.00 µg/kg/min IV	Immediate	1–2 min	Nausea, vomiting, muscle twitching, thiocyanate and cyanide toxicity	Not preferred for most hypertensive emergencies
Nitroglycerin	5–100 µg/min	2–5 min	5–10 min	Headache, vomiting, methemoglobinemia, tolerance with prolonged use	Not preferred but may be useful with coronary ischemia
Fenoldopam (Corlopan)	0.1–0.6 µg/kg/min IV	4–5 min	10–15 min	Tachycardia, increased intraocular pressure	May be indicated with renal insufficiency
Nicardipine ^c (Cardene IV)	5–15 mg/h	5–10 min	1–4 h	Headache, nausea, flushing, tachycardia	Most hypertensive emergencies
Clevidipine (Cleviprex)	1–2 mg IV, rapidly increasing dose to 16 mg maximum	2–4 min	5–15 min		Most hypertensive emergencies
Hydralazine	5–20 mg IV 10–40 mg IM	10–20 min	1–4 h	Tachycardia, flushing, headache, vomiting, aggravation of angina	Eclampsia. Not for aortic dissection
		20–30 min	4–6 h		
<i>Adrenergic inhibitor</i>					
Phentolamine	5–15 mg IV	1–2 min	3–10 min	Tachycardia, flushing, headache	Catecholamine excess
Esmolol (Brevibloc)	250–500 µg/kg/min for 4 min, then 50–300 µg/kg/min IV	1–2 min	10–20 min	Hypotension, nausea	Aortic dissection after surgery
Labetalol (Normodyne, Trandate)	20–80 mg IV bolus every 10 min 2 mg/min IV infusion	5–10 min	3–6 h	Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension	Most hypertensive emergencies except acute heart failure

^aIn order of rapidity of action.

^bHypotension may occur with any.

^cIntravenous formulations of other CCBs are also available.

TABLE 8-6

Recommended Treatment of Hypertensive Emergencies According to End Organ Involved

	Timeline and Target BP	First-Line Therapy	Alternative Therapy
Hypertensive crisis with retinopathy, microangiopathy, or acute renal insufficiency	Several hours, MAP -20% to -25%	Labetalol	Nitroprusside Nicardipine Urapidil ^a
Hypertensive encephalopathy	Immediate, MAP -20% to -25%	Labetalol	Nicardipine Nitroprusside
Acute aortic dissection	Immediate, systolic BP <110 mm Hg	Nitroprusside and esmolol	Labetalol
Acute pulmonary edema	Immediate, MAP 60 to 100 mm Hg	Nitroprusside (with loop diuretic)	Nitroglycerine Urapidil ^a (with loop diuretic)
Myocardial ischemia/infarction	Immediate, MAP 60 to 100 mm Hg	Nitroglycerine	Labetalol
Acute ischemic stroke and BP >220/120 mm Hg	1 h, MAP -15%	Labetalol	Nicardipine Nitroprusside
Cerebral hemorrhage and BP >180 systolic or MAP >130 mm Hg	1 h, systolic BP < 180 mm Hg and MAP < 130 mm Hg	Labetalol	Nicardipine Nitroprusside
Acute ischemic stroke with indication for thrombolytic therapy and BP >185/110 mm Hg	1 h, MAP -15%	Labetalol	Nicardipine Nitroprusside
Cocaine/XTC intoxication	Several hours	Phentolamine (next to benzodiazepines)	Nitroprusside
Adrenergic crisis associated with pheochromocytoma or autonomic hyperreactivity	Immediate	Phentolamine	Nitroprusside Urapidil ^a
Peri- and postoperative hypertension			
During or after coronary bypass graft	Immediate	Nicardipine	Urapidil or nitroglycerine
During or after craniotomy	Immediate	Nicardipine	Labetalol
Severe preeclampsia/eclampsia	Immediate, BP <160/105 mm Hg	Labetalol (next to magnesium sulfate and oral antihypertensive therapy)	Ketanserin ^a Nicardipine

^aUrapidil and ketanserin are not approved in the U.S.

Modified from van den Born BJ, et al. Dutch guideline of the management of hypertensive crisis—2010 revision. *Neth J Med* 2011;69:248–255.

perfusion (Varon, 2008). Therefore, it is not an acceptable first choice for hypertensive emergencies except in patients with acute coronary ischemia.

Fenoldopam

Fenoldopam, a peripheral dopamine I agonist, unlike other parenteral antihypertensive agents, maintains or increases renal perfusion while it lowers BP (Murphy et al., 2001). It maintains most of its efficacy for 48 hours of constant rate infusion without rebound hypertension when discontinued. Although theoretically attractive in maintaining renal perfusion, it was no better than nitroprusside when compared in a sequential study of 43 patients with hypertensive emergencies (Devlin et al., 2004).

Nicardipine

Intravenous formulations of various dihydropyridine calcium channel blockers (CCBs) produce a steady, progressive fall in BP with little change in heart rate and a small increase in cardiac output (Mansoor & Frishman, 2002). Nicardipine has been found to provide responses virtually equal to those seen with nitroprusside, with few side effects (Neutel et al., 1994). It is listed in Table 8-6 as either first choice or alternative in most of the various forms of hypertensive emergencies. In a prospective observational study of 211 patients with a recent intracranial hemorrhagic stroke, intravenous nicardipine was found to be effective in lowering BP to a systolic level of 160 mm Hg and with relatively few side effects (Koga et al., 2012).

Clevidipine

This dihydropyridine CCB is approved for intravenous use in treating severe hypertension. Unlike nicardipine, clevidipine has a very fast onset of action and a short duration of action of about 15 minutes, as it is rapidly metabolized by red blood cell esterases. It reduces blood pressure by selective arterial dilation, reducing afterload without affecting cardiac filling pressure or causing a reflex tachycardia (Varon, 2008).

Hydralazine

The direct vasodilator hydralazine can be given by repeated intramuscular injections as well as intravenously with a fairly slow onset and prolonged duration of action, allowing for less intensive monitoring.

Significant compensatory increases in cardiac output preclude its use as a sole agent except in young patients who can handle the increased cardiac work without the likelihood that coronary ischemia will be induced. Hydralazine's primary use is for severe hypertension during pregnancy, as noted in Chapter 15.

Phentolamine

The α -blocker phentolamine is specifically indicated for pheochromocytoma or tyramine-induced catecholamine crisis.

Esmolol

Esmolol, a relatively cardioselective β -blocker, is rapidly metabolized by blood esterases and has a short half-life (~9 minutes) and total duration of action (~30 minutes). Its effects begin almost immediately, and it has found particular use during anesthesia to prevent postintubation hemodynamic perturbations (Oxorn et al., 1990).

Labetalol

The combined α - and β -blocker labetalol has been found to be both safe and effective when given intravenously either by repeated bolus (Huey et al., 1988) or by continuous infusion (van den Bogaard et al, 2013). It starts acting within 5 minutes, and its effects last for 3 to 6 hours. Labetalol can likely be used in almost any situation requiring parenteral antihypertensive therapy, except when left ventricular dysfunction could be worsened by the predominant β -blockade. Caution is needed to avoid postural hypotension if patients are allowed out of bed. Nausea, itching, tingling of the skin, and β -blocker side effects may be noted.

Diuretic

A diuretic may be needed after other antihypertensives are used, because reactive renal sodium retention usually accompanies a fall in pressure and may blunt the efficacy of nondiuretic agents. On the other hand, if the patient is volume depleted from pressure-induced natriuresis and prior nausea and vomiting, additional diuresis could be dangerous, and volume expansion may be needed to restore organ perfusion and prevent an abrupt fall in BP when antihypertensives are given (Varon, 2008).

The management of hypertensive emergencies in a number of special circumstances is considered in other chapters of this book: renal insufficiency, Chapter 9; pheochromocytoma, Chapter 12; drug abuse, Chapter 14; eclampsia, Chapter 15; and children and adolescents, Chapter 16.

Management After Acute Therapy

After the patient is out of danger, a careful search should continue for possible identifiable causes, as delineated earlier in the section “Evaluation” in this chapter. Identifiable causes, in particular renovascular hypertension, are much more likely in patients with severe hypertension.

After control of the acute presentation, most patients will likely require multiple drug therapy and chronic treatment should likely begin with a diuretic and an appropriate second agent. The guidelines delineated in Chapter 7 should be followed to ensure adherence to effective therapy.

UNCONTROLLED SEVERE HYPERTENSION

Most patients who are diagnosed and treated as a hypertensive urgency are not in the immediate danger of uncontrolled hypertension that this diagnosis connotes. Many such patients have come to an emergency department (ED) for unrelated acute problems, but whose BP is elevated in response to pain, anxiety, or an understandable white-coat effect from being in an inhospitable surrounding.

If there is no evidence of trouble from the elevated BP, additional readings should be obtained after the pain or anxiety is alleviated. If the BP remains above 180/115 mm Hg, an oral antihypertensive drug should probably be given. The 180/115 mm Hg level is chosen with no basis for deciding that this is the “critical” level, but because it is the level used by neurologists to preclude thrombolysis for acute ischemic stroke, as valid a reason as any.

Enough medication should be supplied to cover the time until appropriate follow-up can be obtained in a primary care facility. This will, at the least, relieve the ED physician from concern over not taking some action, as if such action could be lifesaving. However, as the American College of Emergency Physician Clinical Policy (Decker et al., 2006) states, “we could find no evidence demonstrating improved patient outcomes or decreased

mortality or morbidity with acute management of elevated blood pressure in the ED.” Their policy statement concludes with these three recommendations:

1. Initiating treatment for asymptomatic hypertension in the ED is not necessary when patients have follow-up.
2. Rapidly lowering blood pressure in asymptomatic patients in the ED is unnecessary and may be harmful to some patient.
3. When ED treatment for asymptomatic hypertension is initiated, blood pressure management should attempt to gradually lower blood pressure and should not expect to be normalized during the initial ED visit.

We will now leave the realm of primary hypertension and examine the various identifiable (secondary) forms of hypertension, starting with the most common: renal parenchymal disease.

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Renal Parenchymal Hypertension

Renal parenchymal diseases are among the most common identifiable causes of hypertension, and their incidence will continue to increase as the population grows older and fatter (Jha et al., 2013; Tonelli and Riella, 2014). Before covering in reverse order, from acute to chronic to transplant, some general issues about their overall significance deserve mention.

Chronic kidney diseases (CKD) are one of the many factors that can lead to resistant hypertension. The approach that should be taken to elucidate the causes and improve the management of resistant hypertension is covered in Chapter 7. Out-of-office measurements of BP are essential for those with CKD (Cohen et al., 2014), thereby slowing the rush to renal denervation (Zoccali and Mallamaci, 2014).

THE SCOPE OF THE PROBLEM

One of the major crises facing health care in the United States (U.S.) and all developed societies is the need to provide renal replacement therapy (RRT) to the rapidly growing number of people with kidney damage that progresses into end-stage renal disease (ESRD). Hypertension is responsible for much of this progressive damage, playing a major role as well in the other major risk factor, obesity-induced diabetes. Between them, they represent by far the most common risk factors across the entire spectrum of renal disease (Whaley-Connell et al., 2008) (Fig. 9-1). The definition and clarification of CKD used in these surveys include both microalbuminuria (more than 30 mg/g creatinine) and an estimated glomerular filtration rate (eGFR) below 60 mL/minute/1.73 m² (Table 9-1). In addition to hypertension and diabetes, low hemoglobin, higher serum uric acid, history of

nocturia, and the family history of kidney disease are independent risk factors for ESRD (Hsu et al., 2009).

By 2020, with the aging of the population and the increasing prevalence of diabetes, nearly 150,000 persons in the U.S. are projected to begin therapy for ESRD, nearly 800,000 will be living on chronic dialysis or with a kidney transplant, and costs for ESRD are projected to reach \$54 billion.

The Role of Hypertension

Hypertension is second only to diabetes as the primary cause of ESRD. Even prehypertension, defined as blood pressure (BP) >120/80 mm Hg but <140/90 mm Hg, is associated with an increased risk of the onset of CRD (Huang et al., 2014). Moreover, higher nocturnal levels of BP, unrecognized without rarely performed 24-hour ambulatory monitoring, have been found to be much more closely related to the development of CRD than are daytime readings (Kanno et al., 2013). Unfortunately, in blacks with CRD, higher nocturnal BPs persisted despite the dosing of antihypertensive drugs at bedtime (Rahman et al., 2013).

Overall, few CKD patients have their BP adequately controlled to below 140/90 mm Hg: Only 13.2% of over 10,000 people screened in the Kidney Early Evaluation Program were well controlled, although 80% of these participants were aware of their hypertension and 70% were being given antihypertensive medication (Sarafidis et al., 2008a). Those who were poorly controlled more likely had elevated systolic pressure and were more likely elderly, obese, black, and male.

These data are likely related to two factors. First, since RRT for ESRD is totally compensated by Medicare, black men have unrestricted access to RRT (Duru et al., 2008) and actually do better than Caucasian men when they start dialysis (Norris

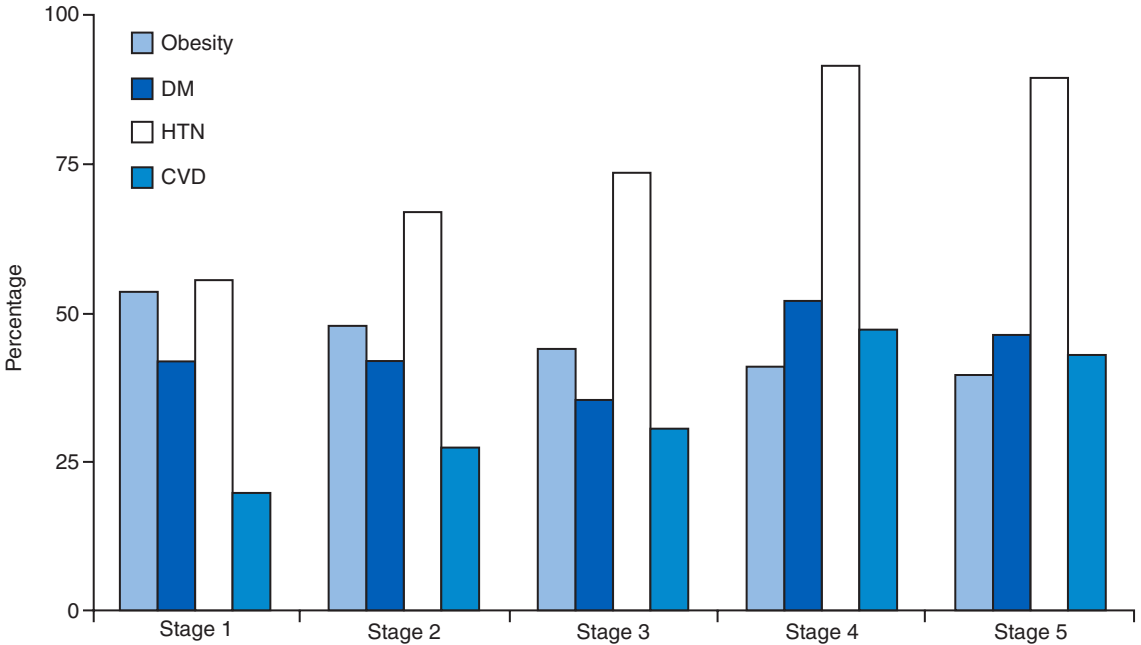


FIGURE 9-1 • The prevalence of four risk factors (obesity, diabetes, hypertension, and cardiovascular disease) in patients screened in the Kidney Early Evaluation Program, grouped by the stage of chronic renal disease. (Reproduced from Whaley-Connell AT, Sowers JR, Stevens LA, et al. CKD in the United States: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999–2004. *Am J Kidney Dis* 2008;51:S13–S20.)

et al., 2008). On the other hand, black men are much less likely to receive medical care that could prevent their progressing into ESRD (Evans et al., 2011) reflecting the absence of a rational health care system in the U.S. Unfortunately, black men in particular, and poor people in general, will continue to suffer the consequences of a skewed health care delivery system willing to pay millions to keep ESRD patients alive but

unwilling to pay hundreds to prevent their progression into ESRD. The waste, in both money and suffering inherent in the U.S. system, is seen when our data are compared to countries with universal access to care: Norway has the same prevalence of CKD as the U.S., but the rate of progression from stage 3 to stage 4 and to ESRD is threefold higher in the U.S. (Hallan et al., 2006).

Poverty and limited access to comprehensive health care add yet another mechanism for CKD— inadequate nutrition during pregnancy and prematurity, which diminish renal development in low birth weight babies (Luyckx et al, 2013).

TABLE 9-1

Classification of Chronic Kidney Disease

	GFR (Estimated from MDRD Equation in mL/min/1.73 m ²)	Albuminuria (Calculated from Urine Albumin/ Creatinine Rate in mg/g)	Percent of CKD
Stage 1	>90	>30	20
Stage 2	60–89	>30	27
Stage 3	30–59	—	50
Stage 4	25–29	—	(4 and 5) 3
Stage 5	<15	—	

Practical Solutions

As societal changes are being sought, two simple changes in current practices need implementation:

First, increase the performance of spot urine testing for albuminuria and calculation of eGFR from a serum creatinine (Rule et al., 2013) or cystatin C (Shlipak et al., 2013). Second, encourage primary caregivers to treat those with stage 1 or 2 disease more intensively. There are not enough nephrologists to care even for those with stage 3 disease, which is the level of CKD that

TABLE 9-2

Measures to Prevent Progression of Kidney Disease

1. Control hypertension to a level <130/80 mm Hg
2. Control diabetes to a hemoglobin A1c level <7.0
3. Control lipid levels to an LDL-C level <100 mg/dL
4. Use antiproteinuric antihypertensive agents: Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone inhibitors, diltiazem
5. Avoid NSAIDs
6. Recommend dietary modification: low fat, low salt, fewer calories if overweight
7. Avoid radiocontrast radiographic tests and premedicate the patient if required
8. Advise patients to discuss their condition with any physician who intends to prescribe a new medication
9. Encourage regular visits to a nephrologist (every 6–12 months)

SI conversion factor: To convert LDL-C values to mmol/L, multiply by 0.0259.

LDL-C, low-density lipoprotein cholesterol; NSAIDs, nonsteroidal anti-inflammatory drug.

Modified from Graves JW. Diagnosis and management of chronic kidney disease. *Mayo Clin Proc* 2008;83:1064–1069.

is now the criterion for referral to a nephrologist. Table 9-2 provides a nine-item list for prevention of the progression of kidney damage (Graves, 2008).

We will now examine the specific varieties of renal disease and how they relate to hypertension, starting from acute renal insults and progressing eventually to posttransplantation. Renovascular hypertension is covered in the next chapter. It should always be kept in mind as a potentially curable form of CKD.

ACUTE KIDNEY DISEASE

A rapid decline in renal function may appear from various causes: prerenal (e.g., volume depletion), intrinsic (e.g., glomerulonephritis), or postrenal (e.g., obstructive uropathy). Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most common causes of acute renal failure, particularly in patients whose already reduced renal perfusion depends on prostaglandin-mediated vasodilation.

Acute Kidney Injury

Acute kidney injury (AKI) is defined differently in different studies (Zappitelli et al., 2008). Perhaps the best is the RIFLE classification, which provides a gradation of severity, starting with stage 1 or “risk” as oliguria for more than 6 hours or an increase in serum creatinine of more than 50% and proceeding to stage 2 as “injury” and stage 3 as “failure” with greater disease severity (Kellum et al., 2008).

Waikar et al. (2008), in their review of AKI, list these as the most common precipitants, all more common in the elderly, the diabetic, and those with preexisting CKD (Hsu et al., 2008):

- Sepsis
- Coronary interventions: catheterization, angioplasty, and bypass surgery
- Aortic aneurysm repair
- Intravenous contrast for radiologic examinations
- Nephrotoxic antibiotics

Gadolinium and Nephrogenic Systemic Fibrosis

Contrast agents have long been known to reduce renal function (Weisbord et al., 2008), but a more specific syndrome—nephrogenic systemic fibrosis—has been identified as a serious consequence of the use of gadolinium as contrast for magnetic resonance imaging in patients with preexisting ESRD (Kallen et al., 2008).

Recognition of AKI

The need for an early recognition of AKI is obvious, since immediate correction of causative factors is critical for survival. Among many markers that have been proposed, the plasma and urine measurements of neutrophil gelatinase-associated lipocalin (NGAL) are the most promising. NGAL is one of the most rapidly induced proteins in the kidney after acute injury (Mishra et al., 2003), and it can easily be measured in

one drop of blood or 0.2 mL of urine (Devarajan, 2008). In a prospective cohort study of 635 patients with suspected AKI, the urinary NGAL provided a 90% sensitivity and a 99.5% specificity, superior to other markers and highly predictive of clinical outcomes (Nickolas et al., 2008).

Hypotension, rather than hypertension, is frequent in many AKI patients because vasodilation and volume depletion may occur at the onset of the injury. If hypertension supervenes, it often reflects iatrogenic volume overload in an attempt to increase renal perfusion. Renin released from hypoperfused kidneys may also be involved.

Acute Glomerulonephritis

The classic presentation of acute glomerulonephritis is a child with recent streptococcal pharyngitis or impetigo who suddenly passes dark urine and develops facial edema. The renal injury represents the trapping of antibody–antigen complexes within the glomerular capillaries. Although the syndrome has become less common, it still occurs, sometimes in adults past middle age. Typically, in the acute phase, patients are hypertensive, and there is a close temporal relation between oliguria, edema, and hypertension. On occasion, hypertension of a severe, even malignant, nature may be the overriding feature.

The hypertension should be treated by salt and water restriction and, in mild cases, diuretics and other oral antihypertensives. In keeping with an apparent role of renin, ACEI and ARB therapies have been effective (Catapano et al., 2008). In the classic disease, the patient is free of edema and hypertension within days, of proteinuria within weeks, and of hematuria within months. Hypertension was found in only 3 of 88 children followed up for 10 to 17 years (Popovic-Rolovic et al., 1991).

More common than poststreptococcal glomerulonephritis are a variety of primary renal diseases (e.g., IgA nephropathy) and systemic diseases (e.g., systemic lupus erythematosus), which may present with acute renal crises marked by hypertension (Haas et al., 2008). The hypertension may be effectively treated with an ACEI or an ARB (Catapano et al., 2008).

Various viral infections may precipitate renal damage, more likely chronic than acute (Berns & Bloom, 2008). HIV-infected patients may present with a continuum from only microalbuminuria (Baekken et al., 2008) to severe antiglomerular basement membrane disease (Wechsler et al., 2008), manifested by

heavy proteinuria (Rhee et al., 2008) or malignant hypertension (Morales et al., 2008).

Urinary Tract Obstruction and Reflux

Vesicoureteric reflux is seen in 1% to 2% of otherwise normal children and can lead to hypertension, renal scarring, and ESRD (Gargollo & Diamond, 2007). Hypertension may develop after obstruction of the urinary tract, either unilateral (Shin et al., 2008) or bilateral (Kirylyuk et al., 2008). In most patients, the hypertension is fairly mild, but significant hypertension and severe renal insufficiency may occur with hydronephrosis from prostatic obstruction (Sacks et al., 1989). Catheter drainage of the residual urine may lead to rapid resolution of the hypertension and circulatory overload (Ghose & Harindra, 1989).

Other Causes of Acute Renal Disease

Other causes of acute renal disease with hypertension include the following:

- Bilateral renal artery occlusion, by either emboli or thromboses (Svarstad et al., 2005).
- Removal of angiotensin II support of blood flow with ACEI or ARB therapy in the presence of bilateral renal artery disease (Safian & Textor, 2001).
- Trauma to the kidney (Watts & Hoffbrand, 1987).
- Cholesterol emboli, which may shower the kidney after radiologic or surgical procedures, producing rapidly worsening renal function and hypertension (Vidt, 1997).
- Extracorporeal shock wave lithotripsy for kidney stones is only rarely followed by rises in BP (Eassa et al., 2008).

Renal Donors

Removal of half of a living donor's renal mass could be looked upon as an acute injury, but in normal humans, the removal of a kidney does not usually result in hypertension, likely because of downward adjustments in glomerular hemodynamics to maintain normal fluid volume (Kasiske et al., 2013). In a meta-analysis of 48 studies with 5,145 donors whose average age at donation was 41 years and whose BP averaged 121/77, follow-up for at least 5 years revealed a 6/4–mm Hg increase in BP (Boudville et al., 2006). However, at a mean follow-up of 12.2 years, the survival and incidence of ESRD were similar in 255 donors compared to those in the general population (Ibrahim et al., 2009).

No additional risk for cardiovascular events has been seen in kidney donors than in the general population (Garg et al., 2012).

CHRONIC KIDNEY DISEASE

Of the various discernable primary causes of ESRD among patients starting dialysis in the U.S., diabetic nephropathy is the most common, comprising about 40%, followed by vascular diseases, including hypertensive nephrosclerosis (20%), primary glomerular disease (18%), tubulointerstitial diseases (7%), and cystic diseases (5%) (Whaley-Connell et al., 2008).

There are some differences in the prevalence of hypertension and the responses to antihypertensive therapy among these various causes of kidney disease: Chronic pyelonephritis may be less commonly associated with hypertension (Goodship et al., 2000); polycystic diseases may be more commonly associated (Grantham, 2008), even before significant renal dysfunction develops (Reed et al., 2008). Patients with these various causes of CKD may start at either end of the spectrum: Hypertension without overt renal damage on the one end and severe renal insufficiency without hypertension on the other. Eventually, however, both groups move toward the middle—renal insufficiency with hypertension—so that hypertension is found in approximately 85% of patients with CKD of diverse causes (Sarafidis et al., 2008a) and is closely related to the progression of nephropathy. Renal insufficiency as a consequence of primary hypertension is described in Chapter 4. Attention will be directed to data associating genetic variants in blacks rather than “hypertensive nephrosclerosis” as the mechanism for their higher prevalence of CRD, in particular focal segmental glomerulosclerosis (FSGS) (Parsa et al., 2013).

This section examines the development of hypertension as a secondary process in the presence of primary renal disease or diabetes. The special features of diabetic nephropathy are covered separately, but most cases of CKD are similar in their course and treatment. Moreover, almost half of patients clinically defined as having diabetic nephropathy have been shown to actually have nondiabetic renal disease by kidney biopsy (Zhou et al., 2008).

Patients whose underlying problem is bilateral renovascular disease may present with refractory hypertension and renal insufficiency (Guo et al., 2007). The recognition of the renovascular etiology of these

patients' condition is critical because revascularization may relieve their hypertension and improve their renal function. More about this important group of patients with ischemic nephropathy is provided in the next chapter, as well as hypertension associated with renal tumors.

The Role of Hypertension

Hypertension accelerates the progression of renal damage, regardless of the cause. Perhaps the best evidence for this tight relationship is the repeatedly observed slowing of the progression of established CKD as initially elevated BPs are lowered. This was demonstrated first for patients with diabetic nephropathy (Mogensen, 1976) and subsequently for those with other causes of CKD, as in the Modification of Diet in Renal Disease (MDRD) Study (Lazarus et al., 1997). In the MDRD trial, 585 patients with a glomerular filtration rate (GFR) between 25 and 55 mL/minute and 255 patients with a GFR between 13 and 24 mL/minute were studied. Among those with proteinuria of more than 1 g/day at baseline, the rate of decline in GFR was significantly less over a mean follow-up of 2.2 years in both groups whose BPs remained an average of 5 mm Hg lower as a result of more intensive therapy.

Along with their higher prevalence of hypertension, African Americans have an increased susceptibility to CKD and ESRD. Nondiabetic CKD in African Americans has been attributed to “hypertensive nephrosclerosis,” i.e., hypertension-causing CKD. The diagnosis is usually made by exclusion and with non-specific FSGS on biopsy. However, missense mutations in the *APOL1* gene (initially attributed to the nearby *MYH9* gene (Kao et al., 2008; Kopp et al., 2008)) have explained the increased prevalence of CRD in blacks (Tzur et al., 2010).

In patients with CKD, ambulatory BP monitoring, which often identifies a loss of nocturnal dipping, is better than office readings in predicting progression of renal damage and mortality (Pogue et al., 2009). Nondipping in CKD has been attributed to a compensation for diminished natriuresis during the daytime and to enhanced pressure–natriuresis during the night (Kimura, 2008). Out-of-office BP measurements in patients with CKD are also critical to identify the considerable proportion with white-coat hypertension, overtreatment (De Nicola et al., 2013), to avoid unnecessary and potentially harmful overtreatment.

TABLE 9-3

Features Associated with High BP in Chronic Kidney Disease

Preexisting primary (essential) hypertension
 Extracellular fluid volume expansion
 Arterial stiffness
 Renin–angiotensin–aldosterone system stimulation
 Increased sympathetic activity
 Endothelin
 Low birth weight with reduced nephron number
 Decrease in vasodilatory prostaglandins
 Obesity and insulin resistance
 Sleep apnea
 Smoking
 Hyperuricemia
 Erythropoietin administration
 Parathyroid hormone secretion/increased intracellular calcium/hypercalcemia
 Renal vascular disease and renal arterial stenosis
 Aldosterone-induced fibrosis and sodium retention
 Asymmetric dimethylarginine
 Advanced glycation end products
 Chronic allograft dysfunction
 Cadaver allografts, especially from a donor with a family history of hypertension
 Immunosuppressive and corticosteroid therapy
 Heritable factors

Mechanisms

Hypertension develops and progresses in patients with renal diseases for multiple reasons (Table 9-3). Most of these funnel into a common path: Impaired renal autoregulation that normally attenuates the transmission of elevated systemic pressure to the glomeruli, resulting in high perfusion pressure (Mori et al., 2008). The resultant glomerular hypertension damages the glomerular cells and leads to progressive sclerosis, setting off a vicious cycle (Anderson & Brenner, 1989) (Fig. 9-2).

As the extent of renal damage increases, arteries within the kidneys and throughout the body become sclerotic and stiff. As a consequence, systolic pressure rises, diastolic falls, and pulse pressure widens (Cheng et al., 2008). The stiffness that is responsible for the rising systolic pressure makes it increasingly difficult to lower this pressure. As more and more antihypertensive drugs are added, the systolic barely moves, but the diastolic falls, exposing the CKD patient to potential harm from too low a diastolic pressure to maintain

perfusion to the brain, heart, and kidneys (Kovesdy et al., 2013).

Of the contributing or aggravating factors listed in Table 9-3, volume expansion from impaired natriuresis has traditionally been given primacy. However, in view of the increased peripheral vascular resistance typically seen in these patients, both an activated renin–angiotensin–aldosterone mechanism (Hollenberg et al., 2004) and an overactive sympathetic nervous system (Phillips, 2005) have received increasing attention. Obesity, particularly abdominal, accelerates the progression of CKD and the attendant hypertension (Ritz, 2008; Wang et al., 2008).

Proteinuria

The degree of proteinuria serves as a strong predictor of the rate of progression of CKD. Increased protein trafficking through the glomerular capillaries directly damages the podocytes and tubular interstitium (Schieppati & Remuzzi, 2003). The role of heavy proteinuria in progression of renal damage was documented in a meta-analysis of data from 11 randomized controlled trials involving 1,860 patients (Jafar et al., 2003). As seen in Figure 9-3, proteinuria above 1 g/day was associated with a higher relative risk for progression at all levels of systolic BP above 120 mm Hg. The greater the proteinuria, the more the progression. Beyond its inherent toxicity, proteinuria is a useful marker of the type and extent of CKD.

Measures of Glomerular Filtration Rate

In addition to proteinuria, the presence and degree of CKD are based on the rate of glomerular filtration (see Table 9-1). Until recently, the GFR has been estimated from equations measuring creatinine clearance. These equations have been shown to be less accurate when the GFR is above 60 mL/minute/1.73 m² and to underestimate measured decreases in renal function over time (Xie et al., 2008). Therefore, attention has turned to the measurement of serum cystatin C, an endogenous protein filtered by glomeruli and reabsorbed and catabolized by tubular epithelial cells with only small amounts excreted in the urine. Unlike equations using serum creatinine, cystatin C levels are not affected by muscle mass, and they are closely correlated to outcomes in patients with CKD (Shlipak et al., 2013).

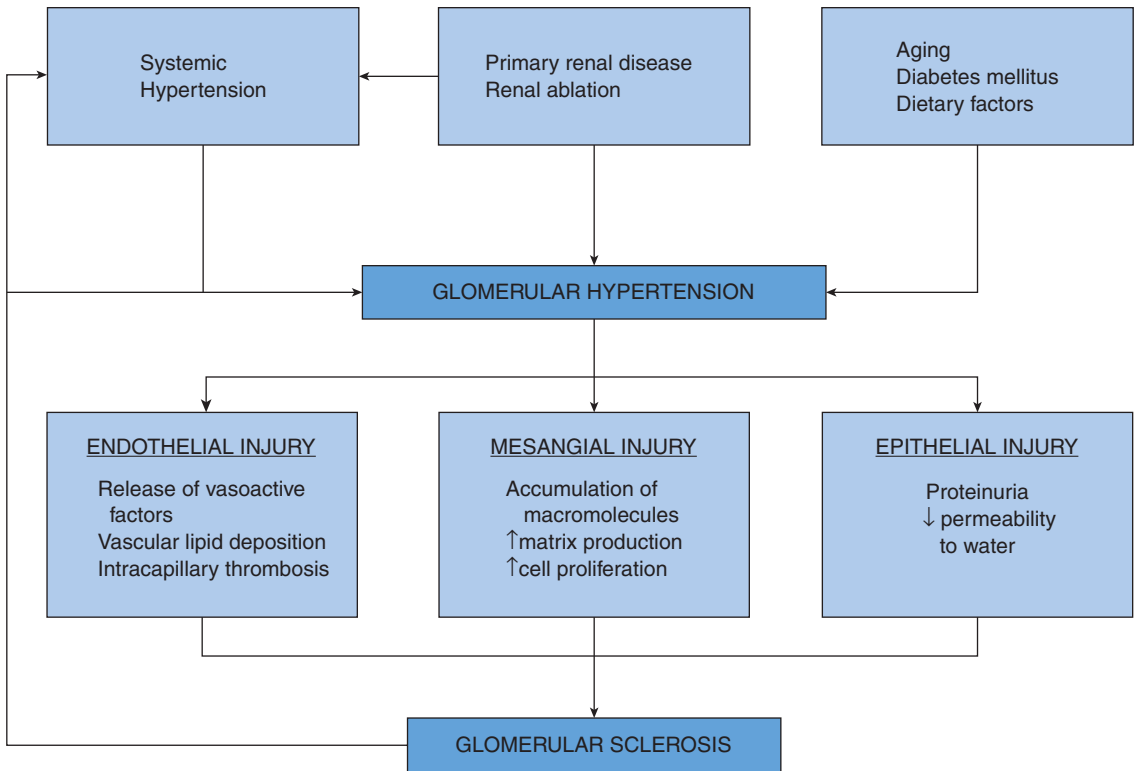


FIGURE 9-2 • Pivotal role in glomerular hypertension in the initiation and progression of structural injury. (Modified from Anderson S, Brenner BM. Progressive renal disease: A disorder of adaptation. *QJM* 1989;70:185–189.)

Management

Intensity of Therapy

Reduction of BP and proteinuria has been clearly shown to slow the rate of progression of CKD (Jafar et al., 2003; Lewis, 2007). However, as seen in Figure 9-3, only those with proteinuria above 1 g/day have been shown to benefit from more intensive lowering of BP. This was found in the MDRD study (Lazarus et al., 1997) and reconfirmed in the African American Kidney Disease and Hypertension (AASK) study (Wright et al., 2002). In the AASK study, no additional slowing of the progression of hypertensive nephrosclerosis was found in those given more therapy to provide an average BP of 128/78 compared to those given less therapy who ended up with an average BP of 141/85. Moreover, 759 of the original 1,094 enrollees in the AASK were followed for another 9 to 12 years while receiving an ACEI (Appel et al., 2010). Despite achieving a mean BP of 133/78, most of the patients continued to suffer a decline in renal function although the decline was less in those with heavy proteinuria.

The reason why there is no benefit of lowered BP on renal function in those with lesser degrees of proteinuria remains unknown. The reason why those with heavy proteinuria benefit likely reflects the damage induced by heavy loads of protein traversing the nephron, and the slowing of this damage as proteinuria is reduced, either by any drug that lowers renal perfusion pressure or by drugs that have a special ability to lower intraglomerular pressure, i.e., renin-angiotensin blockers.

Hazards of More Intensive Therapy

In multiple trials of patients with CKD, an *increased* incidence of cardiovascular morbidity and mortality has been noted when systolic pressures are lowered to below 130 mm Hg or diastolic pressure below 70 mm Hg (Kovesdy et al., 2013). However, in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS Collaborative Group, 2001), in which all 6,105 participants had known cerebrovascular disease, half were treated with an ACEI plus a diuretic, if needed, to

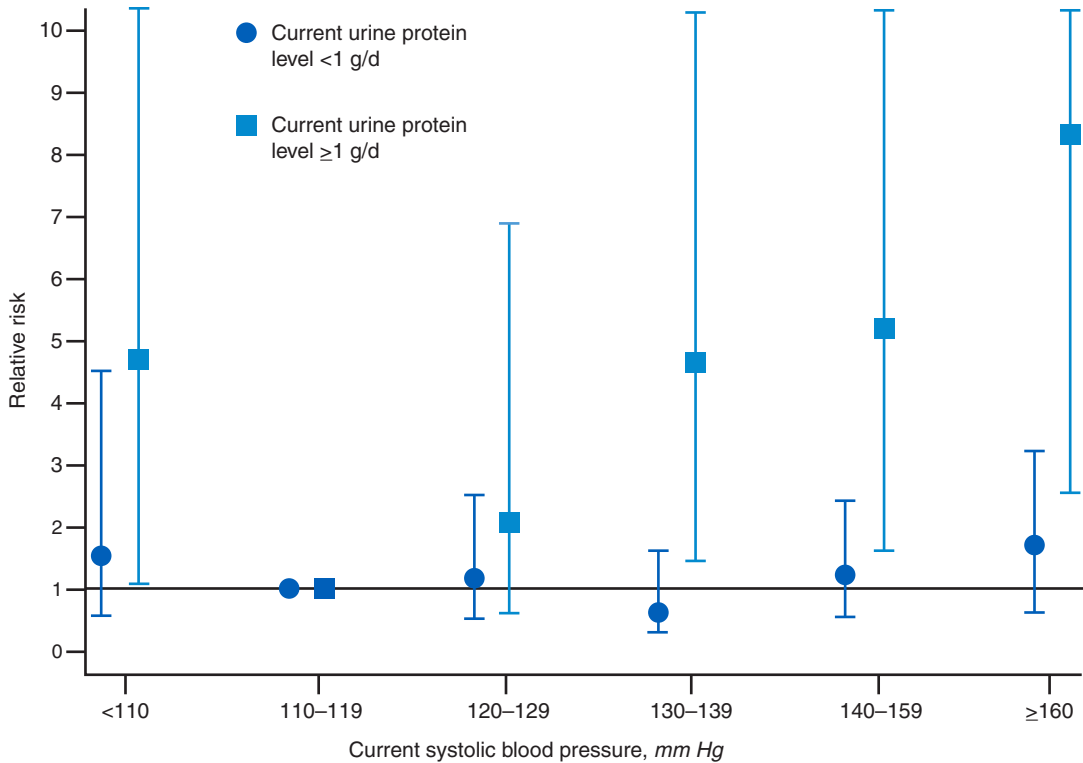


FIGURE 9-3 • The relative risk for progression of renal disease in patients with proteinuria either below or above 1 g/day by levels of systolic BP. The reference group (RR = 1) is a systolic pressure of 110 to 119 mm Hg. (Modified from Jafar TH, Stark PC, Schmid CH, et al. Progression of chronic kidney disease; The role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: A patient-level meta-analysis. *Ann Intern Med* 2003;139:244-252.)

lower the BP. The 1,757 patients with CKD had a progressively lower rate of recurrent stroke with reductions of BP even to below 120/70 mm Hg (Ninomiya et al., 2008).

Lifestyle Changes

All hypertensives with or without CKD, with or without diabetes, should be intensively encouraged to change their unhealthy lifestyles and given as much help as possible to achieve these changes.

Cessation of smoking is paramount, since smoking is a major risk for progression of CKD (Orth & Hallan, 2008).

Reduction in dietary sodium becomes increasingly more critical as CKD progresses and renal sodium excretory capacity becomes weaker (Mimran & du Cailar, 2008). Sodium reduction to the range of 1 to 2 g/day (sodium, 44 to 88 mEq/day) is both feasible and often necessary to control the hypertension in CKD patients (De Nicola et al., 2004). The importance of dietary sodium restriction in proteinuric

patients goes beyond the ability to enhance the effect of antihypertensive drugs (Slagman et al., 2011). In a study of 38 patients with CKD and an average of 3.8 g/day proteinuria, reduction of dietary sodium from 196 to 92 mmol/day provided a 22% reduction in proteinuria (Vogt et al., 2008).

Weight reduction: Obese hypertensive people are now likely to develop CKD (Gomez et al., 2006). Abdominal obesity rather than weight per se is the culprit (Elsayed et al., 2008). An increased likelihood of sleep apnea adds to the risk of obesity (Tsioufis et al., 2008).

Renin-Angiotensin System Blockers

Both ACEIs and ARBs reduce proteinuria and slow the progression of CKD equally (Kunz et al., 2008; Sarafidis et al., 2008b). The renoprotective effect has been shown in CKD caused by diabetes (Sarafidis et al., 2008b), nondiabetic disease (Jafar et al., 2003), and polycystic disease (Jafar et al., 2003). Among 28,487 hypertensive adults with a serum creatinine >6 mg/dL,

those given an ACEI or ARB had a statistically significant 6% lower risk for requiring long-term dialysis than did those not given a renin–angiotensin system (RAS)-inhibiting drug (Hsu et al., 2013). The prevention of progression to ESRD is directly related to the existing degree of renal impairment (O’Hare et al., 2014).

Despite their benefits, neither ACEIs nor ARBs have been found to reduce all-cause mortality in patients with CKD. Presumably, nonrenal events, which may become increasingly common the longer the CKD is held in check, are responsible.

These better effects of RAS inhibitors likely reflect their greater ability to reduce intraglomerular pressure by their preferential dilation of efferent arterioles (Fig. 9-4) (Tolins & Raji, 1991). The reduction in intraglomerular pressure protects the glomeruli from

progressive sclerosis and reduces the escape of protein into the tubule. At the same time, GFR is reduced and serum creatinine increased, usually to only a small degree. This expected, initial slight lowering of GFR is not a cause for stopping the use of an ACEI or ARB and is, in fact, followed by even greater renal protection (Holtkamp et al., 2011). If the serum creatinine rises or GFR falls more than 30% of the pre-ACEI or pre-ARB level, the ACEI or ARB should be stopped and other possible contributing causes identified and corrected, including volume contraction, concomitant use of NSAIDs, or, most dramatically, the presence of bilateral renovascular hypertension.

Another reflection of RAS inhibition is a rise in serum potassium, usually less than 0.5 mEq/L. However, if hyperkalemia above 5.5 mEq/L develops, the dose of ACEI or ARB should be reduced or the drug discontinued. Obviously, blood chemistries should be monitored within a few days of starting ACEI or ARB therapy in patients with CKD as a rapid and sustained rise in serum creatinine may occur with unrecognized bilateral renovascular disease or significant hyperkalemia may develop.

Combination of ACEI and ARB

Kunz et al. (2008) showed that the combination of an ACEI and an ARB reduced proteinuria an additional 20% over that seen with either drug alone. However, in the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET), the combination of the ACEI and the ARB in the same doses as were used alone did not reduce proteinuria more than either drug alone but *worsened* major renal outcomes (Mann et al., 2008). The worsening was reflected in more hypotension, more doubling of serum creatinine, and more entering dialysis. Messerli (2009) concluded that “dual RAS blockade should no longer be used in clinical practice” as more recently confirmed in a study with an ACEI and an ARB in patients with diabetic nephropathy (Fried et al., 2013).

Anemia with RAS Inhibitors

Both ACEIs and ARBs have been found to reduce hemoglobin levels in CKD patients, an effect attributed to the blockade of erythropoietic effects of angiotensin II on RBC precursors and to the improved oxygenation from increased renal blood flow (Mohanram et al., 2008). In the patients enrolled in the RENAAL trial given the ARB losartan, the greatest

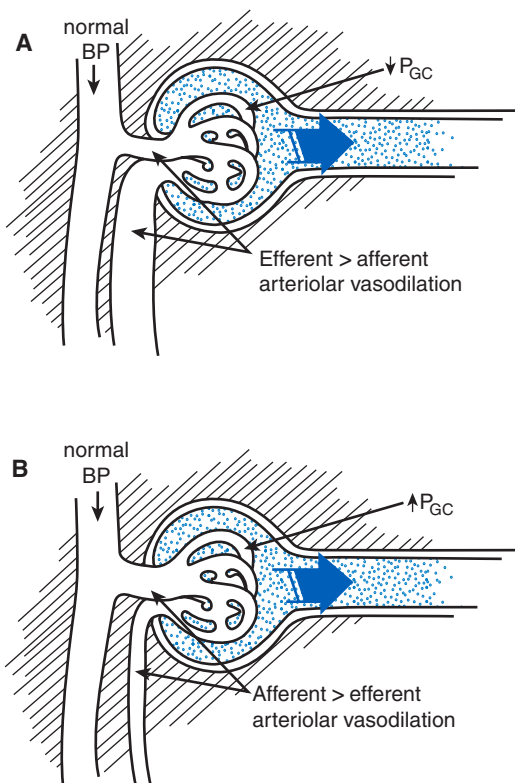


FIGURE 9-4 • Effect of antihypertensive treatment on glomerular hemodynamics as determined by micropuncture studies in rats. **A:** Angiotensin-converting enzyme inhibition results in normalization of BP associated with vasodilation, predominantly of the efferent arteriole, resulting in the normalization of intraglomerular capillary pressure (P_{Gc}). **B:** With CCBs, reduction of BP is offset by afferent arteriolar vasodilation, and, therefore, P_{Gc} remains elevated. (Modified from Tolins JP, Raji L. Antihypertensive therapy and the progression of chronic renal disease: Are there renoprotective drugs? *Semin Nephrol* 1991;11:538–548.)

effect on hemoglobin was seen at 1 year, but there was no impact on the renoprotective effect of the ARB.

Diuretics

A diuretic will likely be needed to bring the hypertension to near the 130/80-mm Hg goal that current guidelines recommend for CKD patients (Agarwal & Sinha, 2012). A therapeutic cross fire is often encountered: On the one hand, the need for a diuretic becomes progressively greater as renal function deteriorates and sodium cannot be excreted, so the intravascular volume is expanded and the BP rises (Sica, 2008). On the other hand, as renal function deteriorates, diuretics may not work. All diuretics must gain entry to the tubular fluid and have access to the luminal side of the nephron to work. They reach the tubular fluid by secretion across the proximal tubule by way of organic acid secretory pathways. Patients with CKD are thus resistant to acidic diuretics such as thiazides and the loop diuretics because of the accumulation of organic acid end products of metabolism that compete for the secretory pump.

In practice, thiazide diuretics in usual doses (12.5 to 50 mg) are usually not adequate when eGFR falls to below 50 mL/minute/1.73 m². Fortunately, loop diuretics can be safely given at high enough doses to cross the secretory barrier and exert a diuresis, even with much lower eGFR. To do so, enough must be given by the process of “sequential doubling of single doses until a ceiling dose is reached” (Brater, 1988). Once the ceiling dose is reached, that dose should be given as often as needed as a maintenance dose. If volume control is still not achieved, metolazone alone, or, even better, with a loop diuretic, will usually achieve a diuresis even in ESRD, if some residual renal function is present (Sica & Gehr, 2003). Caution is needed not to overdiurese by carefully monitoring the body weight.

Aldosterone Blockers

Aldosterone is now recognized to be an accelerator of renal damage by stimulating inflammation and fibrosis (Remuzzi et al., 2008). Since its secretion is largely controlled by angiotensin, the suppression of aldosterone synthesis by RAS inhibitors is considered to be responsible for at least part of the overall benefits of RAS inhibitors. However, a breakthrough of aldosterone secretion in the face of continued RAS inhibition has been recognized, first in the treatment of heart

failure (Lee et al., 1999), then in the treatment of hypertension (Sato & Saruta, 2001), and then in patients with CKD (Sato et al., 2003). Bomback and Klemmer (2007) identified eight well-performed studies with a range of incidence of breakthrough varying from 10% over 6 months to 53% over 1 year.

When an aldosterone blocker is added to an ACEI or ARB in CKD patients, proteinuria decreases from the level achieved by the RAS inhibitor by 15% to 54% and a significant fall in BP occurs in 40% of the patients (Bomback et al., 2008). Whether these impressive benefits occur only, or usually, in the presence of aldosterone breakthrough is not known, but aldosterone blockers are being increasingly used in CKD patients not adequately managed by RAS inhibition. An aldosterone blocker is usually relegated to the fourth line of therapy and only in those with a normal serum potassium because of the potential for hyperkalemia from the inhibition of potassium excretion by the aldosterone blocker. However, with the recognition of their remarkable ability to bring resistant hypertension into control even in hemodialysis patients (Flevari et al., 2013), the cautious use of aldosterone blockers even earlier in the treatment of CKD may become more acceptable.

Calcium Channel Blockers

As either second or third choice in treatment of hypertension in CRD patients, nondihydropyridine calcium channel blockers (non-DHP-CCBs) have usually been recommended based on their greater antiproteinuric effect than seen with DHP-CCBs in a review of 28 randomized trials (Bakris et al., 2004). This difference is attributed by Bakris et al. to a greater effect of non-DHP-CCBs on efferent arteriolar vasodilation than seen with DHP-CCBs in experimental models (Griffin et al., 1999). In addition, non-DHP-CCBs have been found to reduce glomerular permeability (Russo et al., 2002).

These differences in antiproteinuric effects have *not* been shown to eventuate in differences in renal protection between DHP-CCBs and non-DHP-CCBs. However, additional concern arose from the AASK trial of patients with CKD from hypertensive nephrosclerosis, wherein those with proteinuria greater than 300 mg/day had a faster decline in GFR if started on the DHP-CCB amlodipine than if started on the ACEI ramipril (Agodoa et al., 2001). However, the majority of the patients in the AASK trial had proteinuria less than 300 mg/day, and among them, GFR was better preserved in those on amlodipine. Moreover, in the

Ramipril Efficacy in Nephropathy trial, the use of DHP-CCBs improved renoprotection when added to an ACEI and when BP was reduced effectively (Ruggenti et al., 1998).

More recently, the combination of a DHP-CCB, either amlodipine or azelnidipine, with the ARB olmesartan lowered BP more and reduced cardiovascular events more than seen by doubling the dose of the ARB (Kim-Mitsuyama et al., 2013). Therefore, either type of CCB can safely and effectively be used when added to an ACEI or ARB in patients with CKD.

α -Blockers

Peripheral α -blockers, e.g., doxazosin, may be used without dose adjustment. The central α -blocker clonidine is often used as a bridge to lower BP on the days between dialysis, but its side effects and propensity to rebound makes it a poor substitute for adequate control of fluid volume.

β -Blockers

Now that their use has been shown to be less effective for primary prevention (see Chapter 7), β -blockers should be used only for secondary prevention of cardiac problems, e.g., post-MI, CHF, or tachyarrhythmias. If one is to be used, the choice should logically be one that is not cleared through the kidney, e.g., propranolol or timolol. The vasodilating α - β -blocking agents carvedilol and labetalol will cause less metabolic mischief than a β -blocker, and carvedilol has been shown to reduce proteinuria in CKD patients (Bakris et al., 2006). The vasodilating β -blocker nebivolol likely would do as well.

Minoxidil

In the past, those with refractory hypertension and CKD were often treated with minoxidil (Toto et al., 1995). However, when added to a regimen that included maximal doses of an ACEI or ARB, proteinuria increased despite the lower BP (Diskin et al., 2006).

Timing of Therapy

The potential for additional adverse effects of the persistently elevated nocturnal BP, i.e., nondipping, that is frequently present in patients with CKD has prompted studies comparing a shift in the timing of antihypertensive drug intake from morning to evening. Hermida

et al. (2005) found a decrease in the level of microalbuminuria among 200 hypertensives when the ARB valsartan was given at bedtime, compared to when it was given in the morning. A similar benefit was reported among 32 CKD patients whose proteinuria was decreased from 235 to 167 mg/day, when they took any one of their average daily intake of 2.4 medications in the evening (Minutolo et al., 2007).

However, as previously noted, bedtime dosing did not reduce the elevated nocturnal BP among black patients in the AASK follow-up study (Rahman et al., 2013).

The addition of a diuretic (Uzu et al., 2005) or the use of a long-acting antihypertensive taken in the morning may reduce the nocturnal pressure, at least in one study by increasing the daytime natriuresis, so the residual vascular volume is reduced (Fukuda et al., 2008). Similar benefit should be provided by a lower dietary sodium intake since, by the nature of CKD, renal sodium excretion is impaired (Bankir et al., 2008).

Restriction of Dietary Protein

A protein-restricted diet has been recommended for predialysis patients (Walser et al., 1999), and an analysis of multiple randomized trials has shown a delay in ESRD or death (Fougue et al., 2000), but individualized decisions seem appropriate in view of the malnutrition often seen with CKD (Levey, 2002).

Correction of Anemia

Anemia is a risk factor for progression of CKD and left ventricular hypertrophy (Rossing et al., 2004). However, treatment with erythropoietin to achieve a hemoglobin level above 12 g/L has been found to increase serious adverse events, so the current recommendations are to maintain a level of 11 g/L (Moist et al., 2008).

Lipid-Lowering Agents

In view of the common presence of dyslipidemia in CKD patients and the high rate of atherosclerotic vascular disease they suffer, the use of lipid-lowering agents seems appropriate. In a review of 50 trials involving 30,144 patients with CKD, statin therapy was found to reduce the risk of cardiovascular morbidity and mortality but had no effect on all-cause mortality and had uncertain renoprotective effects (Strippoli et al., 2008).

Increased Nitric Oxide

The potential of phosphodiesterase type 5 inhibition, now used to treat erectile dysfunction, to increase nitric oxide-induced vasodilation has been proposed (Brown et al., 2014).

Dose Modification of Other Drugs

The presence of CKD can influence the dosing of a variety of drugs, in particular those with considerable renal clearance (Table 9-4) (Kappel & Calissi, 2002). In stage 4 and 5 CKD, the metabolism and transport of nonrenally cleared drugs may also be altered (Nolin et al., 2008).

Beyond the impact of CKD on the handling of various drugs, used either for its own treatment or for the treatment of concomitant diseases, it is important

to recognize the potential for renal damage from both commonly used drugs, e.g., analgesics (Chang et al., 2008), and over-the-counter herbal remedies (Laliberte et al., 2007), as well as newer chemotherapeutic agents (Jain & Townsend, 2007).

CKD in the Elderly

With ageing, renal size and function decrease. Whether these changes are indicative of disease or an expected consequence of ageing is arguable. The presence of hypertension, whether cause or effect, hastens the loss of renal function (Rifkin et al., 2013).

Those over age 65 are becoming the largest burden of CKD: The medium age of new dialysis patients in the U.S. is now 65 years of age, and the fastest growing group of new dialysis patients is of those older than 75 years of age (Stevens et al., 2008)

TABLE 9-4

Dose Modification for Patients with Renal Insufficiency

Drugs Requiring Dose Modification	Drugs Not Requiring Dose Modification	
All antibiotics	EXCEPT	Cloxacillin, clindamycin, metronidazole, macrolides
<i>Antihypertensives</i>	<i>Antihypertensives</i>	
Atenolol, nadolol, angiotensin-converting enzyme inhibitors	CCBs, minoxidil, angiotensin receptor blockers, clonidine, α -blockers	
<i>Other cardiac medications</i>	<i>Other cardiac medications</i>	
Digoxin, sotalol	Amiodarone, nitrates	
<i>Diuretics</i>	<i>Narcotics</i>	
AVOID potassium-sparing diuretics in patients with creatinine clearance <30 mL/min	Fentanyl, hydromorphone, morphine	
<i>Lipid-lowering agents</i>	<i>Psychotropics</i>	
HMG-CoA reductase inhibitors, bezafibrate, clofibrate, fenofibrate	Tricyclic antidepressants, nefazodone, other selective serotonin reuptake inhibitors	
<i>Narcotics</i>	<i>Antidiabetic agents</i>	
Codeine, meperidine	Repaglinide, rosiglitazone	
<i>Psychotropics</i>	<i>Miscellaneous</i>	
Lithium, chloral hydrate, gabapentin, trazodone, paroxetine, primidone, topiramate, vigabatrin	Proton pump inhibitors	
<i>Antidiabetic agents</i>		
Acarbose, chlorpropamide, glyburide, glipizide, metformin, insulin		
<i>Miscellaneous</i>		
Allopurinol, colchicine, histamine ₂ receptor antagonists, diclofenac, ketorolac, terbutaline		

Modified from Kappel J, Calissi P. Nephrology: 3. Safe drug prescribing for patients with renal insufficiency. CMAJ 2002;166:473-477.

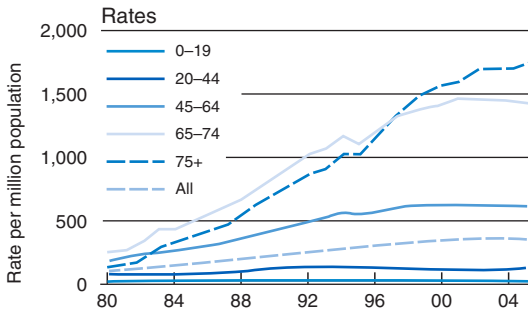


FIGURE 9-5 • Rates of new cases of ESRD in patients at various ages treated by dialysis or transplantation in the U.S., by years from 1980 to 2004. (Modified from U.S. Renal data systems. Chronic Kidney Disease. *USRDS 2007*, Bethesda NIH, NIDDKD 2008.)

(Fig. 9-5). Although the diminution of renal structure and function with age may largely reflect the impact of nonrenal diseases, e.g., hypertension or diabetes (Rifkin et al., 2013), the kidney ages even in their absence (Rule et al., 2011).

The loss of renal function with age is often heralded by increasing nocturia, as sodium ingested during the day is more slowly excreted into the night (Kujubu & Aboseif, 2008). More seriously, cognitive impairment closely accompanies progressive CKD (Barzilay et al., 2011).

More in the U.S. than elsewhere, older patients with advanced CKD are increasingly started on RRT, including dialysis and transplantation. However, the societal costs and the individual discomforts of such intensive treatment are well recognized. Calls for more limited management are being made, particularly for those afflicted with other life-threatening conditions (Schell & Holley, 2013).

DIABETIC NEPHROPATHY

Most of the preceding coverage of CKD applies to the most common of its causes—diabetic nephropathy. However, diabetes provokes additional pathology and requires additional therapy (Table 9-5) (KDIGO, 2012).

Pathology and Clinical Features

As delineated by Kimmelstiel and Wilson (1936), renal disease occurs among diabetics with a high incidence and with a particular glomerular pathology—nodular intercapillary glomerulosclerosis. The clinical

TABLE 9-5

Goals for Risk Factor Management in Diabetic Patients

Risk Factor	Goal of Therapy
Cigarette smoking	Complete cessation
BP	<140/90 mm Hg
LDL-C	<100 mg/dL
Triglycerides >200 mg/dL; HDL-C <40 mg/dL	Increase HDL-C
Prothrombotic state	Aspirin
Glucose	HbA _{1c} < 7%
Overweight and obesity (BMI ≥ 25 kg/m ²)	Significant weight loss
Physical inactivity	Regular exercise

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA_{1c}, hemoglobin A_{1c}.

description has been improved very little since their original paper (Kimmelstiel & Wilson, 1936):

The clinical picture appears... to be almost as characteristic as the histological one: the patients are relatively old; hypertension is present, usually of the benign type, and the kidneys frequently show signs of decompensation; there is a history of diabetes, usually of long standing; the presenting symptoms may be those of edema of the nephrotic type, renal decompensation or heart failure; the urine contains large amounts of albumin and there is usually impairment of concentrating power with or without nitrogen retention.

The clinical description should be altered to include younger patients who have been diabetic for more than 15 years, to involve hypertension in approximately 50% to 60% of patients, and to almost always be accompanied by retinal capillary microaneurysms.

Course

Persistent microalbuminuria, as the first manifestation of diabetic nephropathy, has been observed in about one-third of newly diagnosed type 1 diabetics within 20 years (Hovind et al., 2004) and in about one-quarter of newly diagnosed type 2 diabetics within 10 years (Adler et al., 2003). The difference in time of onset may largely reflect the long asymptomatic background of type 2 compared to the usual abrupt onset of type 1. Rather surprisingly, regression of microalbuminuria has been observed in a significant

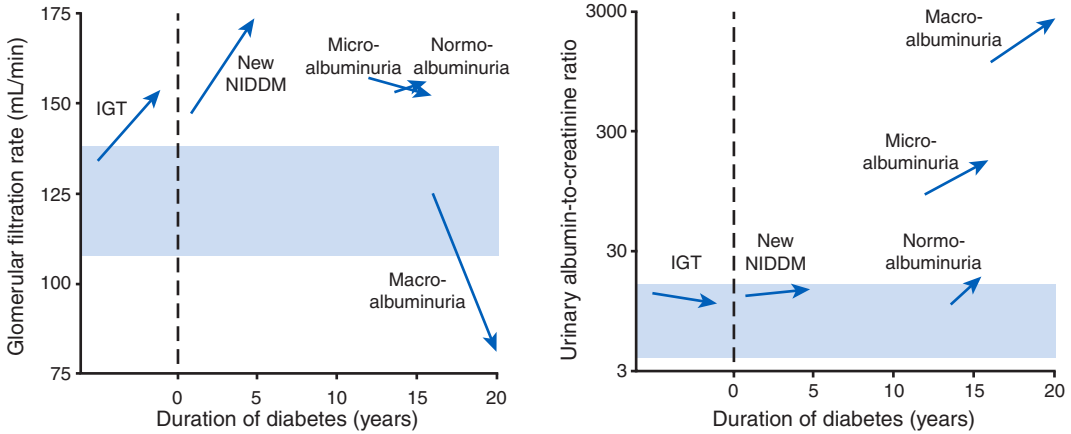


FIGURE 9-6 • Changes in the mean GFR and median urinary albumin (mg/L) to creatinine (g/L) ratio from baseline to the end of follow-up in subjects with impaired glucose tolerance (IGT), newly diagnosed non-insulin-dependent diabetes mellitus (New NIDDM), NIDDM and normal urinary albumin excretion (normoalbuminuria), NIDDM and microalbuminuria, and NIDDM and macroalbuminuria. Arrows connect the value of the baseline examination with the value at the end of follow-up; dashed lines indicate the time of diagnosis; shaded areas indicate the 25th and 75th percentiles of values in subjects with normal glucose tolerance. (Modified from Nelson RG, Bennet PH, Beck GH, et al. Development and progression of renal disease in Pima Indians with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1996;334:1636-1642.)

percentage of type 1 diabetics, generally associated with lower levels of BP and glycemia (Hovind et al., 2004; Perkins et al., 2003).

Nelson et al. (1996) studied renal function every 6 to 12 months over 4 years in 194 Pima Indians who were selected as the representatives of different stages in the development of diabetic nephropathy: from normal glucose tolerance to overt diabetes and from normal albumin excretion to macroalbuminuria. As shown in Figure 9-6, the major findings generally were as follows: Glomerular hyperfiltration is present from the onset until macroalbuminuria appears. Thereafter, GFR declines rapidly because of a progressive loss of intrinsic ultrafiltration capacity. Although the rather abrupt fall in GFR that occurs after approximately 15 years was not prevented by the control of BP, higher baseline pressures predicted an increasing urinary albumin excretion, which in turn mediated a fall in GFR.

Mechanisms

The mechanisms of diabetic nephropathy involve the interplay of multiple factors (Friederich-Persson et al., 2013; Jefferson et al., 2008) (Fig. 9-7).

The critical role of glomerular hypertension has been strongly supported by the ability of antihypertensive therapy to prevent the progression of nephropathy. In addition to multiple clinical studies, the role is supported by the observation that

nodular glomerulosclerosis developed in only the nonobstructed kidney of a diabetic patient with unilateral renal artery stenosis (Berkman & Rifkin, 1973). Moreover, normal kidneys transplanted into diabetic patients develop typical diabetic lesions (Mauer et al., 1983), denying an essential role for genetic factors.

The progression from glomerular hypertension to overt nephropathy has been portrayed by Adler (2004):

Mesangial expansion is the defining lesion in diabetic nephropathy... The mesangial expansion encroaches on capillary lumina and results in slow progression toward end-stage renal disease. But the diabetic lesion also involves podocyte injury mediated by signal transduction change, cytoskeletal change, alterations in the podocyte slit pore membrane, detachment from the GBM, and apoptosis, all of which contribute to the development of proteinuria. In turn, proteinuria accelerates progression by its effects on tubulointerstitial fibrosis and atrophy, the final common pathway of progressive renal insufficiency. Adding insult to injury are the arterial and arteriolar sclerotic lesions, which superimpose ischemia on each of the other three renal regions.

Dr. Adler identifies angiotensin II as the primary mediator of this progression. She states that:

angiotensin II interacts on the cell membrane with its receptor(s), and then triggers the elaboration of signaling

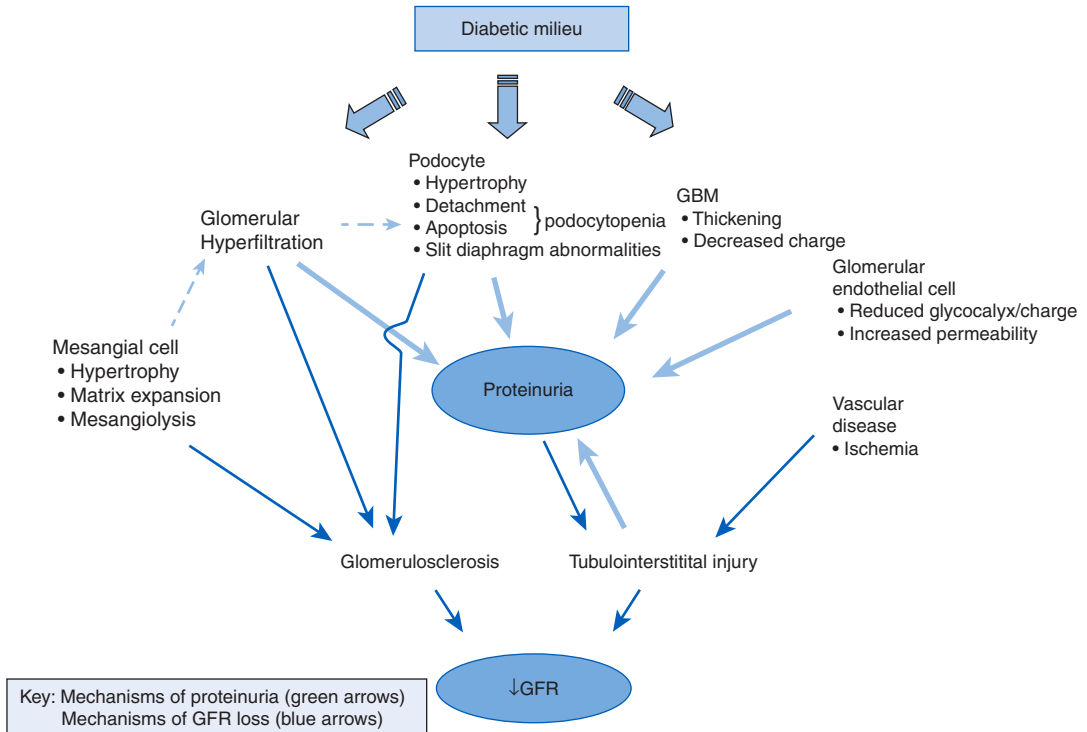


FIGURE 9-7 • Scheme for unifying the mechanisms of proteinuria (lighter arrows) and the decreases in GFR (darker arrows) in patients with diabetic kidney disease. (Reproduced from Jefferson JA, Shankland SJ, Pichler RH. Proteinuria in diabetic kidney disease: A mechanistic viewpoint. *Kidney Int* 2008;74:22–36, with permission.)

molecules, the activation of transcription factors, and the up-regulation of gene expression, ultimately inducing the fibrosis, cell growth, and even the inflammation that characterize the renal damage in diabetic nephropathy... Angiotensin II interacts with many other growth factors and cytokines that also are activated in diabetic nephropathy and that simultaneously utilize the same and parallel signaling pathways, all factors or systems contributing to the histologic picture and functional decline of the diabetic kidney.

Hypertension

As recalled by Mogensen (1999), the associations between hypertension and both increasing albuminuria and falling GFR have been recognized for more than 40 years and repeatedly confirmed. An increase in nocturnal systolic BP has been found to precede the development of microalbuminuria (Lurbe et al., 2002).

Renin–Angiotensin

The progressive glomerulosclerosis would be expected to knock out the juxtaglomerular cells that secrete

renin, and, in some diabetics, a state of *hyporeninemic hypoaldosteronism* appears, usually manifested by hyperkalemia (Perez et al., 1977). However, serum renin and prorenin levels are often increased before the onset of microalbuminuria, serving as a potential marker for the development of nephropathy (Dronavelli et al., 2008). Moreover, the intrarenal RAS is activated in both type 1 (Hollenberg et al., 2003) and type 2 (Mezzano et al., 2003) diabetics. These findings suggest autonomy of the intrarenal renin system and set the stage for the major benefits of RAS inhibitors seen in diabetic nephropathy. Moreover, elevated plasma aldosterone levels have been noted in type 1 diabetics (Hollenberg et al., 2004), presumably reflecting an activated systemic RAS.

Management

Management of hypertension in patients with diabetic nephropathy is similar to that of hypertension in all CKDs, but there are differences. The management of hypertension in diabetics without nephropathy is covered in Chapter 7.

Glycemic Control

Control of hyperglycemia was shown to slow the progress of nephropathy in the long-term follow-up of the Diabetes Control and Complications Trial study of 1,349 type 1 diabetic patients (Writing Team, 2003). However, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, more intensive control of hyperglycemia was associated with *increased* all-cause mortality and did not prevent ESRD although there was a slower progression of albuminuria (ACCORD Study Group, 2008).

Antihypertensive Therapy

Evidence has been available since 1976 that reduction of elevated BP will slow the progression of diabetic nephropathy (Mogensen, 1976). The evidence accumulated from multiple subsequent trials has made two certain conclusions: First, the degree of BP reduction needed to protect against progression is lower than the previously accepted goal of 140/90 mm Hg, and, second, multiple drugs will usually be needed to achieve the necessary goal (KDIGO, 2012).

Although there were few patients with overt nephropathy enrolled, the ACCORD trial provides the best evidence about the level of BP reduction that would be most protective of patients with diabetes (ACCORD Study Group, 2010a). Half of the 4,733 patients with diabetes and hypertension were randomly assigned to more intensive antihypertensive therapy to lower their systolic BP to below 120 mm Hg and the other half to less intensive therapy to lower the systolic BP to below 140 mm Hg. At the end of the trial, with a mean follow-up of 4.7 years, the more intensively treated group had a mean SBP of 119.3 mm Hg, and the less intensively treated an SBP of 133.5 mm Hg. The primary composite outcomes of nonfatal myocardial infarction or stroke or death from cardiovascular disease did not differ between the two groups. There were fewer strokes and increases of serum creatinine to above 1.5 mg/dL (8.4% vs. 12.9%) or falls in eGFR to below 30 (2.2% vs. 4.2%) in the more intensively treated group but more serious adverse effects (3.3% vs. 1.3%). The authors concluded that overall, there was no benefit from more intensive BP lowering to a systolic level below 130 mm Hg in patients with diabetes and hypertension.

Despite these negative findings, the 2012 KDIGO guidelines continue to recommend reductions to below 130/80 mm Hg in diabetic patients with proteinuria (Stevens and Levin, 2013).

Choices of Drugs

ACEIs, ARBs, and DRIs

Although the renoprotection provided in the original trials by Mogensen (1976) and Parving et al. (1983) used diuretics, β -blockers, and direct vasodilators—the major drugs available in the 1970s—more recent trials have almost all used ACEIs or ARBs as the primary drug. As reviewed earlier in this chapter, ACEIs and ARBs (and DRIs) theoretically should reduce intraglomerular pressure better than do other drugs, and, practically, they do. The evidence, starting with overt nephropathy in hypertensive type 1 diabetics and extending to those with severe CKD (Hsu et al., 2013), goes down to encompass normotensive diabetics with, or without, microalbuminuria (Estacio et al., 2006).

As with nondiabetic CKD, the wisest course is to start with an ACEI or an ARB but not to combine RAS-blocking drugs (Fried et al., 2013).

Additional Drugs

More than one drug will usually be needed and the second one should usually be a diuretic (Mogensen et al., 2003), as volume expansion is usual with any degree of renal insufficiency. A CCB could be the appropriate choice, sometimes second but always third.

Other choices for third or fourth add-ons include α -blockers or vasodilating β -blockers. Although aldosterone antagonists were usually avoided in CKD patients because of the threat of hyperkalemia, particularly on top of an ACEI or ARB, aldosterone escape has been noted in 40% of ACEI-treated patients with diabetic nephropathy (Sato et al., 2003). Therefore, cautious use of an aldosterone antagonist is appropriate, and perhaps earlier, in the algorithm (Mehdi et al., 2009).

Other Therapies

As with nondiabetic CKD, a *low-protein diet* should be helpful. *Moderate sodium restriction* is clearly necessary (Vogt et al., 2008). However, in the ACCORD Study Group (2010b), intensive lipid-lowering did not reduce the incidence of the primary cardiovascular events. The potential of phosphodiesterase 5 inhibition to increase nitric oxide–induced vasodilation has been suggested (Brown et al., 2014).

Gaede et al. (2008) provided a striking demonstration of the ability of a multifaceted approach involving tight control of hypertension, hyperglycemia, and dyslipidemia, along with aspirin and an ACEI, to

reduce the progression of nephropathy as well as retinopathy and autonomic neuropathy in patients with type 2 diabetes and microalbuminuria. Despite the costs and problems of such intensive therapy, the benefits are surely worth the expense and effort.

CHRONIC DIALYSIS

Although only a small proportion of CKD patients progress to ESRD and start dialysis, they constitute an inordinate personal and societal burden. They represent 1.7% of U.S. Medicare patients but consume 6.4% of Medicare's budget, and, as noted at the beginning of this chapter, their numbers are projected to continue to climb rapidly.

The Role of Hypertension

Hypertension in the dialysis patient can be attributed to a host of factors (Table 9-6). Preexisting hypertension is a major risk factor for progression to ESRD, along with the other expected suspects: age, gender, eGFR, diabetes, and anemia (Johnson et al., 2008; Levin et al., 2008). The most useful BP measurements are those taken outside the dialysis center (Agarwal, 2010).

BP is usually higher before dialysis from volume overload and lower after dialysis. In a retrospective cohort study of 113,255 hemodialysis patients over a 5-year interval with a median follow-up of 2.2 years, there was a U-shaped association between changes from predialysis to postdialysis BP and all-cause mortality (Park et al., 2013). Postdialysis drops in systolic BP between -30 and 0 mm Hg were associated with greater survival, whereas both greater falls and any increase were associated with increased mortality rates.

Intradialytic hypotension is often seen. Davenport et al. (2008) found that the incidence of this serious problem was significantly greater in centers that achieved the highest rate of meeting the postdialysis BP target. As reviewed by Palmer and Henrich (2008), there are many factors responsible and many ways to avoid, or treat, this hemodynamic instability (Table 9-7).

As to hypertension, the simplest, but perhaps the most difficult to obtain, is rigid reduction of dietary sodium intake to maintain the "dry weight" and limit the fluid volume expansion between dialysis, as long preached by the late Belding Scribner (1999) and repeatedly shown to be helpful (Agarwal et al., 2009; Ozkahya et al., 2006). More antihypertensive drugs will almost certainly not play a prominent role.

TABLE 9-6

Mechanisms of Hypertension in the Hemodialysis Patient

Preexisting hypertension
Extracellular fluid volume expansion
Inability to excrete sodium
Blood volume–related vasoactive substances
Dietary salt noncompliance
Renal-dependent mechanisms
Dysregulation of RAS
Sympathetic hyperactivity
Loss of inherent renal vasodilatory factors
Vascular mechanisms
Elevated calcium/phosphate product
Secondary hyperparathyroidism
Vascular calcification and stiffening
Medications and toxins
Sympathomimetics
Erythropoietin
Cigarette smoking
Lead exposure
Circulating factors
Endogenous inhibitors of nitric oxide system
Endogenous inhibitors of vascular Na ⁺ , K ⁺ -ATPase
Parathyroid hormone
"Uremic toxins"
Hemodialysis prescription
Dialysate Na ⁺ and K ⁺ concentrations
Shorter dialysis sessions
Overestimation of dry weight
Impaired sleep; sleep apnea

Modified from Khosla UM, Johnson RJ. Hypertension in the hemodialysis patient and the "lag phenomenon": Insights into pathophysiology and clinical management. *Am J Kidney Dis* 2004;43:739–751.

The best solution to almost all of the problems faced by dialysis patients, including their hypertension and hypotension, has been described in over 300 papers over the past 40 years—daily hemodialysis. The survival data on 415 patients treated by short daily hemodialysis, either at home or in centers, are striking: much better than with thrice-a-week dialysis and similar to what is achieved by renal transplantation (Kjellstrand et al., 2008).

HYPERTENSION AFTER KIDNEY TRANSPLANTATION

As more patients are receiving renal transplants and living longer thereafter, hypertension has been recognized as a major complication, one that may, if uncontrolled,

TABLE 9-7

Causes of Dialysis-Related Hypotension

Excessive ultrafiltration
 Decrease of plasma osmolality
 Dialysate problems: temperature, bioincompatibility
 Hyperinsulinemia from dialysate-induced hyperglycemia
 Reflex sympathetic inhibition
 Autonomic neuropathy
 Bleeding
 Electrolyte abnormalities (hypokalemia, hyperkalemia, hypocalcemia)
 Sepsis
 Heart disease (ischemia, arrhythmias, pericardial effusion with cardiac tamponade)
 Restoration of nitric oxide by the removal of endogenous inhibitors

quickly destroy the transplant or add to the risk of cardiovascular disease (Gill, 2008). The majority of transplant recipients are hypertensive, and the higher the level of BP at 1 year after transplantation, the lower is the rate of allograft survival (Mange et al., 2004). Naesens et al. (2013) found that the noninvasive

TABLE 9-8

Causes of Posttransplantation Hypertension

Immunosuppressive therapy
 Steroids
 Cyclosporine, tacrolimus
 Allograft failure
 Chronic rejection
 Recurrent disease
 Potentially surgically remediable causes
 Allograft renal artery stenosis
 Native kidneys
 Volume expansion
 Erythrocytosis
 Sodium retention
 Speculative cause
 Recurrent essential hypertension
 As a primary cause of ESRD
 From a hypertensive or prehypertensive donor
 Other pressor mechanisms including:
 Endothelin
 Transforming growth factor β
 Decreased nitric oxide

measurement of the intrarenal resistive index provided an accurate indicator of the viability of the transplanted kidney. Table 9-8 lists a number of causes of posttransplantation hypertension beyond the persistence of primary hypertension.

Management

Absent any reversible cause, most posttransplant hypertension will require at least two drugs for control. An ACEI or ARB and a CCB are the most likely combination. However it is done, the intensive control of hypertension to below 130/80 mm Hg is necessary to protect the kidney, while close attention is directed toward all other treatable cardiovascular risk factors.

Now that renal parenchymal diseases have been covered, hypertension caused by renovascular diseases will be examined.

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Renovascular Hypertension

Of all of the fairly common identifiable causes of hypertension, renovascular hypertension (RVHT) remains the most puzzling: Although its pathophysiology would seem clear, uncertainty remains as to its prevalence, natural history, diagnosis, and treatment (Textor & Lerman, 2013).

These uncertainties reflect a confluence of factors:

- ▶ Atherosclerotic renal artery stenosis (ARAS) is becoming more prevalent as the population becomes older, hypertensive, and atherosclerotic (Benjamin et al., 2014).
- ▶ Need to further increase awareness among clinicians that ARAS is a rare but reversible cause of flash pulmonary edema (Ritchie et al., 2014).
- ▶ Hesitation of physicians to prescribe angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) for patients with ARAS despite mounting evidence (Chrysochou et al., 2012a) to support grade A recommendations that these drugs rarely precipitate acute renal failure even in patients with bilateral ARAS and should be first-line therapy (Anderson et al., 2013).
- ▶ Major randomized controlled trials (RCTs) have shown substantially greater risks but no benefit of renal artery angioplasty and stenting over intensive medical therapy on renal or cardiovascular outcomes (Bax et al., 2009; Cooper et al., 2014; Wheatley et al., 2009).
- ▶ However, experienced interventional cardiologists continue to argue that the trials were substantially flawed due to selection bias, with the more severely affected patients—those who stand to benefit most from renal artery stenting—being excluded from study (White, 2014).
- ▶ Observational data (Ritchie et al., 2014), meta-analyses (Weinberg et al., 2014), and American College of

Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines (Anderson et al., 2013) continue to endorse benefits of radiologic evaluation and stenting for patients with severe ARAS (>70% stenosis or evidence of hemodynamic compromise) *plus* one or more of the following three scenarios: (1) medically refractory hypertension, (2) progressive azotemia, and/or (3) repeated episodes of “flash” pulmonary edema.

- ▶ Lack of an accurate well-established diagnostic test to select severe hemodynamic lesions for stenting (White, 2014).
- ▶ Renal microvessel disease that may not be reversed by proximal artery stenting alone (Saad et al., 2013) but may be amenable to stem cell therapy (Eirin et al., 2012). Intriguing new translational research from Textor and coworkers at Mayo Clinic indicating that ARAS—which characteristically involves the proximal main renal artery by angiography—can be accompanied by inflammation and impaired function of renal microvessels that are distal to the angiographic stenosis. Opening the proximal stenosis may have no effect on the distal vasculopathy.

The dilemma is obvious: More patients have renovascular atherosclerosis that can induce hypertension/renal ischemia/pulmonary edema, but uncertainty remains as to how to diagnose and treat them (Textor & Lerman, 2013). In the words of White (2014):

The Achilles’ heel of renal artery intervention is our dependence on invasive angiography to determine which renal artery stenosis cause renal ischemia. Angiography has been shown to poorly discriminate the hemodynamic severity of moderate renal artery stenosis. There is no relationship between moderate (50% to 70%) renal artery stenosis determined by quantitative angiography

and the hemodynamic severity of a renal artery stenosis. Without measuring the hemodynamic severity of the renal artery stenosis, one cannot hope to separate patients with true RVHT from those with atherosclerotic renal artery disease and essential hypertension.

On the other hand, patients with refractory hypertension, worsening renal function, or recurrent flash pulmonary edema should be evaluated for ARAS and considered for renal artery stenting. In such patients, it is important to consider this disease because, if identified, it can be relieved; if left untreated, it may destroy the kidneys. The presence of bilateral renal artery stenosis should be considered in all patients with unexplained progressive renal insufficiency leading to dialysis, because ischemic nephropathy may be involved in as many as 11% of such patients (Guo et al., 2007). Even in patients with end-stage renal disease (ESRD), relief of renal artery stenosis may prevent, delay, or overcome the need for dialysis (Thatipelli et al., 2008).

RENOVASCULAR STENOSIS VERSUS RVHT

RVHT refers to hypertension caused by renal ischemia. It is important to realize that renovascular stenosis may or may not cause sufficient hypoperfusion to set off the processes that lead to hypertension and renal atrophy. The problem is simply that ARAS is much more common than is RVHT. For example, arteriography revealed some degree of ARAS in 32% of 303 normotensive patients and in 67% of 193 hypertensives with an increasing prevalence with advancing age (Eyler et al., 1962) (Table 10-1). Note that in Table 10-1, almost half of normotensive patients older than 60 had atherosclerotic lesions in their proximal renal arteries.

More recent studies show similar data. ARAS is detected in up to 30% of patients undergoing screening ("drive by") renal angiography during diagnostic cardiac catheterization (Sattur et al., 2013).

As a historical note, before 1960, unilateral nephrectomy was frequently performed on hypertensive patients with a unilateral small kidney who did not have reversible atherosclerotic renovascular hypertension (AVRHT). Smith (1956) recognized this as early as 1948 as a misguided application of Goldblatt's experimental model of hypertension induced by clamping the renal artery. Smith reported that only 25% of patients were relieved of their hypertension by nephrectomy and warned that only about 2% of all hypertensives probably could be helped by this surgery.

TABLE 10-1

Prevalence of Renal Arterial Lesions in Normotensive and Hypertensive Patients

Age	Normotensive		Hypertensive	
	Normal	Lesion	Normal	Lesion
31-40	7	3	6	10
41-50	26	8	14	22
51-60	99	35	28	50
60+	69	56	15	48

Data from Eyler WR, Clark MD, Garman JE, et al. Angiography of the renal areas including a comparative study of renal arterial stenosis in patients with and without hypertension. *Radiology* 1962;78:879-892.

PREVALENCE OF RVHT

Smith's (1956) estimate of the true prevalence of ARVHT may be right. The prevalence varies with the nature of the hypertensive population:

- In nonreferred hypertensive patient populations, the prevalence is likely less than 1% (Kalra et al., 2005).
- In patients with resistant hypertension, the prevalence is higher: For example, in one recent series, 24% of 285 patients of mean age 73 with suggestive clinical features had at least a 50% stenosis of one or both renal arteries by renal angiography (Benjamin et al., 2014). The prevalence estimate clearly would be less if a 70% stenosis were required.
- Since most renovascular disease is atherosclerotic in origin, the prevalence, not surprisingly, increases with age and often coexists with peripheral artery disease (Benjamin et al., 2014). ARAS occurs in over 40% of patients with peripheral artery disease and 7% to 14% of patients undergoing diagnostic cardiac catheterization for suspected coronary disease (Boateng & Greco, 2013). Of 1,734 patients (mean age 72) undergoing nonemergent diagnostic coronary catheterization for chest pain, 72% had CAD and 7% had renal artery stenosis by Doppler ultrasound (Imori et al., 2014).
- Diabetic hypertensives, surprisingly, do not have an increased risk of ARAS (Benjamin et al., 2014).
- ARAS may or may not be less common in black hypertensives; data are scarce and ascertainment bias is an issue (Svetkey et al., 1991).

- ARVHT has been recognized in neonates (Ramaswamy et al., 2011) and children (Zhu et al., 2014).

A systemic review of 40 studies involving a total number of 15,879 patients found the following prevalence estimates for ARAS (de Mast & Beutler, 2009):

- Hypertension and diabetes, 20%
- Coronary angiography, 10.5%
- Coronary angiography in hypertensive patients, 18%
- Coronary angiography and suspected renovascular disease, 17%
- Heart failure, 54%
- Peripheral vascular disease, 25%
- Abdominal aortic aneurysm, 31%
- End-stage renal disease, 41%

MECHANISMS OF HYPERTENSION

Animal Models

The pathophysiology of RVHT was first identified by Goldblatt et al. (1934) who—looking not for RVHT but for a renal cause for primary hypertension—put clamps on both main renal arteries of dogs. The clamps were inserted on separate occasions so that they could observe the effect of unilateral obstruction (Fig. 10-1). However, with the modest degree of constriction that they used, unilateral clamping caused only transient hypertension. For permanent hypertension, both renal arteries had to be clamped, or one clamped and the contralateral kidney removed (Goldblatt, 1975).

After significant renal ischemia and the initial marked rise in renin secretion, renin levels fall but remain inappropriately high and are largely responsible for the hemodynamic changes (Welch, 2000). Figure 10-2 shows a stepwise scheme for the hemodynamic and hormonal changes that underlie ARVHT.

Activation of the sympathetic nervous system amplifies the effects of renin–angiotensin system activation in the 2-kidney-1-clip animal model of ARAS (Pradhan & Rossi, 2013), a topic pioneered by Page (1982). Renal ischemia activates renal afferent nerves that project to the subformal organ (SFO), a circum-ventricular organ that lacks a blood–brain barrier and is thus permeant to circulating angiotensin II (Ang II), which also is increased secondary to increased

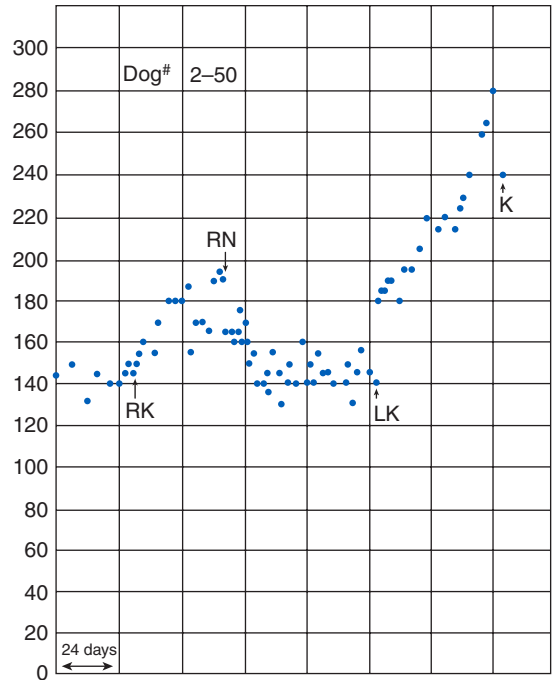


FIGURE 10-1 • Results from one of Goldblatt's original experiments. The graph shows the mean BP of a dog whose right kidney was first moderately constricted (RK), with subsequent hypertension that was relieved after right nephrectomy (RN). After severe constriction of the left renal artery (LK), more severe hypertension occurred, and the animal was sacrificed (K). (From Hoobler SW. History of experimental RVHT. In: Stanley JC, Ernst CB, Fry WJ, eds. *Renovascular Hypertension*. Philadelphia, PA: Saunders; 1984:12–19.)

renin during renal ischemia. These converging neural and hormonal inputs into the SFO activate cardiovascular circuits in the rostral brain stem that increase efferent renal sympathetic nerve activity to the contralateral kidney, further increasing plasma renin activity (Fig. 10-3) (Pradhan & Rossi, 2013).

New Clinical Translational Research

Textor and coworkers have made a recent breakthrough in our understanding of the pathogenesis and progression of ARAS in patients using blood oxygen level–dependent renal magnetic resonance imaging (BOLD-MRI) (Textor & Lerman, 2013). As diagrammed in Figure 10-4, they propose three stages in the progression of ARAS:

- With mild–moderate/early- to mid-stage ARAS, renal blood flow is reduced by up to 50%, but renal tissue oxygenation is well preserved due mainly to a compensatory reduction in GFR and thus

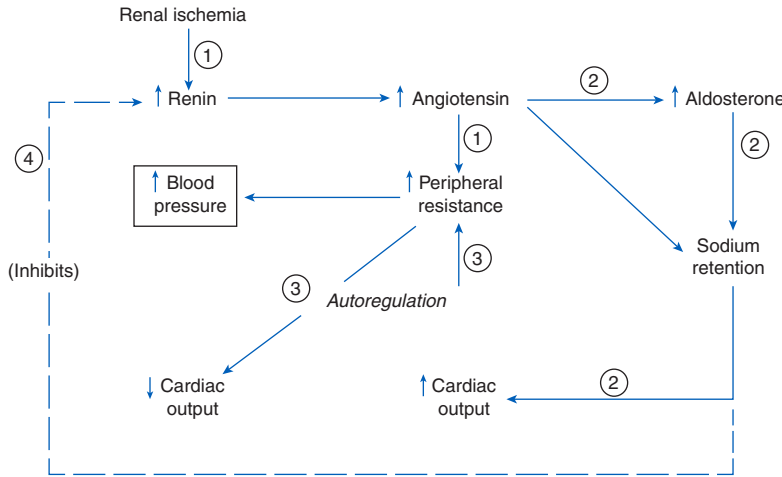


FIGURE 10-2 • Hypertension with renovascular disease. Stepwise hemodynamic changes in the development of RVHT.

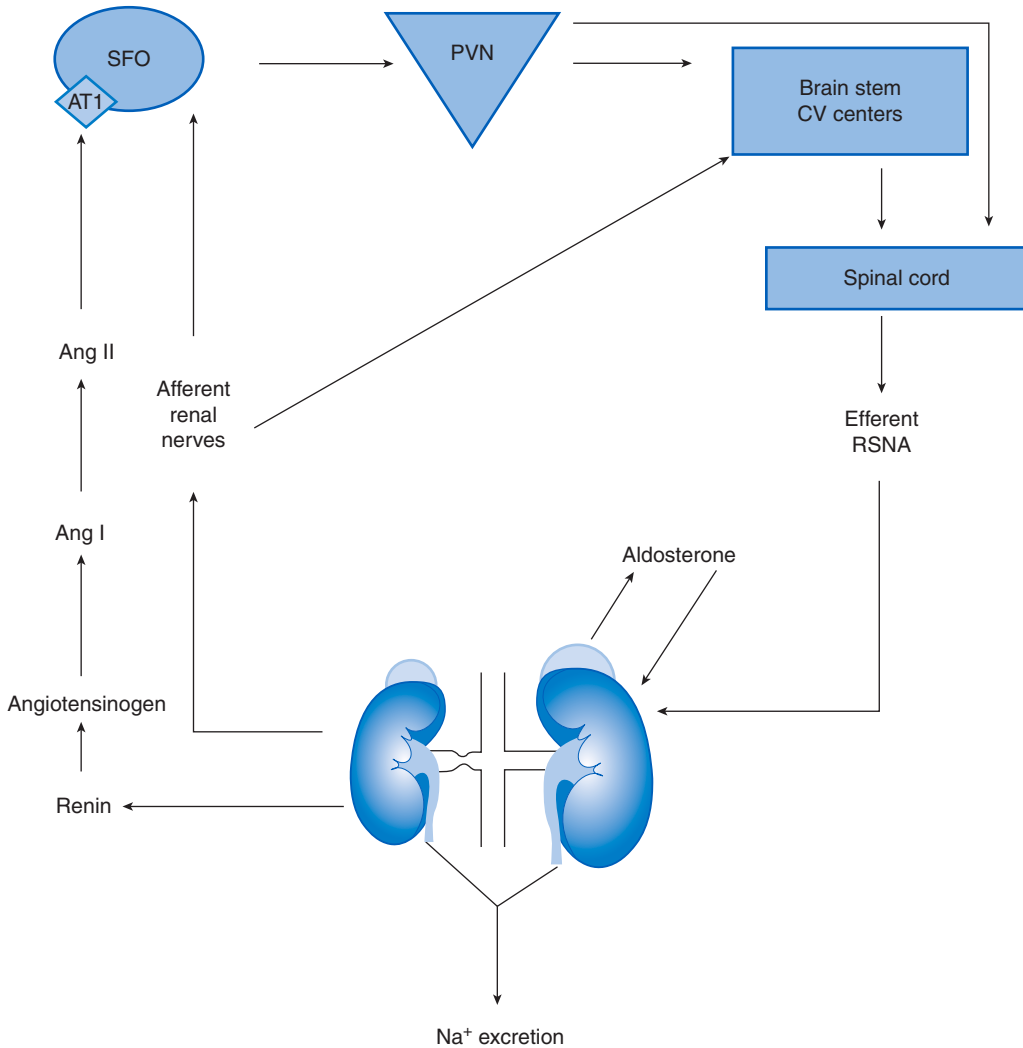


FIGURE 10-3 • Synergistic interactions between the renal nerves and the renin–angiotensin–aldosterone system in the 2-kidney, 1-clip rat model of unilateral renal artery stenosis. Ang, angiotensin; SFO, subfornical organ; PVN, paraventricular nucleus; RSNA, renal sympathetic nerve activity (i.e., efferent renal nerves). (From Pradhan N, Rossi NF. Interactions between the sympathetic nervous system and angiotensin system in renovascular hypertension. *Curr Hypertens Rev* 2013;9:121–129.)

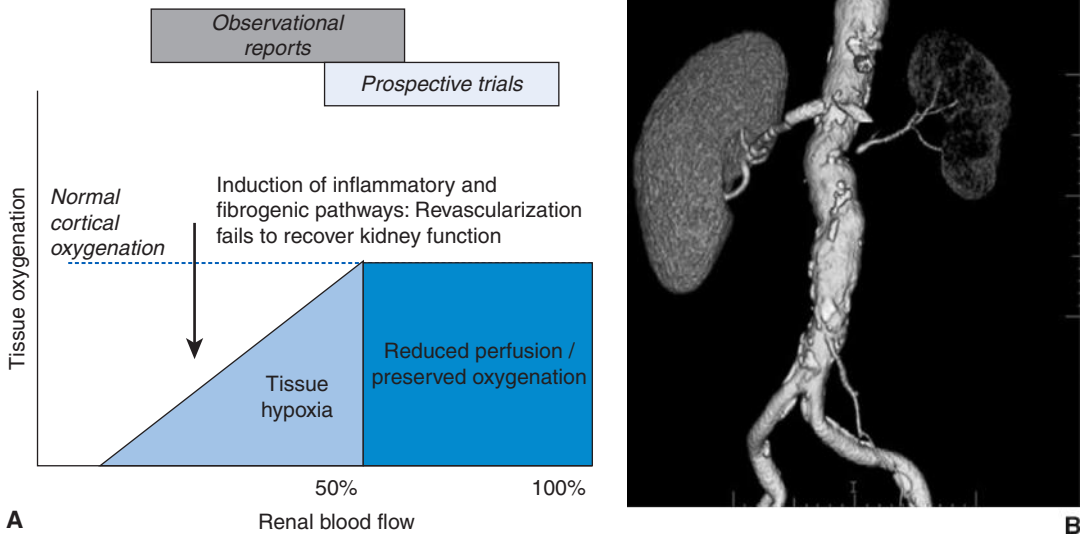


FIGURE 10-4 • A: Schematic of tissue oxygenation within the kidney as blood flow falls beyond an ARAS. Despite moderate hemodynamic reduction in blood flow, medullary and cortical oxygenation is well tolerated in many patients. Beyond a certain limit, further reductions lead to overt cortical hypoxia, which is associated with inflammation and fibrosis that can persist despite restoration of main vessel patency. **B:** CT angiogram with a stent in the right kidney, with normal perfusion and function. The left kidney has lost volume, blood flow, and function that likely will not recover if renal patency is restored with stenting. (From Textor SC, Lerman LO. Renal artery stenosis: Medical versus interventional therapy. *Curr Cardiol Rep* 2013;15:409.)

tissue oxygen demands (Gloviczki et al., 2010). These data were obtained in patients with unilateral moderate ARAS on stable ACEI- or ARB-based antihypertensive therapy. In such patients, renal artery stenting would not be expected to have any effect on renal perfusion, which is already normal. This may help explain the negative findings in the Angioplasty and Stenting for Renal Artery Lesion (ASTRAL) and Cardiovascular Outcomes with Renal Atherosclerotic Lesions (CORAL) trials, which enrolled patients with mainly moderate rather than severe ARAS.

- With moderately severe/more advanced stage ARAS, renal cortical hypoxia occurs and begins to induce production of inflammatory cytokines and fibrotic pathways such as those involving transforming growth factor- β (TGF- β). Renal artery stenting is most likely to improve or stabilize kidney function if the cortical hypoxia is caught soon enough—before irreversible damage to the microvasculature has occurred (Chrysochou et al., 2012b).
- With far advanced/end-stage ARAS, pruning of renal microvessels closes the window of opportunity to

rescue renal function with stenting. Cortical blood flow can be restored, but it is too late to reverse renal inflammation/fibrosis and salvage the kidney (Saad et al., 2013). Early preclinical studies in pigs suggest the promise of stem cell therapy to rescue partially atrophic kidneys from such far-advanced ARAS (Textor & Lerman, 2013).

Thus, these elegant studies suggest that there is a very narrow middle-ground sweet spot in the natural history of ARAS where renal artery stenting will save the kidney. It is not clear if the same concept applies to effects of ARAS stenting on BP reduction, which are addressed later in the chapter.

CLASSIFICATION AND COURSE

The most common cause of RVHT is atherosclerotic stenosis of the main renal artery; most of the remaining cases are fibroplastic, but a number of both intrinsic and extrinsic lesions can induce RVHT (Table 10-2). The general features of the most common types of renal artery stenosis are listed in Table 10-3.

TABLE 10-2

Types of Lesions Associated with RVHT

Intrinsic lesions

- Atherosclerosis
- Fibromuscular dysplasia
 - Intimal
 - Medial
 - Dissection (Edwards et al., 1982)
 - Segmental infarction (Salifu et al., 2000)
 - Adventitial
- Aneurysm (English et al., 2004)
- Emboli (Scolari et al., 2007)
- Arteritis
 - Large artery vasculitis (Slovut & Olin, 2004)
 - Takayasu's (Cakar et al., 2008)
- Arteriovenous malformation or fistula (Lekuona et al., 2001)
- Renal artery (Kolhe et al., 2004) or aortic dissection (Rackson et al., 1990)
- Angioma (Farreras-Valenti et al., 1965)
- Neurofibromatosis^a (Watano et al., 1996)
- Tumor thrombus (Jennings et al., 1964)
- Thrombosis with the antiphospholipid syndrome (Riccialdelli et al., 2001)
- Thrombosis after antihypertensive therapy (Dussol et al., 1994)
- Rejection of renal transplant (Kasiske et al., 2004)
- Injury to the renal artery
 - Stenosis after transplantation (Tedla et al., 2007)
 - Trauma (Myrianthefs et al., 2007)
 - Radiation (Shapiro et al., 1977)
 - Lithotripsy (Smith et al., 1991)
- Intrarenal cysts (Torres et al., 1991)
- Congenital unilateral renal hypoplasia^a (Ask-Upmark kidney) (Steffens et al., 1991)
- Unilateral renal infection (Siamopoulos et al., 1983)

Extrinsic lesions

- Pheochromocytoma or paraganglioma (Nakano et al., 1996)
- Congenital fibrous band^a (Silver & Clements, 1976)
- Pressure from diaphragmatic crus^a (Deglise et al., 2007)
- Tumors (Restrict et al., 1992)
- Subcapsular or perirenal hematoma (Nomura et al., 1996)
- Retroperitoneal fibrosis (Castle, 1973)
- Perirenal pseudocyst (Kato et al., 1985)
- Stenosis of celiac axis with steal of renal blood flow (Alfidi et al., 1972)

^aMore common in children.

Atherosclerotic Lesions

As compared to patients with primary hypertension, patients with atherosclerotic RVHT are older and have higher systolic pressure, more extensive renal damage, and atherosclerotic vascular disease elsewhere. As a group, they also have more extensive left ventricular hypertrophy, ischemic heart disease, renal insufficiency, and, not surprisingly, lower probability of survival from these conditions (Sattur et al., 2013).

Natural History and Secular Trends

Since ARAS is a local manifestation of a systemic atherosclerosis, the relatively slow rate of progression of the renal lesion is countered by the more common cause of death by cardiovascular disease (Kalra et al., 2005). Medicare data show that ARAS patients have a threefold greater risk of death than do their non-ARAS counterparts (Kalra et al., 2010) and dialysis patients with ARAS have an annual mortality rate as high as 36% (Guo et al., 2007).

Medicare claims data show that between 1992 and 2004, the detection of ARAS increased threefold among patients over age 65 while the rate of revascularization peaked in 1999 and then started to decline (Kalra et al., 2010). A further (70%) decline in revascularization for ARAS has occurred in the United Kingdom (Health and Social Care Information Centre, 2014) with publication of 3 negative RCTs: Stent Placement and Blood Pressure and Lipid-Lowering for the Prevention of Progressive Renal Dysfunction Caused by Atherosclerotic Ostial Stenosis of the Renal Artery (STAR) (Bax et al., 2009), ASTRAL (Wheatley et al., 2009), and CORAL (Cooper et al., 2014).

Fibromuscular Dysplasia

Fibromuscular dysplasia (FMD) is a nonatherosclerotic, noninflammatory disease of the renal arteries and other medium-sized arteries (especially the carotid artery) that can lead to stenosis, occlusion, dissection, and aneurysm (Olin et al., 2014).

Figures 10-5 and 10-6 show the two most common types of fibromuscular stenoses (Olin et al., 2014). The most common angiographic appearance in FMD is an artery that looks like a string of beads located in the mid and distal portion of the artery (see Fig. 10-5), in contrast to focal atherosclerotic stenosis

TABLE 10-3

Features of the Two Major Forms of Renal Artery Stenosis

Renal Artery Disease History	Incidence, %	Age, Years	Location of Lesion in Renal Artery	Natural History
Atherosclerosis	90	>50	Ostia and proximal 2 cm	Progression is common, sometimes to occlusion
Fibromuscular dysplasias	1–2	Children, young adults	Middle main renal artery	Progression in most
Intimal Medial	10	15–50	Distal main renal artery and branches	Progression in 33%
Adventitial	<1	15–30	Mid to distal main renal artery	Progression in most

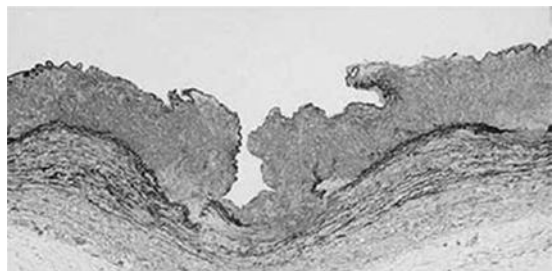


A



B

FIGURE 10-5 • Multifocal (medial) FMD in the carotid (A) and renal (B) arteries. There are multiple areas of alternating stenosis and dilatation (string of beads), located in the mid to distal portion of the internal carotid and renal arteries. C: High-magnification photomicrograph showing a gap in the arterial media. In medial fibroplasia, there are alternating areas of thinned media and thickened fibromuscular ridges in which the arterial muscle is replaced by fibroplasia with loose collagen. (From Virmani R, Carter-Monroe N, Taylor AJ. Congenital anomalies and malformations of the vasculature. In: Creager MA, Beckman JA, Loscalzo J, eds. *Vascular Medicine: A Companion to Braunwald's Heart Disease*. 2nd ed. Philadelphia, PA: Elsevier Saunders; 2013.)



C

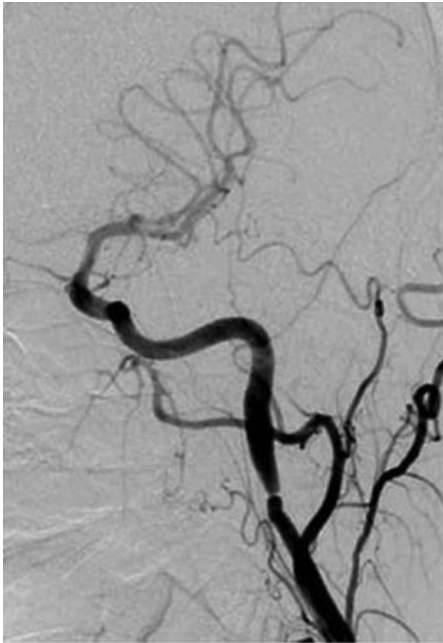
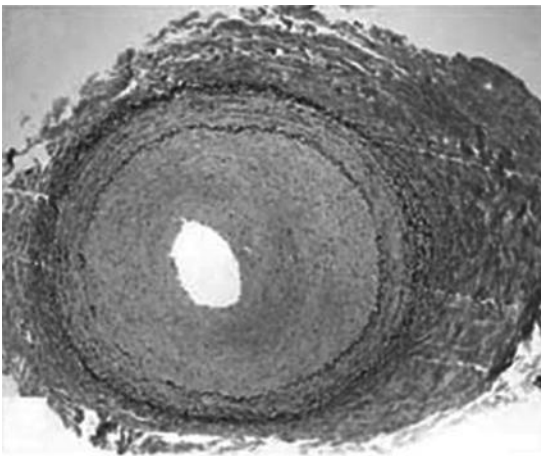
**A****B****C**

FIGURE 10-6 • Focal FMD in the renal and internal carotid arteries. This angiographic pattern is most consistent with intimal fibroplasia. This can present with a concentric band (focal constriction) as shown in the right internal carotid artery (**A**) or the right renal artery (**B**). **C**: Histopathologic findings: concentric thickening of the intima. The media and adventitia are relatively normal. (**A and B** from Olin JW, Gornik HL, Bacharach JM, et al. Fibromuscular dysplasia: state of the science and critical unanswered questions: a scientific statement from the American Heart Association. *Circulation* 2014;129, 1048–1078. **C** from Virmani R, Carter-Monroe N, Taylor AJ. Congenital anomalies and malformations of the vasculature. In: Creager MA, Beckman JA, Loscalzo J, eds. *Vascular Medicine: A Companion to Barunwald's Heart Disease*. 2nd ed. Philadelphia, PA: Elsevier Saunders; 2013.)

located at the origin or proximal portion of the artery (see Fig. 10-4). The string of beads indicates multifocal medial fibroplasia. The next most common type is unifocal FMD characterized angiographically as a focal or tubular stenosis in the midportion of the artery (see Fig. 10-6). In the retrospective series of Savard et al. (2012) of 337 patients with established renal artery FMD, 82% were classified as multifocal and the other 18% as unifocal. Patients with unifocal versus multifocal lesions differed significantly in median age at diagnosis of FMD (30 vs. 49 years, unifocal vs. multifocal), hypertension (26 vs. 40 years),

sex distribution (female:male ratio, 2:1 and 5:1), initial blood pressure (157/97 and 146/88 mm Hg), current smoking (50% and 26%), prevalence of unilateral renal artery lesions (79% vs. 38%), presence of kidney asymmetry (33% vs. 10%), renal revascularization procedures (90% vs. 35%), and hypertension cure rates in patients who underwent revascularization (54% vs. 26%).

A third type, termed perimedial FMD, occurs almost exclusively in children in whom it can cause hypertension and CKD (Olin et al., 2014). This unusual type of FMD was found in only 2 of 577 adult

patients in the U.S. Registry for FMD (Olin et al., 2012).

As a historical aside, FMD was discovered serendipitously by Leadbetter and Burkland (1938). They cured severe hypertension in a 5-year-old boy by surgical removal of his solitary pelvic kidney and discovered the renal artery narrowing during pathologic examination of the postoperative specimen.

FMD involves not only the renal arteries but other medium-sized arteries, most notably the extracranial carotid, vertebral, mesenteric, and lower-extremity arteries. While aneurysms are most common with renal FMD, dissection is most common with carotid artery FMD occurring in 75% of cases (Olin et al., 2012).

The presenting symptoms and signs of FMD are shown in Table 10-4 (Olin et al., 2012). The most frequent presenting complaints are hypertension, headache, and pulsatile tinnitus—the last being described as a swooshing sound in the ears and a tip-off to the presence of carotid FMD. Only 5% of patients are asymptomatic at presentation; rarely, FMD is discovered during evaluation of an asymptomatic carotid or renal bruit or is an incidental finding on unrelated abdominal imaging.

The cause of FMD and explanation for the 10:1 female predominance is an enigma. Some studies suggest cigarette smoking as a risk factor, but others do not (Olin et al., 2014). Familial occurrence is only in

TABLE 10-4

Consider the Diagnosis of FMD in the Following Circumstances

Onset of hypertension before age 35
Resistant hypertension
Epigastric bruit and high blood pressure
Cervical bruit before age 60
Pulsatile tinnitus (swooshing or whooshing sound in the ears with each heartbeat)
Severe or recurrent headaches
TIA or stroke before age 60
Dissection of a renal, carotid, or vertebral artery
Aneurysm in a visceral or intracranial vessel
Aortic aneurysm before age 60
Subarachnoid hemorrhage
Renal infarction

TIA, transient ischemic attack. (From Olin JW, Froehlich J, Gu X, et al. The United States Registry for Fibromuscular Dysplasia: Results in the first 447 patients. *Circulation* 2012;125:3182–3190.)

7% of cases (Olin et al., 2012). Few candidates have been proposed and none confirmed.

Other Causes

Of the myriad causes of RVH listed in Table 10-5, a few deserve additional comment.

TABLE 10-5

Interactive Mechanisms Underlying Hypertension and Kidney Injury in Atherosclerotic RAS

Tissue Underperfusion

Activation of renin–angiotensin system
Altered endothelial function (endothelin, NO, prostaglandins)
Sympathoadrenergic activation
Increased reactive oxygen species
Cytokine release/inflammation (NF- κ B, TNF, TGF- β , PAI-1, IL-1)
Impaired tubular transport functions
Apoptosis/necrosis

Recurrent Local Ischemia

ATP depletion
Tubulointerstitial injury
Microvascular damage
Immune activation
Vascular remodeling
Interstitial fibrosis
Renin–angiotensin activation
Sympathoadrenergic activation
Endothelin
Disturbances of oxidative stress
Oxidized LDL

Modified from Textor SC. Atherosclerotic renal artery stenosis: Overtreated but underrated? *J Am Soc Nephrol* 2008;19:656–659.

Aneurysm

Aneurysms are common with multifocal renal FMD. Saccular aneurysms, usually at the bifurcation of the renal artery, may induce hypertension by various mechanisms. They rarely rupture and need not be ablated if less than 2.0 cm in diameter in the absence of symptoms or severe hypertension (English et al., 2004).

Emboli

Most commonly seen as a complication of angiography or vascular surgery, renal cholesterol emboli can induce renal failure or RVHT (Scolari et al., 2007). Cutaneous, ocular, and other visceral lesions are usually seen, and the diagnosis may be documented by biopsy of skin lesions.

Arteritis

Progressive aortic arteritis (Takayasu arteritis or pulseless disease) is seen infrequently in North America and Europe but is a common cause of RVHT in China, India, Japan, Mexico, and Brazil occurring in up to 60% of such patients (Chaudhry & Latif, 2013). If unrecognized, this can lead to renal failure and/or RVHT. It is seen mainly in children and young adults and is often associated with signs of chronic inflammation (Cakar et al., 2008) and requires stenting or surgical revascularization (Chaudhry & Latif, 2013).

Renal artery stenosis (or complete occlusion) is a common feature of antiphospholipid syndrome, a multisystem disorder characterized by arterial or venous thrombosis in association with antiphospholipid antibodies, namely anticardiolipin antibodies, lupus anticoagulant, and anti-beta2-glycoprotein I antibodies (Pons-Estel & Cervera, 2014). The syndrome and its associated renal artery stenosis may be primary or secondary to systemic lupus erythematosus or antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis of small- to- medium-sized blood vessels, with the antibodies being directed against cytoplasmic proteins (proteinase 3 [PR3] and myeloperoxidase [MPO]) expressed on the surface of neutrophils. The ANCA-positive vasculitides include granulomatosis with polyangiitis (formerly known as Wegener granulomatosis); Kawasaki disease; polyarteritis nodosa; microscopic polyangiitis; eosinophilic granulomatosis with polyangiitis (Churg-Strauss), IgA vasculitis (Henoch-Schönlein), and erythematosus;

vasculitis related to rheumatoid arthritis; and Sjögren syndrome. Patients may enter into an acute, severe hypertensive phase, usually associated with markedly elevated plasma renin levels, likely reflecting intrarenal stenosis from multiple arteriolar lesions. The high-renin hypertension can sometimes be rather remarkably reversed by ACEI therapy (Tektonidou, 2009). The RVHT can be accompanied by renal vein thrombosis with nephrotic-range proteinuria (Pons-Estel & Cervera, 2014). Renal artery stenosis has been reported rarely in antiphospholipid syndrome with polycythemia vera (Zahra Ha-ou-Nou et al., 2014).

Aortic Dissection

Renal artery occlusion was found in nearly 20% of patients with distal aortic dissection (Rackson et al., 1990). The resulting renal ischemia and impaired renal function can be normalized by repair of the dissection (Verhoye et al., 2005).

CLINICAL FEATURES

Most patients with ARAS are older persons with hypertension and hyperlipidemia and often have clinically evident PAD, coronary disease, and/or cerebrovascular disease. As mentioned, the three most specific presentations of severe ARAS are drug-resistant hypertension, ischemic nephropathy, and flash pulmonary edema.

Hypertension

Clinical features suggestive of renovascular disease as the cause of hypertension are presented in Table 10-6 (Sattur et al., 2013). Some of these features were identified many years ago in a cooperative study involving 2,442 hypertensive patients, 880 with renovascular disease (Maxwell et al., 1972). Of the 880, 502 had surgery; of these, 60% had ARAS, and 35% had FMD. The clinical characteristics of 131 patients with surgically cured renovascular disease were compared to those in a carefully matched group with primary hypertension (Simon et al., 1972). Of the clinical features more common in patients with RVHT, only an abdominal bruit was of clear discriminatory value, heard in 46% of those with renovascular but in only 9% of those with primary hypertension. The bruit was heard over the flank in 12% of those with RVHT and in only 1% of those with primary hypertension.

TABLE 10-6

Clinical Clues for RVHT

History

- Onset of hypertension before age 30 in women with no family history (fibromuscular dysplasia)
- Abrupt onset or worsening of hypertension
- Severe or resistant hypertension
- Symptoms of atherosclerotic disease elsewhere
- Smoker
- Worsening renal function with ACE inhibition or all receptor blockade
- Recurrent flash pulmonary edema

Examination

- Abdominal bruits
- Other bruits
- Advanced hypertensive retinopathy

Laboratory

- Secondary aldosteronism
 - Higher plasma renin
 - Low serum potassium
 - Low serum sodium
- Proteinuria, usually moderate
- Elevated serum creatinine
- >1.5 cm difference in kidney size on sonography
- cortical atrophy on CT angiography

Most systolic bruits are innocent, but systolic-diastolic bruits in hypertensives are suggestive of RVHT (Turnbull, 1995).

Hypertensive Heart Disease

In patients with RVHT and relatively preserved renal function, BP is more difficult to control than in patients with primary hypertension, and echocardiograms show a greater degree of concentric left ventricular hypertrophy with more diastolic and systolic dysfunction (Khangura et al., 2014). The combination of pressure overload and neurohormonal activation with cardiovascular inflammation conspire to aggravate hypertensive heart disease, which sets the stage for episodes of acute (“flash”) pulmonary edema.

Hyperaldosteronism

Patients with RVHT occasionally have profound secondary aldosteronism with hypokalemia due to urinary potassium wasting but low serum sodium unlike the high serum sodium seen in primary aldosteronism

(Agarwal et al., 1999)—all reversed with relief of RVHT. The explanation for the association is unknown.

Ischemic Nephropathy

Beyond hypertension, the second most common clinical presentation of renal artery stenosis is ischemic nephropathy, which is estimated to be the cause of ESRD in at least 5% of patients entering chronic dialysis (Levin et al., 2007).

Patients with ischemic nephropathy may be difficult to distinguish from the larger number with primary hypertension or primary renal parenchymal disease that progresses into renal failure. The possibility of bilateral renovascular disease should be considered in the following groups (Sattur et al., 2013):

- ▶ Young women with severe hypertension, in whom fibroplastic disease is common.
- ▶ Older patients with extensive atherosclerotic disease who suddenly have a worsening of renal function.
- ▶ Any hypertensive patient who develops rapidly progressive renal failure without evidence of obstructive uropathy.
- ▶ Patients in whom renal function deteriorates abruptly and progressively after treatment with an ACEI or ARB.
- ▶ Hypertensives who develop multiple episodes of acute pulmonary edema.

Flash Pulmonary Edema

Pickering et al. (1988) was first to implicate ARAS as a reversible cause of recurrent sudden (i.e., “flash”) pulmonary edema (Fig. 10-7) (Sarkodieh et al., 2013). Of 11 patients with ARAS and multiple episodes of pulmonary edema, 7 had stenosis of both renal arteries, 2 had stenosis of the artery to a solitary kidney, and 2 had unilateral stenosis with an intact contralateral kidney. Successful revascularization (by angioplasty in eight and surgery in three) improved BP and renal function, and virtually eliminated pulmonary edema. In their second series of 55 consecutive patients with advanced CKD and ARAS, pulmonary edema occurred in 23%.

A recent observational study of 467 with ARAS treated at the Manchester Academic Health Sciences Centre found that the 37 patients presenting with flash pulmonary edema had a threefold increase in CV

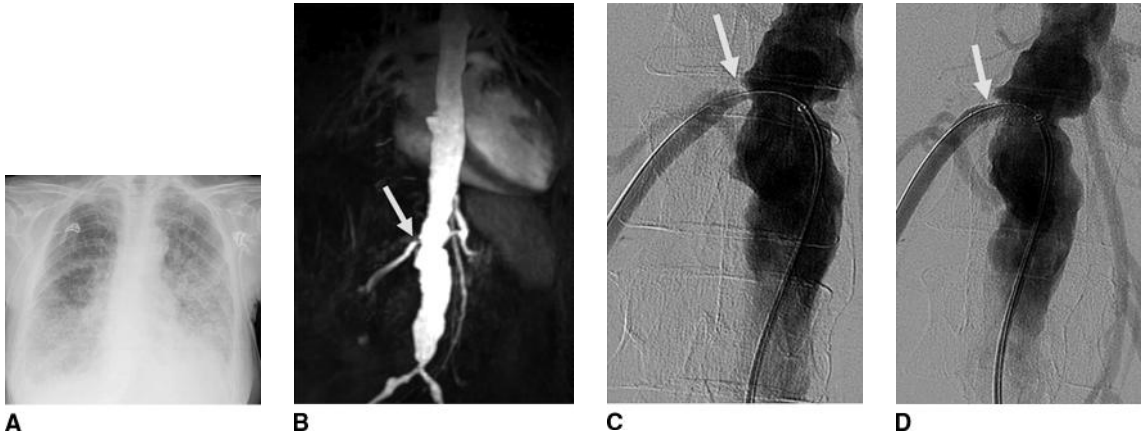


FIGURE 10-7 • A patient with a single functioning kidney who presented with acute shortness of breath. **A:** Chest radiograph shows flash pulmonary edema. **B:** Renal magnetic resonance angiogram (MRA) shows right renal artery stenosis (*arrow*). **C:** Digital subtraction angiography (DSA) confirms severe short segment stenosis of the right renal artery origin (*arrow*). **D:** A 6- × 17-mm stent (*arrow*) was inserted producing a good angiographic result. (From Sarkodieh JE, Walden SH, Low D. Imaging and management of atherosclerotic renal artery stenosis. *Clin Radiol* 2013;68:627–635.)

events and a twofold increase in death than did patients without this presentation (Ritchie et al., 2014). In this subgroup, stenting rather than medical treatment (according to physician preference) was associated with a 60% reduction in mortality.

Other Scenarios

Hypertension After Renal Transplantation

As described in Chapter 9, patients who develop severe hypertension after renal transplantation should be evaluated for stenosis of the renal artery. Posttransplant stenosis have been reported in 2% about of renal allografts in experienced transplant centers and generally have an excellent outcome with renal angioplasty (Su et al., 2012).

Impact of ARAS on Outcomes After Open Heart Surgery

Renal artery stenosis may be one cause of acute kidney injury after open heart surgery particularly in older patients undergoing coronary bypass grafting, aortic valve replacement, or aortic aneurysm repair. However, in a recent Cleveland Clinic series of 714 patients undergoing open heart surgery, no association was found between ARAS (detected by duplex ultrasonography in 29% of the patients) and surgical outcomes (Philip et al., 2014). While older patients

and those undergoing descending aortic grafting were at high risk for postoperative acute kidney injury, the risk was similar in those with and without ARAS.

DIAGNOSTIC TESTS

Before any tests are performed to diagnose RVHT, the clinician should consider whether, if renal stenosis is present, revascularization would be indicated to provide likely benefit despite the possible complications (Textor & Lerman, 2013). As listed on the right side of Table 10-7, for those patients with stable renal function and long-standing stable hypertension that is responsive to easily tolerated antihypertensive drugs, revascularization would likely provide no benefit; therefore, no tests should be performed. On the other hand, in those with one or more factors that make a favorable response to revascularization more likely, listed on the left side of Table 10-6, testing should be performed to define the extent of renovascular disease and estimate its functional significance. In those with a high likelihood of reversible RVHT, invasive angiography and, if significant stenosis is seen, angioplasty with stenting are appropriate.

Imaging for suspected clinically important ARAS can be divided into three steps: (1) Noninvasive functional imaging, (2) computed tomography (CT) or MR angiography, and (3) invasive digital subtraction angiography (DSA).

TABLE 10-7

Factors Indicative of Response to Revascularization for Atherosclerotic RVHT

Favorable	Nonfavorable
BP response likely Treatment-resistant hypertension Recent onset/progression of hypertension Hypertension aggravating acute coronary syndromes Impaired cardiac function/“flash” pulmonary edema Renal functional response likely Entire renal mass affected: solitary functioning kidney/bilateral RAS Recent fall in GFR Viable kidneys: blood flow preserved on nephrogram/ favorable resistance index by Doppler ultrasound Acute renal failure during antihypertensive therapy, especially with angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) Patient considered viable with reasonable life expectancy	BP response less likely Long-standing stable hypertension Acceptable BPs/tolerable medication regimen Renal function less likely to benefit Unilateral RAS with normal contralateral circulation Bilateral parenchymal disease (elevated resistance index in contralateral kidney) Stable kidney function Patient with limited viability Severe comorbid disease likely to limit life expectancy

Noninvasive Functional Imaging

As mentioned, there are no perfect tests to predict with certainty a favorable response to renal artery stenting. The available noninvasive tests are Doppler ultrasound with resistive index and nuclear medicine scans (renography).

Duplex Ultrasonography with Resistive Index

A Doppler flow signal from a normal renal artery and from a stenotic artery are shown in Figures 10-8 and 10-9. The conventional criterion for diagnosis of renal artery stenosis is a greater than 3.5-fold greater flow velocity at the site of the stenosis (postobstructive jet) in the proximal main renal artery than in the unobstructed aorta (Soulez et al., 2000). However, it is easy to underestimate the peak velocity if the Doppler signal is not directly in line with the jet or obscured by overlying soft tissue and bowel gas. A more sensitive but semiquantitative method is to search for a diminished (“parvus et tardus”) flow velocity waveform in the intrarenal arteries distal to the stenosis (Fig. 10-9). The sensitivity is 75% and specificity 90% when compared with the gold standard of DSA (Hashemi et al., 2011).

To measure vascular resistance in the renal microcirculation, the velocity of blood flow within the renal parenchyma is estimated by Doppler ultrasonography and the resistive index calculated by the equation: $[1 - (\text{end-diastolic velocity} \times \text{maximal systolic velocity})] \times 100$. A value of 0.7 is considered the upper limit of normal (Sarkodieh et al., 2013). Higher values indicate small vessel disease from primary hypertension, renal parenchymal disease, or inflammatory changes due to advanced atherosclerosis. In primary hypertension, a high renal resistive index correlates with microalbuminuria (as well as left ventricular hypertrophy (LVH), carotid intima-media thickness, and aortic stiffness) and, in the setting of chronic kidney disease (CKD), predicts poor cardiovascular disease (CVD) and renal outcomes (Doi et al., 2012). In ARAS, a low resistive index has predicted a therapeutic response to revascularization for both BP and renal function in some studies but not in others.

In the landmark study by Radermacher et al. (2001), the resistive index was measured in 138 patients with renovascular disease before revascularization by angioplasty or surgery. In the 35 who had a resistive index value of 80 or higher, only one had a subsequent 10 mm Hg or greater fall in BP. In the 96 patients with a resistive index value of less than 80, the mean BP fell by at least 10 mm Hg in 90. In other series, the index has predicted favorable

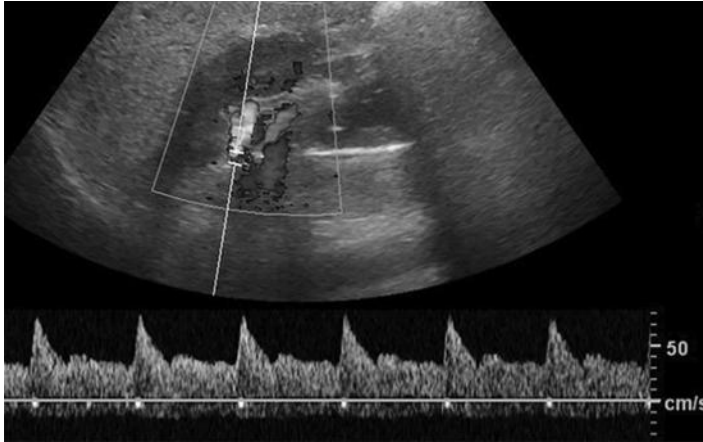


FIGURE 10-8 • Duplex Doppler ultrasound of the main renal artery in a healthy adult, showing a sharp systolic upstroke and peak systolic velocity of 70 cm/s. (From Sarkodieh JE, Walden SH, Low D. Imaging and management of atherosclerotic renal artery stenosis. *Clin Radiol* 2013;68:627–635.)

postrevascularization changes in renal function but not in BP (Crutchley et al., 2009), BP but not renal function (Viazzi et al., 2014), and neither (Garcia-Criado et al., 2005). Whereas all these studies measured resistive index of the affected kidney, a recent

study suggests that the presence of a resistive index less than 0.7 in both the affected and contralateral nonaffected kidney is a better predictor of a beneficial renal (but not BP) outcome in patients with unilateral ARAS (Bruno et al., 2014).

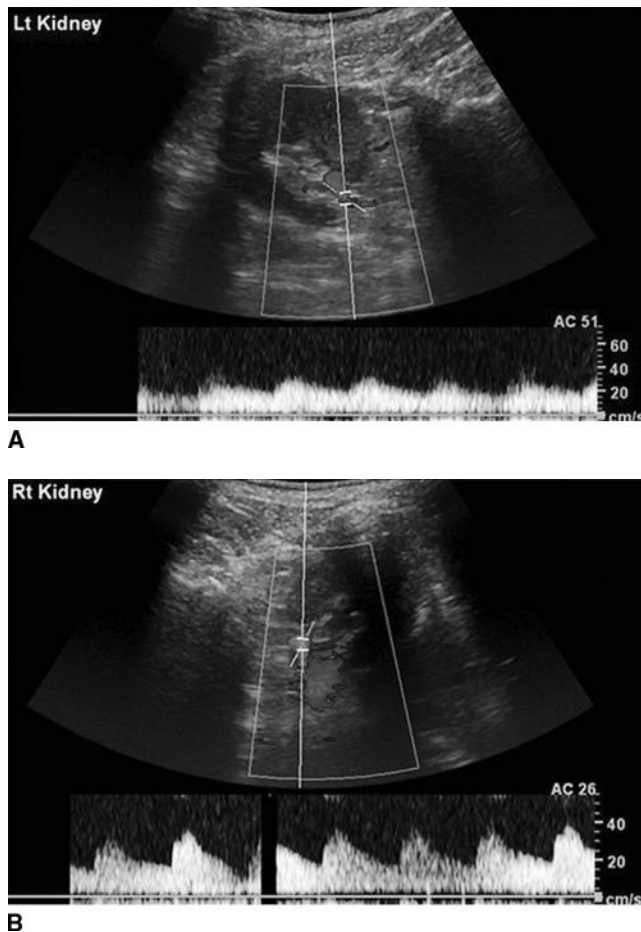


FIGURE 10-9 • Duplex Doppler ultrasound of the distal left and right renal arteries in a patient with unilateral renal artery stenosis. **A:** Left kidney: tardus-parvus waveform indicating renal artery stenosis. **B:** Right kidney of the same patient showing a normal Doppler waveform. (From Sarkodieh JE, Walden SH, Low D. Imaging and management of atherosclerotic renal artery stenosis. *Clin Radiol* 2013;68:627–635.)

Renography

It seems logical that hypoperfusion of the affected kidney would be seen with RVHT. However, at least two factors may be involved in reducing the discriminatory power of renal perfusion studies. First, for reasons that are not apparent, considerable asymmetry of renal blood flow is present in the absence of ARAS. Asymmetry, defined as a 25% or greater difference between the two kidneys, was found in 51% of 148 hypertensive patients whose renal arteries were patent by angiography (Van Onna et al., 2003). Not surprisingly, the presence of asymmetry increases the rate of false-positive results of renal scintigraphy.

The second factor that may play a role is the frequent development of either bilateral renovascular disease or ischemic nephropathy in the contralateral kidney, both leading to a decreased differential of blood flow (Sarkodieh et al., 2013). Nonetheless, renal perfusion scans can help to predict the response to revascularization.

Renography may be done with radiolabeled agents that are excreted either by glomerular filtration—technetium-99 diethylenetriamine pentaacetic acid (^{99}Tc -DTPA)—or partially by filtration but mainly by tubular secretion to measure renal blood flow— ^{99}Tc -mercaptoacetyl triglycine (^{99}Tc -MAG₃). When used alone, isotopic renograms provided about 75% sensitivity and specificity for the diagnosis of RVHT (Sarkodieh et al., 2013).

Soon after the observation that renal function in an ischemic kidney could abruptly be reduced further after a single dose of the ACEI captopril (Hricik et al., 1983), the effect of captopril on renal uptake of ^{99}Tc -DTPA was reported (Wenting et al., 1984). Either a reduction of the uptake of dimercaptosuccinic acid (DMSA) or a slowing of the excretion of $^{99\text{m}}$ DTPA or ^{99}Tc -MAG₃ can be used to identify the effect of the ACEI in removing the protective actions of the high

levels of Ang II on the autoregulation of glomerular filtration and on the maintenance of renal blood flow, respectively (Fig. 10-10) (Sarkodieh et al., 2013). In the setting of chronic renal ischemia, high levels of Ang II maintain intraglomerular perfusion pressure by constricting mainly the efferent arteriole; when the selective postrenal vasoconstriction is blocked with acute ACEI, glomerular filtration rate (GFR) falls.

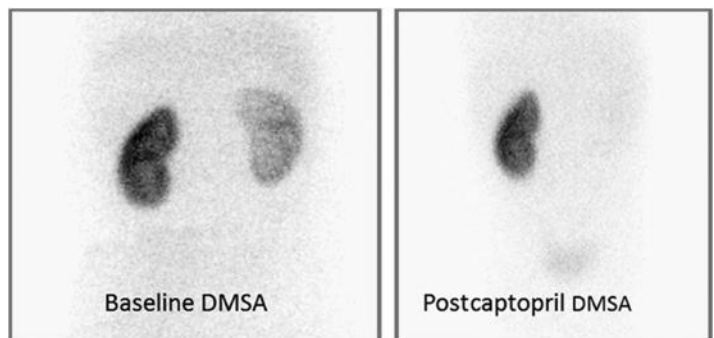
To reduce the cost and time of the workup, the postcaptopril renal scan should be done first. If the result is negative (as it will be most of the time), there is no need for a precaptopril renogram. If the test is positive, the procedure should be repeated the next day without captopril to ensure that the differences are related to reversible vascular disease and not parenchymal damage. Giving Lasix before each scan magnifies renin–angiotensin system activation and thus the difference between pre- and postcaptopril renal perfusion.

As reviewed by Taylor (2000), ACEI renography is highly accurate in patients with a moderate likelihood of RVHT and normal renal function, wherein sensitivity and specificity are approximately 90%. By combining data from 10 studies that evaluated the effects of revascularization in 291 patients, the mean positive predictive value of ACEI renography was 92%. As expected, the test is less sensitive in patients with renal insufficiency, which was the norm in patients enrolled in the STAR, ASTRAL, and CORAL trials; as many as half will have an “indeterminate” test. The test can be done in patients taking various antihypertensive drugs except for ACEIs and ARBs, which must be held at least 3 days before renography (Sarkodieh et al., 2013).

CT and MRI Angiography

Both spiral-CT and MRI are routinely used to visualize the renal arteries with only intravenous injection of contrast material (see Figs. 10-4 and 10-7). The

FIGURE 10-10 • Static renogram with dimercaptosuccinic acid (DMSA). The precaptopril study shows globally reduced uptake in the right kidney. Following captopril administration, activity in the right kidney diminishes completely indicating functionally significant renovascular disease. (From Sarkodieh JE, Walden SH, Low D. Imaging and management of atherosclerotic renal artery stenosis. *Clin Radiol* 2013;68:627–635.)



sensitivity and specificity are said to be 90%. Both techniques are contraindicated in advanced CKD. Gadolinium-enhanced MRA involves no ionizing radiation but is contraindicated in patients with advanced CKD, who are at risk for gadolinium-induced fatal nephrogenic systemic fibrosis (Daftari et al., 2014). If a greater than 50% stenosis is seen by either technique, the patient should proceed to invasive angiography. A unilateral small kidney with reduced concentration of contrast media essentially proves that an ipsilateral stenosis is causing renal ischemia; revascularization should be carefully considered.

Invasive Digital Subtraction Angiography

Catheter-based DSA is the gold standard for assessing the severity of ARAS. The 2013 ACCF/AHA guidelines for peripheral arterial disease (Anderson et al., 2013) recommend renal stenting when DSA shows an ostial/proximal narrowing of a main renal artery of greater than 70% or one between 50% and 70% with a peak gradient of greater than 20 mm Hg. Yet, even then, the patient cannot be assured that revascularization will control their medically refractory hypertension and preserve their renal function. Underscored by the disappointing results of three major RCTs, the discordance between a consistently high procedure success rate in restoring proximal vessel patency and the uncertain clinical benefit derived underscores the need to better quantify which lesions are accompanied by reversible renal ischemia. The angiographic appearance of the atherosclerotic lesion in the proximal main renal arterial alone may underestimate hemodynamic severity, and it provides absolutely no information about the integrity of the renal microcirculation.

In 62 patients with 50% to 90% unilateral ARAS by DSA and mean age 62, BP 170/91, and serum creatinine 1.2, a systolic gradient of ≥ 21 mm Hg measured by a pressure guide wire after papaverine-induced renal hyperemia was better than the resting hemodynamic gradient or plaque burden by renal intravascular ultrasound (IVUS) in predicting hypertension improvement (and reduction in number of BP medications) with stenting (Leesar et al., 2009). Papaverine may have been a very good choice as it dilates mainly microvessels. In contrast, diameter stenosis measured by quantitative renal angiography was not predictive

at all and IVUS was not much better. These data, while encouraging, should be confirmed independently, and the outcomes compared with a medically treated control group before the level of evidence is considered high enough to impact the guidelines.

CONCLUSION

The algorithm shown in Figure 10-11 recommends testing for atherosclerotic RVHT only in those patients who are more likely to have a beneficial clinical response to revascularization. No accurate estimates of the numbers of such patients are available, but they likely make up less than 5% of the total hypertensive population. The algorithm can be applied to patients with FMD. Being younger, they are usually easier to identify on clinical grounds, less likely to have renal insufficiency or extensive atherosclerosis, and more likely to have a favorable response to balloon angioplasty without stenting.

Except in those relatively few patients with such high likelihood of RVHT in whom immediate DSA is indicated, the algorithm starts with a study to confirm the clinical evidence for a favorable response to revascularization. Only those likely to respond would then have an imaging study to visualize the extent of renovascular disease, thereby pointing to the appropriate mode of revascularization.

Since Doppler ultrasonography with measurement of the resistive index can both identify renovascular disease and, according to still limited experience, ascertain the likelihood of a response to revascularization, this procedure is a logical way to begin. If duplex sonography is unavailable or technically inadequate, captopril renography is recommended.

THERAPY

Even if ARAS is incidentally detected, its presence indicates systemic atherosclerosis and the patient is at increased risk for future cardiovascular and renal events (Textor & Lerman, 2013). Therefore, all patients with recognized ARAS—regardless of severity/hemodynamic significance of the stenosis and clinical scenario—should be given intensive medical therapy. The goals of therapy are to control the hypertension, preserve renal function, and reduce the risk of CV events.

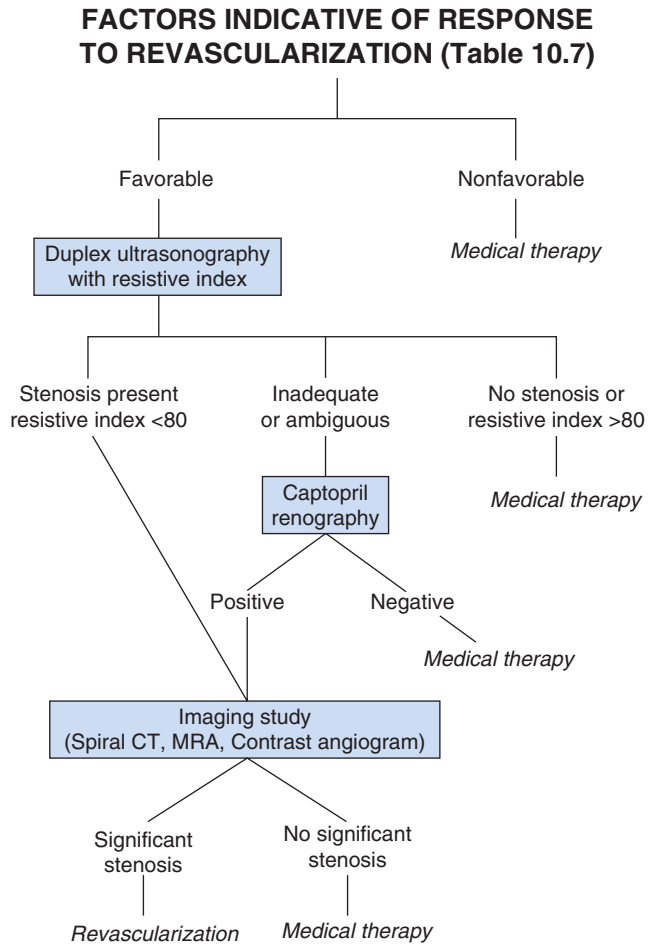


FIGURE 10-11 • An algorithm for evaluation and therapy of RVHT based on the presence of factors indicative of a response to revascularization (shown in Table 10-7).

Medical Therapy

The largest experience has been with ACEIs and ARBs. While there are no RCTs, the largest published experience is a population-based cohort study of 3,570 patients in whom the diagnosis of renovascular disease had been made by various techniques (Hackam et al., 2008). All patients were 65 years of age or older with a mean age of 75. Hypertension was diagnosed in over 85%, and 64% had CKD. The mean follow-up was 2 years.

The primary end point of death, myocardial infarction or stroke, occurred in 10 per 100 patient years in those patients who were prescribed an ACEI and 13 per 100 patient years in those who were not prescribed an ACEI, a difference that was statistically significant after adjustment for a number of possible confounding factors. In addition, the number of hospitalizations for heart failure and patients requiring initiation of chronic dialysis were reduced by over 30%.

The major problem, as expected in patients whose renal perfusion is based on high level of Ang II, was acute kidney injury. This developed in 1.2 per 100 patient years in those on ACEI versus 0.6 per 100 patient years in those not on ACEI. Again as expected, most acute kidney injury occurred in those with pre-existing CKD, diabetes, or those taking loop diuretics.

The issue of the safety and tolerability of ACEIs and ARBs in ARAS has been reexamined in a recent single-site observational cohort study of 621 patients with angiographic ARAS (half with >60% stenosis) of whom 357 were prescribed an ACEI or ARB by their treating physicians and the other 264 were not (Chrysochou et al., 2012a). Mean age was 72, greater than 80% of patients were hypertensive, mean eGFR was 35 ml/min/1.73m², and mean follow-up was 3 years. ACEI/ARB-based therapy was well tolerated without causing acute kidney injury or hyperkalemia

TABLE 10-8

Randomized Clinical Trials of Medical Therapy ± Renal Angioplasty with Stenting in Patients with ARAS

Trial	Total No.	Study Population	Inclusion Criteria	Outcomes
STAR (Bax et al., 2009)	140	Patients with impaired renal function, ostial ARAS by various imaging studies and stable BP on statin and aspirin.	ARAS > 50% eGFR < 80 mL/min/1.73 m ² Controlled BP 1 mo before inclusion.	No difference in GFR decline, but many did not undergo angioplasty due to ARAS < 50% by DSA.
ASTRAL (Wheatley et al., 2009)	806	Patients with uncontrolled or refractory HTN or unexplained renal dysfunction with unilateral or bilateral ARAS on statin and aspirin.	ARAS with doctor uncertainty of benefit of revascularization.	No difference in BP, renal function, mortality, CV events. Serious adverse events with angioplasty.
CORAL (Cooper et al., 2014)	956	HTN or two or more BP medications or CKD stage 3+ with unilateral or bilateral ARAS on statin.	SBP > 155 mm Hg, at least two BP medications; ARAS > 60%.	No difference in death from CV or renal causes. Modest improvement in BP in stented group. Complication rate 5.5%.

ARAS, atherosclerotic renal artery stenosis; SBP, systolic blood pressure; CV, cardiovascular; DSA, digital subtraction angiography.

Adapted from Herrmann SM, Saad A, Textor SC. Management of atherosclerotic renovascular disease after Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL). *Nephrol Dial Transplant*. 2014 Apr 9. [Epub ahead of print]

and by 15 mm Hg in the medication therapy–only group (Cooper et al., 2014).

- **Group Contamination.** Some patients who failed medical management received “off-label” angioplasty/stenting, reducing the power of the intention-to-treat analysis to detect a treatment effect.

Despite their potential limitations, these important studies have stemmed the previous wide-spread ill-conceived practice of “drive-by renal angiography” for patients undergoing diagnostic cardiac catheterization. They have caused the pendulum to swing away from percutaneous intervention to strictly medical management. But, in the words of Textor and Lerman (2014), “has the pendulum swung too far?” For example, the impressive, though observational, data of Ritchie et al. (2014) provide compelling evidence that revascularization reduces the risk of death by 60% in the small subset of patients presenting with flash pulmonary edema.

Surgery

There are many uncontrolled observational studies showing benefits for both BP and renal function by surgery (Cherr et al., 2002; Marone et al., 2004). Despite the increasing likelihood that patients who are

referred for surgical repair will either have failed to respond to angioplasty or have extensive atherosclerotic disease in the aorta or mesenteric vessels that also needs repair, the overall results with surgery seem generally comparable to those seen with technically successful angioplasty (Galaria et al., 2005). Not surprisingly, mortality is higher, averaging 10% in the immediate postoperative period (Modrall et al., 2008).

Surgery may be the only choice for patients with major renal artery involvement by arteritis (Weaver et al., 2004). In some patients, nephrectomy (or perhaps renal denervation?) may be appropriate for patients with refractory hypertension and an atrophic, nonfunctioning kidney.

The Choice of Therapy

We lack important RCT data and ideal screening tests to inform optimal management of many patients with known or suspected renal artery stenosis. Yet, after reviewing the recent literature, a number of points become clear:

- Patients with FMD do better than do those with ARAS. They are younger, often premenopausal women, and have nonatherosclerotic focal vascular

disease that has a high cure rate when balloon angioplasty (without stenting) is performed by an experienced interventionalist (Olin et al., 2014). ACEI/ARB-based therapy is a good conservative alternative but not for women of childbearing age. Some patients with renal FMD will have concomitant carotid (or other medium-sized artery) FMD, which may need to be addressed.

- In contrast, virtually all patients with ARAS have high global CV risk due to older age, hypertension, hypertensive heart disease, systemic atherosclerosis, and CKD. *Intensive medical therapy* with an ACEI- or ARB-based combination antihypertensive drug regimen is the cornerstone of management (Anderson et al., 2013; Chrysochou et al., 2012a; Textor & Lerman, 2013), which also includes global CV risk reduction with a statin, aspirin, smoking cessation, and, in diabetic patients, tight glucose control.
- *Angioplasty with renal artery stenting* should be reserved for patients with proven severe ARAS who, despite optimal medical therapy, have uncontrolled hypertension, progressive decline in eGFR, ACEI/ARB-induced acute kidney injury, or recurrent flash pulmonary edema (Anderson et al., 2013; Chrysochou et al., 2012a; Ritchie et al., 2014; Textor & Lerman, 2013; White, 2014).
- *Surgical revascularization* is much less commonly indicated, except when angioplasty with stenting is not feasible or is unsuccessful or when abdominal vascular surgery is required.

Clinicians experienced with the management of renovascular disease should be involved in the evaluation and treatment of these complex patients. Hypertension specialist referral is very important.

RENIN-SECRETING TUMORS

Renin-secreting tumors are rare. Since the recognition of the first case (Robertson et al., 1967), only about 90 have been reported (Wong et al., 2008). Since it has been so well described, fewer will be deemed worthy of publication. Most such tumors are relatively small and are composed of renin-secreting juxtaglomerular cells (i.e., hemangiopericytomas). Other causes of hypertension and high renin levels include the following:

- Wilms tumor in children, usually associated with high levels of prorenin (Leckie et al., 1994)

- Renal cell carcinoma (Moein & Dehghani, 2000); tumors of various extrarenal sites, including lung, ovary, liver, pancreas, sarcomas, and teratomas (Pursell & Quinlan, 2003); and adrenal paraganglioma (Arver et al., 1999)
- Large intrarenal tumors that compress renal vessels
- Unilateral juxtaglomerular cell hyperplasia (Kuchel et al., 1993)

Most of the renin-secreting tumors of renal origin fit a rather typical pattern:

- Severe hypertension in relatively young patients: The mean age of the reported cases is 27 years (Wong et al., 2008).
- Female predominance (Wolley et al., 2014)
- Secondary aldosteronism, usually manifested by hypokalemia
- Very high renin levels in the peripheral blood: Even higher levels from the kidney harboring the tumor by renal vein sampling, performed during dietary sodium restriction and with acute ACEI challenge (Wolley et al., 2014)
- Tumor recognizable by computed tomographic scan in most but not all cases (Wolley et al., 2014)
- Morphologically, a hemangiopericytoma arising from the juxtaglomerular apparatus

Now that the renal causes of hypertension have been covered, we turn to those associated with hormonal excesses that are usually adrenal in origin.

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Primary Aldosteronism

For over 40 years after Jerome Conn characterized the syndrome, primary aldosteronism (PA) was generally held to be a relatively rare cause of hypertension, present in fewer than 1% of all patients. However, over the past 20 years, the prevalence of this condition has been reported to be much higher, reaching 40% in highly selected groups and over 10% in all hypertensives (Funder et al., 2008; Harvey, 2014), so it is now referred to as “the most common cause of secondary hypertension” (Monticone et al., 2012a). These figures are almost certainly inflated by the confounding effect of referral and selection (Kaplan, 2012), but the availability of a simple screening test has led to an increased recognition of the milder forms of this condition, particularly those said to be caused by bilateral adrenal hyperplasia (BAH) (Funder et al., 2008). As will be noted, the increasingly higher prevalence of BAH may be, at least in part, a reflection of errors in the evaluation of patients.

This chapter covers those syndromes listed in Table 11-1 in which secretion of the physiologic mineralocorticoid aldosterone is primarily increased. Chapter 13 covers syndromes caused by increased secretion of other mineralocorticoids, e.g., deoxycorticosterone in congenital adrenal hyperplasias, or by cortisol acting on mineralocorticoid receptors, e.g., apparent mineralocorticoid excess.

As milder degrees of PA have been recognized by the wider application of the plasma aldosterone-to-renin ratio (ARR) as a screening or case-finding test, it has become increasingly clear that the majority of patients with an elevated ARR do not have autonomous hyperaldosteronism and are even less likely to have a solitary adrenal adenoma. Therefore, bilateral adrenal venous sampling (AVS), a procedure that requires considerable expertise in performance and adds considerable expense to the workup, is now

recognized to be necessary for confirmation of the type of pathology (Sarlon-Bartoli et al., 2011).

The need to establish the type of pathology is critical: Adenomas usually should be surgically removed; bilateral hyperplasia should never be surgically attacked but will almost always respond to medical therapy (Colussi et al., 2013).

The clinician is left in a dilemma: As the diagnosis of PA has become easier, the recognition of the type of pathology has become more difficult. Since CT imaging and MRI are often misleading and AVS requires considerable expertise, patients increasingly need referral to a center for definitive testing, which is often difficult and always expensive.

To avoid this dilemma, this text will present the view that the ARR screening study is grossly misleading (Jansen et al, 2014), falsely labeling more than half of those who have a ratio determined, and that it should not be done except in hypertensive patients with unexplained hypokalemia, resistance to three-drug therapy, after the finding of an adrenal incidentaloma (as described in Chapter 12), or in the relatives of patients with a familial syndrome. This view does not take in all of the patients recommended for screening in the Clinical Practice Guidelines of the Endocrine Society (Funder et al., 2008) although the major categories are similar. Even if PA is sometimes missed, medical therapy—in particular the aldosterone receptor blockers spironolactone or eplerenone—will almost always control the hypertension and, if present, the hypokalemia and all of the additional harmful effects of aldosterone excess since they are mediated through the mineralocorticoid receptor. Thereby, the patients who have PA will likely be identified, while expensive laboratory procedures, invasive diagnostic tests, and unnecessary surgery will be avoided in the majority of patients who do not. This approach was initially recommended

TABLE 11-1

Syndromes of Mineralocorticoid Excess

Aldosterone-producing adenoma
Bilateral adrenal hyperplasia
Primary unilateral adrenal hyperplasia
GRA familial hyperaldosteronism
Type 1: Glucocorticoid—remediable
Type 2: Unknown mechanism
Type 3: Mutation in potassium channel (KCNJ5)
Adrenal carcinoma

by Funder but, despite his continued eloquent and convincing argument (Funder, 2012), the remainder of the experts' opinions have continued to insist on wide-scale, costly, and often inaccurate screening and further evaluation and surgery.

Current practice misses most patients with PA and, at the same time, mislabels many who do not have the disease. As Funder (2012) states: “we can change our mindset to include low-dose mineralocorticoid receptor antagonists as first-line treatment for newly discovered hypertensive individuals and routinely give it in the drug regimen in established hypertension.... For individuals with occult primary aldosteronism, a first-line mineralocorticoid receptor antagonist, in conjunction with a conventional antihypertensive (and perhaps a low-dose thiazide) would be game-changing. We do not have the resources to diagnose primary aldosteronism but we have the ability to treat it.”

This view, which is detailed in the remainder of this chapter, may be too abrupt to be accepted by most who have worked in this arena. However, as of now, it is the best balance between the multiple costs of diagnosis and the infrequency of the syndrome.

DEFINITIONS

PA is the syndrome resulting from the autonomous hypersecretion of aldosterone, almost always from the adrenal cortex, usually by a solitary adenoma or by bilateral hyperplasia, rarely by the variants of these two (Table 11-1). As will be described, both germline and, more commonly, somatic mutations near the selectivity filter of the potassium channel KCNJ5 have been reported (Gomez-Sanchez, 2014).

The germline mutation was initially found in three members of a single family with severe hypertension and massive BAH, whereas the somatic mutations has been found only in aldosterone-producing adenomas (APAs) (Choi et al., 2011). With expanding genetic research, more such defects will likely be discovered (Williams et al, 2014).

Most hyperaldosteronism seen in clinical practice is secondary to an increase in renin–angiotensin activity in response to a reduced renal perfusion as seen with renal artery stenosis or reduced intravascular volume as in chronic edematous states. The ability to measure plasma renin activity (PRA) has made the differentiation much easier, since PRA is elevated in secondary aldosteronism and suppressed in PA.

INCIDENCE

After recognition of the multiple features of aldosterone excess in a single patient who was found at surgery to have a solitary adrenal adenoma, Conn (1955) went on to characterize the syndrome. Over the next decade, Conn et al. (1965) reported a high frequency of PA, found in almost 20% of the hypertensive patients at the University of Michigan. This high prevalence was subsequently thought to reflect the nature of the patients referred to that center, highly selected and suspected of having the disease. In most series of unselected patients reported in the 1970s and 1980s, classic PA was found in fewer than 0.5% of hypertensives (Gifford, 1969; Kaplan, 1967; Sinclair et al., 1987).

However, in the early 1990s, by the use of a simple screening test—the plasma ARR—one group of investigators in Brisbane, Australia, reported the finding of PA in 8.5% of 199 patients (Gordon et al., 1993, 1994). Subsequently, an abnormal ARR has been reported in 4% to 39% of hypertensives (Kaplan, 2007), but, as will be indicated later, that alone does not establish the diagnosis. Though the incidence of PA is higher than previously thought, it is likely not to be as common as some now believe.

CLINICAL FEATURES

The disease is usually seen in patients between the ages of 30 and 50 years (though cases have been found in patients from the age of 3 to 75 years) and in women more frequently than in men. The syndrome has been recognized during pregnancy in hypokalemic

patients with even higher aldosterone levels than expected and, most important, suppressed PRA (Al-Ali et al., 2007).

The classic clinical features of PA are hypertension, hypokalemia, excessive urinary potassium excretion, hypernatremia, and metabolic alkalosis (Fig. 11-1). The usual presence of these features reflects the pathophysiology of aldosterone excess.

Hypertension

Patients with PA are hypertensive, with very few exceptions (Medeau et al., 2008). The blood pressure (BP) may be quite high—the mean in one series of 136 patients was 205/123 (Ferriss et al., 1978b). In another series of 140 patients, 28 had severe, resistant hypertension (Bravo et al., 1988), whereas in a study of 1,616 patients with resistant hypertension, PA was diagnosed in 11.3% (Douma et al., 2008). More than a dozen cases have had malignant hypertension (Kaplan, 1963; Prejbisz et al., 2013). The BP decline (dip) during the night is usually attenuated (Zelinka et al., 2004).

Looked at in another way, increased levels of aldosterone and lower levels of renin may be seen before hypertension becomes manifest. Among 3,326 normotensive participants in the Framingham Heart Study, there was a continuous gradient of increased risk of BP progression with increasing ARR levels (Newton-Cheh et al., 2007). Similar findings were noted in a 5-year follow-up of 1,984 normotensives in France (Meneton et al., 2008).

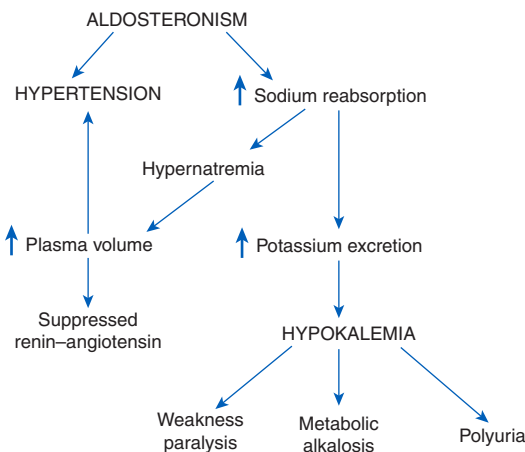


FIGURE 11-1 • Pathophysiology of PA. (Reprinted from Kaplan NM. Primary aldosteronism. In: Astwood EB, Cassidy CE, eds. *Clinical Endocrinology*, Vol. 2. New York: Grune & Stratton; 1968:468–472, with permission.)

Complications

Aldosterone levels inappropriate to sodium status exert deleterious effects on various tissues by rapid, nongenomic effects through their interaction with mineralocorticoid receptors. Thereby, vascular damage (Holaj et al., 2007) and fibrosis in the heart (Diez, 2008) and kidney (Reincke et al., 2009) occur so that cardiovascular complications reflect more than the accompanying hypertension (Milliez et al., 2005; Mulatero et al., 2013a). In particular, left ventricular hypertrophy is usually disproportionate to the level and duration of hypertension (Muiesan et al., 2008).

The vascular injury is mediated, at least in part, by effects of aldosterone on the immune system (Herrada et al., 2011) that involve macrophages and T-helper effector lymphocytes, effects that can be prevented by T-regulatory lymphocytes (Kasal et al., 2012). Moreover, patients with an APA (but not those with BAH) have elevations in angiotensin II type 1 receptor autoantibodies (Kem et al., 2014; Rossitto et al., 2013).

Additional complications have been reported in patients with PA beyond the frequency seen in patients with primary (essential) hypertension, including these:

- Impairment of insulin secretion (Fischer et al., 2013), insulin resistance (Kumagai et al., 2011), and the metabolic syndrome (Vaidya et al., 2013)
- Hyperparathyroidism (Pilz et al., 2012)
- Reversible sympathetic nervous overactivity (Kontak et al., 2010)
- Anxiety (Sonino et al., 2011) and cognitive impairment (Yagi et al., 2011)
- Obesity (Rossi et al., 2011a) although they had reported that plasma aldosterone levels were correlated to body mass index in patients with primary hypertension but not in patients with PA (Rossi et al., 2008a). Even though adipocytes can produce aldosterone, the effects remain local (Briones et al., 2012).

Hemodynamics

Aldosterone infusions in conscious sheep induce hypertension by effects on the kidney (Sosa León et al., 2002), and, in humans, the hypertension is hemodynamically characterized by a slightly expanded plasma volume, an increased total body and exchangeable sodium content, and an increased peripheral resistance (Bravo, 1994; Williams et al., 1984). When 10 patients with PA, previously well controlled on spironolactone, were studied 2 weeks after the drug was stopped and the hypertension reappeared, cardiac output and sodium content (both

plasma volume and total exchangeable sodium) rose initially (Wenting et al., 1982) (Fig. 11-2). Between weeks 2 and 6, the hemodynamic patterns separated into two types: In five patients, the hypertension was maintained

through increased cardiac output; in the other five, cardiac output and blood volume returned to their initial values, but total peripheral resistance rose markedly. Total body sodium space remained expanded in both groups, though more so in those with increased cardiac output (Man in't Veld et al., 1984). After surgery, the cardiac output fell in the high-flow patients, and the peripheral resistance fell in the high-resistance patients.

Mechanism of Sodium Retention

The pressor actions of aldosterone are generally related to its effects on sodium retention via its action on renal mineralocorticoid receptors (Baxter et al., 2004). Even though the kidney mineralocorticoid receptor is equally receptive to glucocorticoids and to mineralocorticoids (Arriza et al., 1987; Farman & Rafestin-Oblin, 2001), relatively small concentrations of aldosterone are able to bind to the mineralocorticoid receptor in the face of much higher concentrations of glucocorticoids (mainly cortisol) because of the action of the 11β -hydroxysteroid dehydrogenase (11β -HSD) enzyme, which converts the cortisol (with its equal affinity) into cortisone, which does not bind to the receptor (Walker, 1993).

Aldosterone stimulates sodium reabsorption through complex genomic effects that collectively act to increase the activity of the epithelial sodium channel (ENaC) in the apical membrane (Stokes, 2000). After a certain amount of persistent volume expansion, the increases in renal perfusion pressure and atrial natriuretic factor inhibit further sodium reabsorption so that “escape” from progressive sodium retention occurs, despite continued aldosterone excess (Yokota et al., 1994).

Hypokalemia

Incidence

Although normokalemia was found occasionally in the classic cases of APAs (Conn et al., 1965), hypokalemia was usual in the series reported prior to the early 1990s. In the MRC series, hypokalemia occurred in all 62 patients with a proved adenoma and was persistent in 53; among the 17 with hyperplasia, plasma potassium was persistently normal in only three patients (Ferriss et al., 1983). On the other hand, most patients in recently described series are normokalemic (Funder et al., 2008). There are a number of possible reasons why hypokalemia is now less common. These include the following:

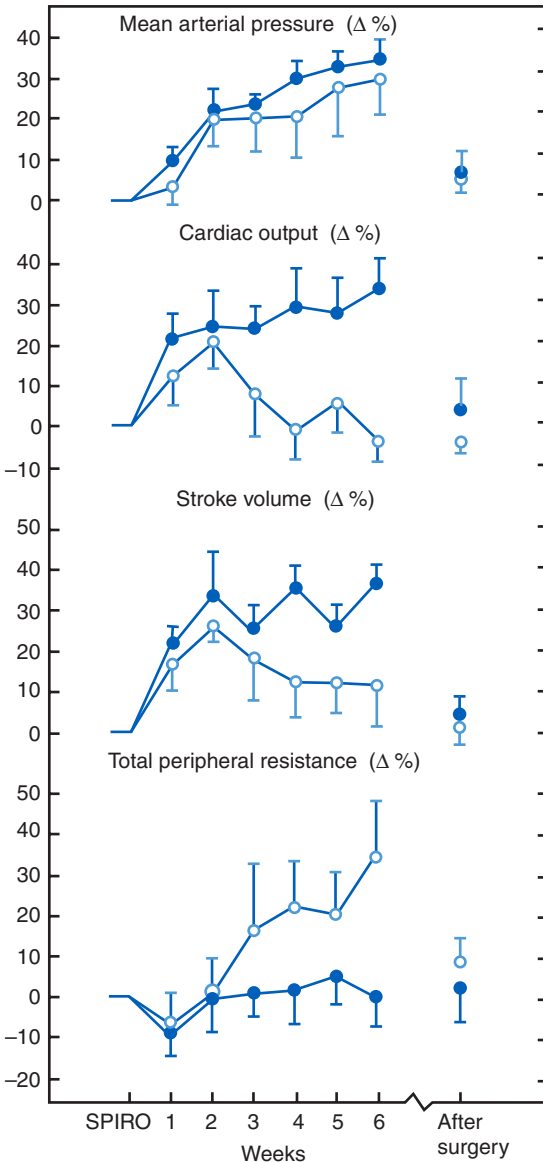


FIGURE 11-2 • Changes (mean \pm SEM) in systemic hemodynamics after discontinuation of spironolactone treatment (SPIRO) and after surgery in 10 patients with PA. Note the fall in stroke volume and cardiac output after 2 weeks in the five patients with high-resistance hypertension (open circles) compared to the five with high-flow hypertension (closed circles). (Reprinted from Wenting GJ, Man in't Veld AJ, Derckx FHM, et al. Recurrence of hypertension in primary aldosteronism after discontinuation of spironolactone: Time course of changes in cardiac output and body fluid volumes. *Clin Exp Hypertens* 1982;A4:1727–1748, with permission.)

- Most cases now being recognized are caused by BAH whose manifestations are usually milder than seen with APA. This includes the degree of potassium wastage.
- With more extensive screening, most cases are being recognized much earlier, before significant hypokalemia develops.
- Patients may experience considerable potassium loss without having the serum K^+ fall to the level as defined as hypokalemia. Whereas a patient's usual K^+ level may be 4.8 mmol/L, a fall to 3.6 mmol/L may reflect significant K^+ loss but not be so recognized.
- There may be a disconnect between hypertension and hypokalemia. Hypertension may develop by other nongenomic effects of aldosterone in addition to the genomic mediation of increased renal sodium reabsorption. Thereby, hypertension may develop before significant K^+ wastage.
- If patients reduce the sodium intake for relief of hypertension, K^+ wastage will decrease.
- Caution should be used to ensure that hypokalemia is not inadvertently missed. A number of factors may cause a temporary and spurious rise in plasma potassium, including the following: A difficult and painful venipuncture may cause plasma potassium to rise for multiple reasons: If the patient hyperventilates, the respiratory alkalosis causes potassium to leave cells; repeated fist clenching causes potassium to leave the exercising muscles; if the tourniquet is left on, plasma potassium rises from venous stasis. In a series of 152 patients with PA, serum potassium was above 3.6 mmol/L in only 10.5% in samples obtained without fist clenching but in 69.1% after fist clenching with a tourniquet in place (Abdelhamid et al., 2003).
- Any degree of hemolysis.
- Efflux of potassium from blood cells if separation of plasma by centrifugation is delayed or if the sample is placed on ice.

With significant falls in serum and body K^+ , aldosterone secretion may fall, even from otherwise autonomous adenomas (Kaplan, 1967). Therefore, potassium levels should be restored before aldosterone levels are measured.

Suppression of Renin Release

As a consequence of the initial expansion of vascular volume and the elevated BP, the baroreceptor mechanism in the walls of the renal afferent arterioles

suppresses the secretion of renin to the point that renin mRNA may be undetectable in the kidney (Shionoiri et al., 1992). Almost all patients with PA have low levels of PRA that respond poorly to upright posture and diuretics, two maneuvers that usually raise PRA (Montori et al., 2001). Rarely, concomitant renal damage may stimulate renin release (Oelkers et al., 2000), but renin levels are almost always suppressed, even in those with malignant hypertension (Wu et al., 2000). The presence of a low renin in patients with therapy-resistant hypertension is a clue to the presence of PA (Eide et al., 2004).

Other Effects

- Hyponatremia is usual, unlike most forms of edematous secondary aldosteronism in which the sodium concentration is often quite low or with diuretic-induced hypokalemia in which slightly low serum sodium is usually found. Thus, the serum sodium concentration may provide a useful clinical separation between primary and secondary aldosteronism.
- Hypomagnesemia from excessive renal excretion of magnesium may produce tetany.
- Sodium retention and potassium wastage may be demonstrable wherever such exchange is affected by aldosterone: Sweat, saliva, and stool.
- Atrial natriuretic peptide levels are appropriately elevated for a state of volume expansion (Opocher et al., 1992).

Resistant Hypertension

Resistant hypertension refers to the persistence of BP above 140/90 mm Hg despite therapy with three anti-hypertensive drugs, including a diuretic, in full doses. PA has been reported to be present in 20% to 40% of patients with resistant hypertension (Calhoun, 2007) based on the findings in small groups of patients. In a larger study of 251 patients with resistant hypertension, Pimenta et al. (2007) made the diagnosis of PA in 59 patients (24%) on the basis of hormonal studies. As in other reports of a high prevalence of PA among resistant hypertensives, the patients were studied while taking a variety of drugs that can variably alter both renin and aldosterone levels. The average number of such drugs was 4.2 per patient, and 71% were on a β -blocker, which is known to lower renin more than aldosterone, giving rise to falsely positive tests for PA.

In a much more convincing study of 1,616 patients with resistant hypertension, a number far larger than the total in all previous reports, the patients were studied after all antihypertensive drugs that could alter renin and aldosterone levels were discontinued (Douma et al., 2008). PA was diagnosed in 11.3% of these patients, using multiple tests to confirm the diagnosis. The authors conclude that since resistant hypertension is found in about 10% of hypertensive patients and since PA is present in about 10% of them, the overall prevalence of PA “in the general unselected hypertensive population is much lower than currently reported.”

DIAGNOSIS

The diagnosis of PA is easy to make in patients with unprovoked hypokalemia and other manifestations of the fully expressed syndrome. The fact that hypokalemia was present in most patients in series published before 1990 likely reflects the failure to look for the syndrome in normokalemic hypertensives. Over the past decade, many more hypertensive patients have been found to have PA, the majority without hypokalemia. This higher frequency is largely the consequence of broader use of the ARR for case detection. The Clinical Practice Guideline (Funder et al., 2008) lists these groups as having a high prevalence of PA and therefore in need of testing:

- Moderate or severe hypertension, i.e., patients with systolic BP greater than 160 or diastolic BP greater than 100 mm Hg
- Resistant hypertension, defined as BP above 140/90 despite treatment with three antihypertensive medications (this definition does not require the inclusion of a diuretic)
- Hypertensives with spontaneous or *diuretic-induced hypokalemia*
- Hypertension with adrenal incidentaloma

The adoption of these guidelines would call for testing of a large segment of the hypertensive population, and, before their adoption, the warning by Grimes and Schulz (2002) should be noted:

Screening has a darker side that is often overlooked. It can be inconvenient, unpleasant, and expensive... A second wave of injury can arise after the initial screening insult: false-positive results and true-positive results leading to dangerous interventions.

It therefore seems prudent to restrict testing to only portions of the four groups listed in the guideline (Funder et al., 2008) for the following reasons:

- “Moderate” hypertension, from 160 to 180 systolic or 100 to 110 diastolic, would subsume about 25% of all hypertensives.
- Hypertension should not be considered “resistant” unless therapy includes a diuretic. The prevalence of apparent resistance may subsume 30% of all hypertensives although far fewer, about 10%, are truly resistant.
- Hypokalemia induced by a diuretic may reflect nothing more than an effective diuretic that induces secondary aldosteronism. If such hypokalemia is resistant to the replacement of potassium, the likelihood of PA is likely greater.
- Only about 1% of adrenal incidentalomas have been found to have PA (Young, 2007a).

Urine Potassium

Although the ARR has largely replaced other case detection testings, if hypokalemia is present, a 24-hour urine sample should be collected for sodium and potassium levels before starting potassium replacement therapy but 3 to 4 days after diuretics have been stopped. If the urine sodium is above 100 mmol/24 hours (to ensure that enough sodium is present to allow potassium wastage to express itself), the presence of a potassium level above 30 mmol/24 hours indicates a driven renal wastage of potassium. In addition to the action of excess mineralocorticoid in the syndromes of PA, a number of other conditions may require consideration, conditions in which hypokalemia is coupled with renal potassium wastage (Table 11-2).

Once the renal origin of hypokalemia is recognized, it may be preferable to correct the hypokalemia with potassium supplements, 40 to 80 mmol/day, after the discontinuation of diuretics before performing additional workup. To restore total body potassium deficits after a prolonged diuretic use, a minimum of 3 weeks is needed, and it may take months. After a suitable interval, the supplemental potassium should be stopped for at least 3 days and the plasma potassium level should be rechecked. If plasma potassium is normal, plasma renin and aldosterone levels should be measured. Recall that if the plasma aldosterone is not definitely elevated in the presence of hypokalemia, it should be rechecked after potassium replenishment.

TABLE 11-2

Causes of Hypokalemia due to Renal Loss of Potassium

- I. High flow rate of potassium in the cortical collecting duct (CCD)
 - A. Increased sodium excretion, e.g., diuretics
 - B. Increased organic osmoles
 1. Glucose
 2. Urea
 3. Mannitol
- II. High potassium concentration in the CCD
 - A. With expanded intravascular volume (low plasma renin)
 1. Primary mineralocorticoid excess (Table 11-1)
 2. Liddle syndrome
 3. Amphotericin B
 - B. With contracted intravascular volume (high plasma renin)
 1. Bartter syndrome
 2. Gitelman syndrome
 3. Magnesium depletion
 4. Increased bicarbonate excretion
 5. Secondary aldosteronism, e.g., nephrotic syndrome

Plasma Aldosterone–Renin Ratio

The ARR is derived by dividing the plasma aldosterone (normal = 5 to 20 ng/dL) by the PRA (normal = 1 to 3 ng/mL/h). If plasma aldosterone is measured in picomoles per liter and PRA in nanograms per liter, the values should be 27.7-fold higher, i.e., a ratio of 20 equals a ratio of 555 in SI units.

If plasma renin concentration (PRC)—also called “direct” or “active” renin assay—is obtained, ARR results will likely be reported as plasma aldosterone in pmol/L divided by PRC in mU/L (PA/PRC). The PRC values are approximately seven times the PRA values. In one study, PRC provided better sensitivity and specificity of the ARR than did the PRA (Lonati et al, 2014).

The ARR should be performed with attention to a number of factors that can interfere with its validity as described in the clinical practice guideline (Funder et al., 2008) (Table 11-3). Unfortunately, the number of invalidating factors keeps growing, now including the use of an antidepressant drug (Ahmed et al., 2011) or oral contraceptives (Pizzolo et al., 2010).

The first evidence that the ARR identified more patients with PA than the small percentage previously recognized came from Gordon et al. (1993, 1994) from

the Greenslopes Hospital in Brisbane, Australia. The Brisbane group found a high prevalence of an elevated ARR, 40 of 199 normokalemic hypertensives referred to their hypertension research unit. Such high prevalences have been replicated by a number of investigators in various countries throughout the world, mostly on patients referred to study centers (Table 11-4).

As noted in Table 11-4, there are considerable differences in the definition of an elevated ARR, with most of the ARR threshold levels representing the upper values obtained in patients presumed to have essential hypertension. The thresholds reported vary from as low as 20 to as high as 100, leading the world's most aggressive promoter for more wide screening with the ARR to state: In essence, the ARR is a crude bivariate analysis of variables that have a skewed distribution (Rossi, 2011a,b). The reported prevalence of an elevated ARR (whatever the threshold used) in hypertensive patients varies from 6% to as high as 39% in those referred because of resistant hypertension (Kaplan, 2012). However, in by far the largest group (2,444) of truly unselected hypertensive subjects, the frequency of an elevated ARR composed of an elevated plasma aldosterone and low PRA was only 0.2% (Hannemann et al., 2012).

Despite the widespread use of the ARR to make important diagnostic and therapeutic decisions, very little study has been made of its test characteristics, i.e., sensitivity, specificity, and likelihood ratios at different cutoff values. In an attempt to better characterize the ARR, Montori et al. (2001) studied 497 patients under varying circumstances. They made two conclusions: First, the ratio varied considerably in the same patients whose posture changed from supine to standing and even more so after diuretic therapy (25 mg of hydrochlorothiazide daily) for 4 weeks; second, the ratio was “strongly and inversely dependent on the PRA level,” leading to the conclusion that “the aldosterone:renin ratio does not provide a renin-independent measure of circulating aldosterone that is suitable for determining whether plasma aldosterone concentration is elevated relative to PRA... Elevation of the ARR is predominantly an indicator of low PRA” (Montori et al., 2001).

Further concern over the sensitivity of the ARR has been raised by the data on repeated studies in 71 patients with a proven unilateral APA (Tanabe et al., 2003). The ARR was normal (below 35) in 31% of these patients on at least one occasion and only 37% had an abnormal ARR on all occasions. Rossi et al. (2010) found a much closer concordance between repeated ARR determinations.

The confounding effect of diuretic therapy noted by Montori et al. (2001) also applies to other

TABLE 11-3

Measurement of the ARR

- A. Preparation
 1. Correct hypokalemia if present
 2. Encourage the patient to liberalize sodium intake
 3. Withdraw agents for at least 4 wk that raise renin but may lower aldosterone causing false negatives
 - a. Spironolactone, eplerenone, amiloride, and triamterene
 - b. Potassium-wasting diuretics
 - c. Products derived from licorice root
 4. Withdraw other medications that may affect the ARR for at least 2 weeks
 - a. β -Adrenergic blockers, central α -2 agonist (e.g., clonidine), nonsteroidal anti-inflammatory drugs that lower renin more than aldosterone causing false positives
 - b. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, dihydropyridine calcium channel blockers that raise renin and lower aldosterone causing false positives
 5. If necessary to maintain hypertension control, use other antihypertensive medications that have lesser effects on the ARR (e.g., verapamil slow release, doxazosin)
 6. Estrogen-containing medications may cause false-positive ARR when PRC (rather than PRA) is measured
- B. Conditions for collection of blood
 1. Collect blood midmorning, after the patient has been out of bed for at least 2 h and seated for 5–15 min
 2. Collect blood carefully, avoiding stasis and hemolysis
 3. Maintain the sample at room temperature (and not on ice, because this will promote conversion of inactive to active renin) before centrifugation and rapid freezing of plasma components pending assay
- C. Factors to take into account when interpreting results
 1. Age: In patients aged >65 y, renin can be lowered more than aldosterone by age alone, leading to a raised ARR
 2. Time of the day, recent diet, posture, and the length of time in that posture
 3. Medications
 4. Method of blood collection, including any difficulty doing so
 5. Potassium levels
 6. Renal disease may raise aldosterone through hyperkalemia while lowering the secretion of renin, causing false positives

ARR, aldosterone-to-renin ratio; PRC, plasma renin concentration; PRA, plasma renin activity.

Modified from Funder JW, Carey RM, Fardella C, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2008;93:3266–3281.

antihypertensive medications. β -Blockers, by reducing PRA more than plasma aldosterone, can increase the number of false-positive ARRs, whereas an ACE inhibitor, angiotensin receptor blocker, or direct renin inhibitor all cause increases in PRA levels, thereby causing false-negative results (Mulatero et al., 2002). As seen in Table 11-3, the effect of these and other drugs must be considered in the preparation of the patient before the performance of the ARR test (Ahmed et al., 2011). However, in order to remove drugs that may interfere, patients may be exposed to marked rises in BP, leading to various target organ damages (Fischer et al., 2011).

As noted by Montori et al. (2001), the most common reason for false-positive ARRs is the presence of a low level of PRA as often found in the elderly, blacks, and hypertensives. With a not-unusual low PRA level of 0.3 ng/mL/h, the presence of a normal plasma

aldosterone level of 12 ng/dL would provide an ARR of 40, which by most investigators' current criteria (Table 11-4) would be abnormal.

To reduce this source of false-positive tests, some require an absolutely elevated plasma aldosterone level of 16 ng/dL or higher to call the ARR abnormal (Young, 2002). However, the Brisbane group does not, since in a description of 54 patients with documented PA, 20 had plasma aldosterone levels of 15 ng/dL or lower (Stowasser et al., 2003). Nonetheless, the wisdom of requiring an elevated plasma aldosterone has been documented, reducing false positives from 30% to 3% in one study (Seiler et al., 2004).

There is a need for establishing the "correct" cutoff of the ARR, so as to miss very few with PA, i.e., high sensitivity, and not to require additional workup in those without PA, i.e., high specificity. Many attempts have been made including a study by Bernini et al.

TABLE 11-4

The Prevalence of Autonomous Hyperaldosteronism and APAs in Patients Tested by Plasma Aldosterone to Plasma Renin Activity Ratio (ARR)^a

Reference	No. of Patients	ARR Threshold ^a	Raised ARR	Abnormal Suppression by Salt Loads	Proven APA
Hiramatsu et al. (1981)	348	40	7.4%	NA ^b	2.6%
Gordon et al. (1993)	199	30	20.0%	8.5%	2.5%
Lim et al. (1999)	125	27	14.0%	NA	NA
Lim et al. (2000)	495	27	16.6%	9.2%	0.4%
Nishikawa and Omura (2000)	1,020	20	6.4%	NA	4.2%
Loh et al. (2000)	350	20 + PA > 15	18.0%	4.6%	1.7%
Rayner et al. (2000)	216	36 + PA > 18	32.0%	NA	2.3%
Fardella et al. (2000)	305	25	9.5%	4.9%	0.3%
Douma et al. (2001)	978	30 + PA ^c	21.2%	13.8%	NA
Rossi et al. (2002)	1,046	35	12.8%	6.3%	1.5%
Hood et al. (2002)	835	40	12.3%	NA	0.7%
Mulatero et al. (2002)	2,160	50	10.6%	7.0%	1.6%
Calhoun et al. (2002)	88	20	NA	20.4%	NA
Girerd et al. (2003)	143	NA	39%	NA	6%
Fogari et al. (2003)	750	25	12%	6%	2%
Strauch et al. (2003)	403	50	21.6%	19%	6.5%
Stowasser et al. (2003)	~300	30	18.6%	17.7%	5%
Mosso et al. (2003)	609	25	10.2%	6.1%	0%
Olivieri et al. (2004)	287	50	32.4%	NA	NA
Giacchetti et al. (2006)	157	40 + PA > 7 after IV saline	38.8%	100	16.6%
Williams et al. (2006)	347	25 + PA > 8	7.5%	3.2	NA
Rossi et al. (2006a,b)	1,125	40	11.2%	NA	4.8%
Douma et al. (2008)	1,616	65 + PA > 15	20.9%	11.3	NA
Ribeiro et al. (2009)	105	25	8.52%	11%	0
Westerdahl (2011)	200	65	18%	5.5%	1.5%
Hannemann (2012)	2,444	25	0.2%	NA	NA

^aARR expressed as plasma aldosterone in ng/dL, divided by PRA in ng/mL/h.

^bNA, not available.

^cincreased.

(2008) that concluded that an ARR of 69 provided the best balance of sensitivity, 98%, and specificity, 85%. However, Jansen et al (2014) found a 5-fold difference in ARR levels obtained under the same conditions.

The continued confusion over the performance and interpretation of the ARR has led the authors of the clinical practice guideline to this conclusion:

Although it would clearly be desirable to provide firm recommendations for ARR and plasma aldosterone cut-offs, the variability of assays between laboratories and the divided literature to date make it more prudent to point out relative advantages and disadvantages, leaving clinicians the flexibility to judge for themselves. (Funder et al., 2008).

This position is clearly not suitable for the guidance of practitioners who must manage most patients. The best advice is to carefully follow all of the steps listed in Table 11-3, ensuring that patients are properly prepared and the blood sample is obtained under appropriate conditions. Then, the levels of plasma aldosterone and renin activity should be examined without calculating a ratio. If the PRA is definitely low (below 0.5 ng/mL/h) and the plasma aldosterone is definitely high (above 15 mg/dL), the same measurement of aldosterone and renin activity should be obtained on another occasion as recommended by Gordon and Stowasser (2007). If both low PRA and high aldosterone levels are found again under as

careful conditions as possible, a confirmatory test should be performed.

All of this, of course, assumes that the patient is willing and able to undergo a laparoscopic adrenalectomy if the remainder of the workup confirms the presence of an APA.

Confirmatory Tests

Elevated and Nonsuppressible Aldosterone

If the PRA is low and the aldosterone is high, the presence of an inappropriately elevated and nonsuppressible aldosterone level should be documented. Four confirmatory tests have been described, with no preference given to any one of them in the 2008 guidelines. Unfortunately, the one least likely to give false-positive results, the Florinef suppression test (FST), is so difficult to perform and expensive that even its most forceful advocate states that “it is the least practical” (Stowasser, 2009).

Three of the four are based on demonstration of a lack of suppression of aldosterone after intravascular volume expansion by either intravenous or oral salt loading. This was first demonstrated with the intravenous saline suppression test of plasma aldosterone (Kem et al., 1971). Plasma aldosterone is measured before and after the infusion of 2 L of normal saline over 4 hours. Patients with PA have higher basal levels but, more importantly, fail to suppress these levels after saline to below 5 ng/dL (Mulatero et al., 2006). False-positive intravenous saline suppression tests were reported in 16.1% (Mulatero et al., 2006), 24.9% (Rossi et al., 2007), and 39% (Giacchetti et al., 2006) of patients with an elevated ARR. Therefore, to provide better specificity, a cutoff of 7 ng/dL was proposed by Giacchetti et al. (2006).

Some prefer to measure urine aldosterone levels after 3 days of oral sodium loading, with an abnormal level being above 12 (Young, 2002) or 14 $\mu\text{g}/24$ hours (Bravo, 1994). However, the Brisbane group reported that both the intravenous and oral salt loading tests are often inaccurate and they utilize a high salt diet plus large doses of the mineralocorticoid fluorohydrocortisone (Florinef) over a 4-day hospitalization, the FST test (Stowasser et al., 2003).

Captopril Suppression

Inhibition of the angiotensin-converting enzyme that converts the inactive angiotensin I to the active angiotensin II should reduce aldosterone production.

Whereas plasma aldosterone levels were markedly suppressed 3 hours after oral intake of 1 mg of the ACE inhibitor captopril per kilogram of body weight in patients with primary hypertension or renovascular hypertension, they remained elevated in patients with primary hyperaldosteronism (Thibonnier et al., 1982). The normal response is a full in plasma aldosterone of 30% or more (Funder et al., 2008). Mulatero et al. (2007) reported misleading results in 4 of 11 patients. It is infrequently recommended.

Rule Out Glucocorticoid-Remediable Aldosteronism

Glucocorticoid-remediable aldosteronism (GRA) or Type I Familial Hyperaldosteronism should be considered in a young patient, particularly if other family members have aldosteronism or hemorrhagic stroke. This is most easily confirmed by demonstrating the hybrid gene in a blood sample (see below).

Excluding Other Diseases

Various causes of secondary aldosteronism are easily excluded by the presence of edema and high levels of peripheral blood PRA. In addition, there are a number of monogenic forms of hypertension, most involving renal tubular disorders and some associated with hypertension and hypokalemia, that should not be confused with PA (Stowasser & Gordon, 2006b) (Table 11-5).

Those listed under hypertension and hypokalemia also have suppressed, low PRA but all have low aldosterone levels, either because of the secretion of other mineralocorticoids (glucocorticoid-remediable hyperaldosteronism and congenital adrenal hyperplasia caused by either 11 β -hydroxylase or 17 α -hydroxylase deficiency) or because of increased cortisol acting as a mineralocorticoid (apparent mineralocorticoid excess, to be covered in Chapter 13), increased sodium reabsorption from activated sodium channels (Liddle syndrome), or increased activity of mineralocorticoid receptors (Geller et al., 2000).

FAMILIAL FORMS OF HYPERALDOSTERONISM

The three forms of familial hyperaldosteronism are outlined in Table 11-6.

TABLE 11-5

Monogenic Forms of Hypertension

Disorder	Inheritance	Consequence of Mutant Gene
Hypertension and hypokalemia		
GRA (familial hyperaldosteronism, type 1)	Dominant	Increased mineralocorticoids from chimeric 11 β -hydroxylase and aldosterone synthase genes
Apparent mineralocorticoid excess	Recessive	Reduced inactivation of cortisol due to 11 β -HSD deficiency
Mutation of mineralocorticoid receptor	Dominant	Increased activity of mineralocorticoid receptor
Liddle syndrome	Dominant	Increased activity of ENaC
Hypertension and hyperkalemia		
Pseudohypoaldosteronism, type 2 (Gordon syndrome)	Dominant	Increased chloride reabsorption in distal tubule

Type 1: Glucocorticoid-Remediable Aldosteronism

Sutherland et al. (1966) described a father and son with classic features of PA whose entire syndrome was completely relieved by dexamethasone, 0.5 mg four times a day (i.e., glucocorticoid remediable). Subsequently, the syndrome was shown to follow an autosomal dominant mode of inheritance and to be associated with increased

levels of 18-hydroxylated cortisol. Ulick et al. (1990) postulated that the syndrome was the result of the acquisition of aldosterone synthase activity by cells of the zona fasciculata. This would explain the high levels of 18-hydroxylated steroids that can be suppressed by exogenous glucocorticoid that in turn suppresses ACTH, the normal stimulus to synthetic activity within the zona fasciculata.

TABLE 11-6

Clinical and Biochemical Phenotypes of Familial Forms of Hyperaldosteronism

	Type 1/GRA	Type 2	Type 3
Causal gene	Hybrid CYP11 B1/CYP11B2	Unknown Linkage to 7p22 in some families	KCNJ5* (germline mutation)
Transmission	Autosomal dominant	Autosomal dominant	Autosomal dominant
Diagnosis	Long PCR	Confirmed PA in two or more members of the family	KCNJ5 sequencing
Onset of hypertension	Variable	Adulthood	Childhood
Severity of hypertension	Normal to resistant	Normal to resistant	Resistant
Hybrid steroids levels	10 times normal	3–4 times normal	50–100 times normal
Aldo response to dexamethasone	Complete Suppression	Partial/transient reduction	Paradoxical increase
Adrenal pathology	Normal	APA/BAH	Marked BAH

As many as 40% of patients with sporadic, nonfamilial APA have been found to have a somatic mutation in KCNJ5 (Boukroun et al., 2012). Unlike the very few with the germline mutation, patients with somatic mutation should be managed in the same way as those without a mutation.

PA, primary aldosteronism; APA, aldosterone-producing adenoma; BAH, bilateral adrenal hyperplasia; FH, familial hyperaldosteronism; GRA, glucocorticoid-remediable aldosteronism; KCNJ5 potassium inwardly rectifying channel, subfamily 1, member 5; CYP11B1, 11-beta-hydroxylase; CYP11B2, aldosterone synthase.

Genetic Confirmation

The correctness of Ulick et al.'s postulate was proven by Lifton et al. (1992) who found "complete linkage of GRA to a gene duplication arising from unequal crossing over, fusing the 5 regulatory region of 11-beta-hydroxylase to the 3' coding sequences of aldosterone synthase" (Fig. 11-3). The two genes lie next to one another on human chromosome 8 and are 94% identical, likely explaining the propensity to cross over (Dluhy & Lifton, 1999).

Clinical and Laboratory Features

As more patients with GRA have been identified, variations in both genotype and phenotype have been identified (Holloway et al., 2009). Different sites of gene crossover do not seem to influence the phenotype, and considerably different phenotypes have been seen within a single family that are not accounted for by different genotypes (Carajaval et al., 2012).

The hyperaldosteronism is usually evident at birth with inheritance as an autosomal dominant trait, occurring equally among men and women. The hypertension is often severe, poorly responsive to usual anti-hypertensive therapy, but some affected subjects in pedigrees are normotensive. An increased prevalence of strokes, particularly cerebral hemorrhage from intracranial aneurysm, has been reported (Dluhy & Lifton, 1999). About half of affected patients are normokalemic, explained by a number of factors, including a lesser mineralocorticoid activity of the

18-hydroxylated steroids and the inability of dietary potassium to stimulate aldosterone secretion when it arises from the zona fasciculata (Litchfield et al., 1997).

Diagnosis

Initially, the definitive diagnosis was based on dexamethasone suppression of aldosterone, but now that genetic testing is so readily available, this is the preferred procedure. The genetic test can be arranged by contacting the Lifton lab at Yale Medical School, either by phone at 203-737-2861 or by FAX at 203-785-3784.

Treatment

Suppressive doses of exogenous glucocorticoid will usually control the hypertension even if all the hormonal perturbations are not normalized (Stowasser et al., 2000). Spironolactone with or without a thiazide diuretic has been used without glucocorticoid suppression (Dluhy & Lifton, 1999).

Type 2: Familial Hyperaldosteronism

Familial occurrence of PA was first reported in 1991 (Gordon et al., 1991) and now has been recognized as an autosomal dominant pattern in 3-5% of members of families of patients with documented PA (Mulatero et al., 2013b), suggesting that this is by far the most common familial form. However, there are no distinguishing clinical features, there is no suppression with

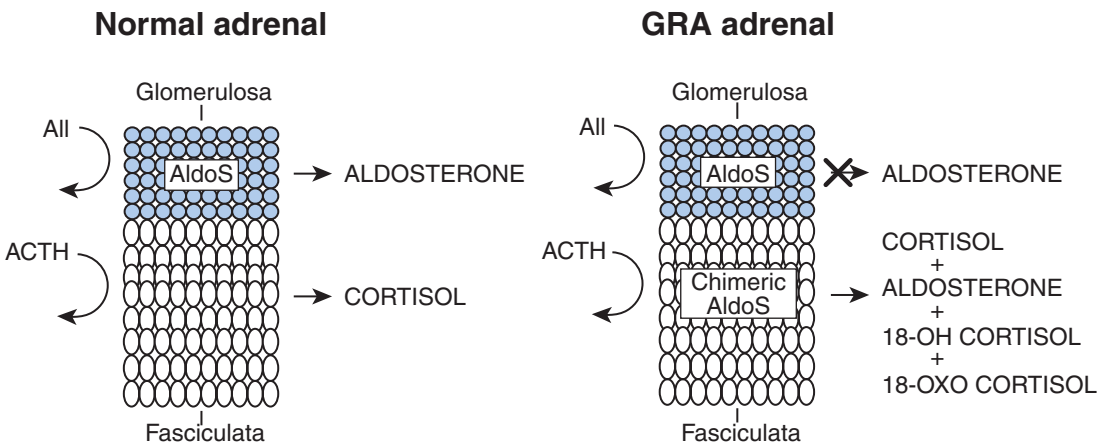


FIGURE 11-3 • Regulation of aldosterone production in the zona glomerulosa and cortisol production in the zona fasciculata in the normal adrenal and model of the physiologic abnormalities in the adrenal cortex in GRA. Ectopic expression of aldosterone synthase enzymatic activity in the adrenal fasciculata results in GRA. (Reprinted from Lifton RP, Dluhy RG, Powers M, et al. Hereditary hypertension caused by chimaeric gene duplications and ectopic expression of aldosterone synthase. *Nature Genet* 1992;2:66–74, with permission.)

dexamethasone, and there is no recognized genetic defect beyond an association with linkage to a locus at chromosome 7p22 (Mulatero et al, 2013b). Therefore, these patients should be evaluated and managed in the same manner as patients with a nonfamilial type of PA.

Type 3: Familial Hyperaldosteronism

Geller et al. (2008) have reported another autosomal dominant familial form of aldosteronism with severe hypertension appearing by age 7 with very high levels of 18-hydroxylated steroids that were not suppressed by dexamethasone. Bilateral adrenalectomy was performed because of unrelenting hypertension and massive hyperplasia was found. The syndrome was later shown to be caused by a germline gain-in-function missense mutation in the *KCNJ5* gene, encoding Kir3,4, a member of the inwardly rectifying K⁺ channel family (Choi et al., 2011). Subsequently, similar mutations were found in kindreds with milder hypertension without adrenal hyperplasia (Scholl et al., 2012) as well as in cases similar to the original with severe hypertension (Charmandari et al., 2012). Such cases are extremely rare (Pallauf et al., 2012).

Somatic Mutations in Aldosterone-Producing Adenomas

In the same paper describing the family with the *germline* mutation, Choi et al. (2011) also reported two *somatic* mutations in the same channel in 8 of 22 APAs. Subsequently, such somatic mutations have been reported in about 40% of APAs (Azizan et al., 2012; Boulkroun et al., 2012; Mulatero et al., 2013b). Such somatic mutations were not seen in hyperplastic tissue, further separating the pathophysiology of APA and BAH.

OTHER SYNDROMES

Liddle Syndrome

Liddle et al. (1963) described members of a family with hypertension, hypokalemic alkalosis, and negligible aldosterone secretion, apparently resulting from an unusual tendency of the kidneys to conserve sodium and excrete potassium even in the virtual absence of mineralocorticoids. Such patients have a mutation of the β or γ subunits of the renal ENaC, which causes increased sodium reabsorption in the distal nephron (Furuhashi et al., 2005). As will be noted in Chapter 13,

these clinical features are also seen in apparent mineralocorticoid excess caused by mutations in 11 β -HSD, preventing conversion of cortisol to cortisone.

Activation of Mineralocorticoid Receptor

Geller et al. (2000) identified a mutation in the mineralocorticoid receptor that causes early-onset hypertension that is markedly exacerbated in pregnancy. The exacerbation is a consequence of an altered receptor specificity so that the high levels of progesterone and other steroids lacking 21-hydroxyl groups become potent agonists.

Gordon Syndrome

In this rare syndrome, increased renal sodium and chloride retention causes hypertension and suppression of the renin–aldosterone mechanism, but with hyperkalemia (Gordon, 1986). The syndrome, known as pseudohypoaldosteronism type 2, is inherited as an autosomal dominant with at least three loci having been recognized (Disse-Nicodème et al., 2000). An elevated ARR has been noted with aldosterone stimulated by hyperkalemia and renin suppressed by volume expansion (Stowasser, 2000).

During Pregnancy

Normal pregnancy is associated with elevated plasma aldosterone but also elevated renin activity. In 31 reported cases of PA diagnosed during pregnancy, usually presenting with marked hypokalemia, renin levels were reduced (Lindsay & Nieman, 2006). Moreover, preexisting hypertension due to PA may be ameliorated during pregnancy, perhaps by antagonism of the effects of elevated aldosterone by the high progesterone levels (Murakami et al., 2000). Management is complicated by the inability to use most medical therapies, and laparoscopic adrenalectomy may be the preferred treatment.

TYPES OF ADRENAL PATHOLOGY

Once the diagnosis of PA is made, the type of adrenal pathology must be ascertained since the choice of therapy is different: Surgical for an adenoma and medical for hyperplasia. This need is even greater today than in the past as recognition of patients with milder

manifestations of aldosteronism is so much easier and more frequently performed.

Aldosterone-Producing Adenomas

Solitary benign adenomas (Fig. 11-4) are almost always unilateral and most are small, weighing less than 6 g and measuring less than 3 cm in diameter. In various series, from 20% to 85% are smaller than 1 cm (Rossi et al., 2001). Histologically, most adenomas are composed of lipid-laden cells arranged in small acini or cords, similar in appearance and arrangement to the normal zona fasciculata, the middle zone of the adrenal cortex. Moreover, focal or diffuse hyperplasia, as seen in Figure 11-4, is usually present in both the remainder of the adrenal with the adenoma and the contralateral gland (Boulkroun et al., 2010).

As noted, somatic mutations in genes controlling potassium channels have been reported in about 40% of APAs.

Bilateral Adrenal Hyperplasia (Idiopathic Hyperaldosteronism)

In the late 1960s, reports of hyperaldosteronism with no adenoma but rather with BAH began to appear (Davis et al., 1967), and it was initially referred to as idiopathic hyperaldosteronism (IHA) (Biglieri et al., 1970). As more patients have been screened, the proportion of PA related to BAH has steadily increased from less than one-third in the 1970s to more than two-thirds in the 2000s (Young, 2007b).

The better detail provided by newer imaging procedures may lead to confusion: Because the hyperplasia that often accompanies an adenoma can now be recognized, bilateral hyperplasia may be mistakenly diagnosed on the one hand; because nodularity is often seen with hyperplasia, an adenoma may be mistakenly diagnosed on the other (Sarlon-Bartoli et al., 2011).

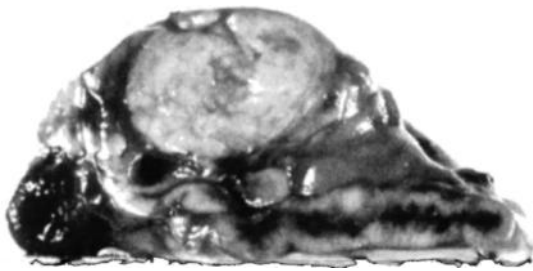


FIGURE 11-4 • Solitary adrenal adenoma with diffuse hyperplasia removed from a patient with PA.

The presence of bilateral hyperplasia suggests a secondary response to some stimulatory mechanism rather than a primary neoplastic growth, but none has been identified. It should be recalled that, soon after the description of hyperaldosteronism associated with BAH, members of the MRC BP Unit at the Western Infirmary in Glasgow published a series of papers with convincing evidence that this condition was totally different from Conn syndrome of APA (Table 11-6) (Ferriss et al., 1970). They referred to BAH as simply a form of “low-renin essential hypertension” (McArdavey et al., 1983).

Moreover, there is a progressive increase in adrenal nodular hyperplasia with age having no relationship to hypertension (Tracy & White, 2002). Therefore, the increased frequency of cases with hyperplasia may simply reflect the natural changes with age: increased adrenal nodular hyperplasia, progressively lower renin, but maintained aldosterone levels (Guthrie et al., 1976), giving rise to an elevated aldosterone–renin ratio without hyperaldosteronism. This scenario is in keeping with the MRC investigators’ belief that these patients have “low-renin essential hypertension” (McArdavey et al., 1983).

Another scenario may explain at least part of the progressive increase in the diagnosis of BAH as more and more hypertensives are screened with the ARR (with a false positivity of >50%) and then confirmed by tests that may have greater than 20% false positivity. The diagnosis of BAH is made by the finding of equal aldosterone levels in blood from both adrenals at AVS, done routinely in patients with a positive confirmatory test. An unknown portion of these patients do not have autonomous hyperaldosteronism, but they have undergone an unnecessary AVS, which reveals the equal aldosterone levels as seen in patients with primary (essential) hypertension.

Unilateral Hyperplasia

Even more difficult to explain than the presence of bilateral hyperplasia are the 30 reported cases of hyperaldosteronism that apparently are caused by hyperplasia of only one adrenal gland (Goh et al., 2007).

Other Pathologies

Carcinoma

Aldosterone-producing carcinomas are rare (Griffin et al, 2014); only 58 were reported from 1955 to 2003 (Seccia et al., 2005). Most are associated with concomitant hypersecretion of other adrenal hormones,

but a few may hypersecrete only aldosterone (Touitou et al., 1992).

Associated Conditions

Patients have been reported with PA caused by an adrenal adenoma in association with acromegaly (Dluhy & Williams, 1969), primary hyperparathyroidism (Pilz et al., 2012), the multiple endocrine neoplasia I syndrome (Gordon et al., 1995), neurofibromatosis (Biagi et al., 1999), familial adenomatous polyposis (Alexander et al., 2000), renal artery stenosis (Mansoor et al., 2002), and end-stage renal disease (Kazory & Weiner, 2007).

Extra-Adrenal Tumors

Single ectopic aldosterone-producing tumors have been found in the kidney (Abdelhamid et al., 1996) and ovary (Kulkarni et al., 1990).

DIAGNOSING THE TYPE OF ADRENAL PATHOLOGY

Various procedures have been used to diagnose the type of adrenal pathology, but AVS is now recommended even when there is no apparent ambiguity by CT scans because of the vagaries of adrenal pathology (Funder et al., 2008). Errors still occur: BAH is operated upon, with limited success (Sukor et al., 2009).

Ancillary Procedures

In general, autonomous lesions that can be cured by surgery (adenomas and the rare primary adrenal hyperplasia) display their autonomy from the normal control of aldosterone production by the renin-angiotensin mechanism by having (a) high levels of aldosterone and its precursor 18-OH-corticosterone (Auchus et al., 2007), (b) little or no response to stimulation of renin-angiotensin such as during an upright posture test, and (c) the production of hybrid steroids such as 18-OH-cortisol. None of these are now recommended for measurement.

Adrenal Computed Tomography

The clinical practice guideline recommends an adrenal CT scan “as the initial study in subtype testing” (Funder et al., 2008). However, as stated by Rossi

et al. (2008b), “adrenal imaging is insufficient to achieve discrimination between APA and IHA” and they did not include CT scanning in their algorithm for the diagnostic workup of PA.

The inaccuracy of CT scans (which are preferable to MRI) was clearly demonstrated in the Mayo Clinic series of 194 patients with PA who had both CT scan and AVS, the most accurate discriminator (Young et al., 2004). The CT scan correctly identified only 53% with either unilateral or bilateral lesion. CT scans showed an APA in 24% who had bilateral lesions and who would thereby be subjected to inappropriate adrenalectomy. CT scans showed bilateral disease in 21% who had an APA and would thereby be denied an indicated adrenalectomy. CT scans showed an APA in the wrong adrenal in 12 patients. Similar data showing the fallibility of CT scans when compared to AVS have been published by other investigators (Magill et al., 2001; Nwariaku et al., 2006; Riester et al, 2014; Sarlon-Bartoli et al., 2011).

Adrenal Venous Sampling

AVS is now recognized as the definitive procedure to differentiate unilateral from bilateral disease in patients with confirmed PA. One of the first reports of the value of AVS was that of Rossi et al. (2001) who reported their findings in 104 patients with PA and equivocal CT or MRI findings. AVS was feasible in 97.1% of attempts, and, in 80.6% of cases, bilateral samples were obtained almost simultaneously. With bilateral selective AVS, a value of aldosterone/cortisol of one side over the contralateral side of 2 or greater identified a unilateral source of excess aldosterone in 80% of the patients.

However, at least 10 ways to perform and interpret AVS have been published (Kline et al., 2008). The current consensus is to use ACTH stimulation (Monticone et al., 2012b) with immediate measurement of cortisol from blood from the two catheters to confirm their positioning before samples for aldosterone are drawn to calculate the lateralization. They also note that the true specificity and sensitivity of AVS have not been validated since only those with lateralization undergo surgery.

AVS should only be performed in centers with experience with the procedure. All who perform AVS or who wish to interpret data from the procedure should read the clinical practice guideline (Funder et al., 2008).

Adrenal Scintigraphy

Adrenal scintiscans with the isotope 6- β -[¹³¹I]-iodomethyl-19-norcholesterol (NP-59) have been used to identify the site of aldosterone hypersecretion (Rossi et al., 2008b). Since small adenomas with relatively low uptake of the tracer may give false-negative results (Nakahama et al., 2003), this procedure will rarely need to be utilized.

Overall Plan

As seen in Figure 11-5, the diagnosis of PA should be looked for in patients considered to have an increased prevalence. Only 10% to 20% of these patients will have the combination of a low PRA and high aldosterone level. Those should then have a test to confirm autonomous hyperaldosteronism. Approximately half of these will be confirmed, and they should have AVS. As noted earlier, there seem to be no value and a potential for serious mistakes by CT scanning, so this is not part of the algorithm.

Remember that young patients and particularly those with a family history of aldosteronism should be evaluated for GRA, as described earlier in this chapter. The problem of excluding adrenal hyperfunction in patients with an adrenal incidentaloma is addressed in the first portion of Chapter 12.

THERAPY

Once the type of adrenal pathology has been ascertained, surgery should be done if the diagnosis is *adenoma*, and medical therapy is indicated if the diagnosis is *bilateral hyperplasia*. There are reports of relief of

aldosteronism by removal of a unilaterally hyperplastic gland (Goh et al., 2007), so surgery should only be performed if AVS clearly defines a unilateral source of the aldosterone hypersecretion.

In a 10-year follow-up of 300 patients with treated PA, 53% medically, overall survival was similar to that seen in 600 patients with treated primary hypertension (Reincke et al., 2012).

Surgical Treatment

Preoperative Management

Once the diagnosis of adenoma is made, a 3- to 5-week course of an aldosterone receptor blocking drug may be given to normalize the various disturbances of electrolyte composition and fluid volume, perhaps easing anesthetic, surgical, and postoperative management.

Surgical Technique

With improved preoperative diagnosis of an adenoma, laparoscopic adrenalectomy has become the procedure of choice (Funder et al., 2008). If hyperplasia is found at surgery despite the preoperative diagnosis of an adenoma, only a unilateral adrenalectomy should be done. In view of the poor overall results with bilateral adrenalectomy and its complications, one gland should be left intact.

Postoperative Course

Hypertension is relieved without the need for antihypertensive drugs in 35% to 60% and improved in most of the remainder (Letavernier et al., 2008;

Hypertensive Patient at Increased Risk for Primary Aldosteronism

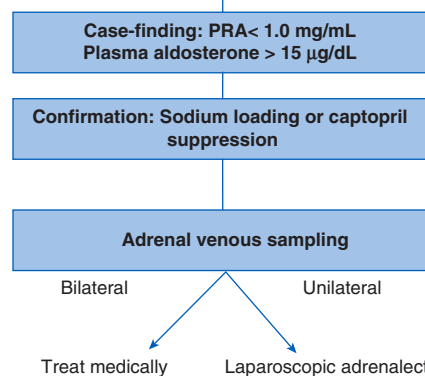


FIGURE 11-5 • A diagnosis flow chart for evaluating and treating patients with PA. PA, primary aldosteronism; PRA, plasma renin activity.

Pang et al., 2007; Zarnegar et al., 2008). The likelihood of complete resolution of hypertension is greater in those patients who required only two or fewer antihypertensive drugs preoperatively, who are not obese, who are female, and who have had hypertension for less than 6 years (Zarnegar et al., 2008).

Postoperative Complications

Hypoaldosteronism

The patient, even if given an aldosterone receptor blocker preoperatively, may develop hypoaldosteronism with an inability to conserve sodium and excrete potassium. This may persist for some time after renin levels return to normal, analogous to the slowness of the return of cortisol production after prolonged ACTH suppression by exogenous glucocorticoids.

The aldosterone deficiency is usually not severe or prolonged and can be handled simply by providing adequate salt without the need for exogenous glucocorticoid or mineralocorticoid therapy.

Sustained Hypertension

The hypertension may persist for some time; a few patients require years for the return of normal BP. If the BP fails to respond, hyperfunctioning adrenal tissue may have been left. More likely is the presence of coincidental primary hypertension, as would be expected in at least 20% of cases, or the occurrence of significant renal damage from the prolonged hypertension (Reincke et al., 2009). In 99 patients who had bilateral hyperplasia, relief of hypertension after unilateral or bilateral adrenalectomy occurred in only 19% (Funder et al., 2008).

Medical Treatment

Chronic medical therapy with spironolactone or eplerenone or, if those are not tolerated, amiloride with or without a thiazide diuretic is the treatment of choice for patients with hyperplasia, patients with an adenoma who are unable or unwilling to have surgery, patients who remain hypertensive after surgery, and patients with equivocal findings (Funder et al., 2008). As noted, Funder (2011, 2012) advocates the routine use of an aldosterone receptor blocker in all hypertensives, regardless of any suspicion of PA.

Most experience has been with spironolactone, which usually lowers the BP and keeps it down (Ferriss et al., 1978a). PA patients treated with spironolactone

had a slower but eventually equal regression of left ventricular hypertrophy as those who had unilateral adrenalectomy (Catena et al., 2007). Although higher doses may initially be needed, a satisfactory response may then be maintained with as little as 25 to 50 mg a day. The combination of spironolactone with a thiazide diuretic may provide even better control and allow for smaller doses of spironolactone. With these lower doses, the various side effects are generally minor, and in only 3 of 95 cases were they severe enough to lead to withdrawal of the drug (Ferriss et al., 1978a). The more selective aldosterone receptor antagonist, eplerenone, requires a higher dose but has fewer side effects than spironolactone (Colussi et al., 2013), and it is now the medical therapy of choice. If additional antihypertensive therapy is needed, calcium channel blockers may be preferable since, in high doses, they have some aldosterone receptor antagonist activity (Dietz et al., 2008).

In patients with adrenal cancer, various inhibitors of steroidogenesis are useful. These are described in the next chapter in the section "Treatment of Cushing Syndrome."

CONCLUSIONS

PA remains a fascinating disease that is more common than previously thought but less common than some now claim. The common defects in current management can easily be relieved by routine use of aldosterone receptor blockers, with appropriate caution in patients with chronic renal disease.

Other mineralocorticoid-induced forms of hypertension are covered in Chapter 13.

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Pheochromocytoma (with a Preface About Incidental Adrenal Masses)

THE INCIDENTAL ADRENAL MASS

In considering the adrenal causes of hypertension in this and the next two chapters, we start with an increasingly common clinical problem—the incidentally discovered adrenal mass. An *adrenal incidentaloma* is an adrenal mass, generally 1 cm or more in diameter, discovered serendipitously on an abdominal CT or MRI scan performed for a nonadrenal indication (Terzolo et al., 2011; Zeiger et al., 2011). While most are benign and nonfunctional, an adrenal incidentaloma must never be ignored because 10% to 15% will be either malignant or functionally active. Early resection can be lifesaving. A missed diagnosis can have life-threatening consequences, including extraadrenal metastasis and hypertensive crisis.

Prevalence

Overall, 4% of all CT scans now uncover an adrenal incidentaloma (Kmietowicz, 2014). The prevalence of adrenal incidentaloma increases sharply with age—from 0.2% of CT scans performed on patients 20 to 29 years of age to 7% on patients over the age of 70 years (Terzolo et al., 2011; Zeiger et al., 2011).

Differential Diagnosis

Every adrenal incidentaloma must be evaluated for (1) malignancy and (2) functional activity. As shown in Table 12-1, the differential diagnosis includes adrenal adenocarcinoma, adrenal metastases, subclinical Cushing syndrome, pheochromocytoma, and aldosterone-producing adenoma.

Evaluation for Malignancy

Potential malignancy is an overriding concern. Adrenocortical carcinoma is detected in 4.7% and metastatic cancer in 2.5% (Young, 2007b).

As shown in Table 12-2, the size of the mass and its appearance on CT (or MRI)—the *imaging phenotype*—are the two key indicators of malignancy (Young, 2007b).

Size

Adrenocortical carcinomas typically are large; 90% are at least 4 cm in diameter. Among the patients with adrenal incidentaloma greater than 4 cm in diameter, one in four will have adrenocortical carcinoma (Young, 2007b). The smaller the carcinoma at the time of resection, the lower will be the tumor stage and the better the prognosis.

Imaging Phenotype

Most adrenal incidentalomas are discovered unexpectedly on contrast-enhanced abdominal or chest CT scans that often are not technically optimal for adrenal imaging (Terzolo et al., 2011). Thus, an *adrenal protocol scan* should be used to further assess the incidentaloma: contiguous 3- to 5-mm-thick CT slices should be obtained without contrast, 1 minute after intravenous injection of contrast media, and 10 to 15 minutes later (Zeiger et al., 2011).

In adenomas, the cytosol typically is laden with fat, yielding characteristic features on CT and MRI (Zeiger et al., 2011). On noncontrast CT, benign adenomas typically have a low attenuation value measured in Hounsfield units (HU). If the noncontrast CT

TABLE 12-1

Clinical Evaluation of an Incidental Adrenal Mass

Disorder	Prevalence* (%)	Suggestive Clinical Features
Cushing syndrome	7.9	Weight gain and metabolic syndrome (glucose intolerance, dyslipidemia, central obesity) <i>plus</i> supraclavicular fat pads, facial plethora, easy bruising, purple striae, proximal muscle weakness, emotional and cognitive changes, opportunistic infections, altered reproductive function, acne, hirsutism, osteoporosis, and leukocytosis with lymphopenia
Pheochromocytoma	5.6	Hypertension (paroxysmal or sustained) <i>plus</i> spells of sweating, headache, palpitations, and pallor
Primary aldosteronism	1.2	Refractory hypertension <i>with or without</i> hypokalemia
Adrenocortical carcinoma	4.7	Abdominal pain (mass effect), Cushing syndrome (cortisol effect), virilization (androgen effect), gynecomastia (estrogen effect), and hypokalemia (aldosterone effect)
Metastatic cancer	2.5	History of extra-adrenal cancer; cancer-specific signs

*Percentage of incidentally discovered adrenal masses with adrenal hyperfunction or cancer.
 Modified from Young WF Jr. Clinical practice: The incidentally discovered adrenal mass. *N Engl J Med* 2007;356:601–610.

attenuation value is less than 10 HU, the patient can be assured that the tumor is a benign lipid-rich adenoma (Zeiger et al., 2011). On T₂-weighted MRI, adenomas are isointense to the liver or spleen. On chemical shift MRI, signal loss occurs on the out-of-phase images. However, up to 30% of adenomas do not contain much fat and thus cannot be distinguished from malignancy or pheochromocytoma (PHEO) by noncontrast CT or MRI. If washout of the contrast material is

greater than 50% complete 10 minutes after injection, the patient can be reassured (with virtually 100% sensitivity and specificity) that this is a benign adenoma (Terzolo et al., 2011). Washout is slower with PHEO or adrenal malignancy. If malignancy is still uncertain, a PET scan with ¹⁸F-FDG has a very high sensitivity (93% to 100%) and specificity (80% to 100%) for identifying malignant lesions, which show excessive uptake of glucose (Terzolo et al., 2011).

TABLE 12-2

Typical Imaging Features (Phenotype) of Incidental Adrenal Masses

Feature	Adrenal Adenoma	Adrenocortical Carcinoma	PHEO	Metastasis
Size	Small (<3 cm)	Large (>4 cm)	Large (>3 cm)	Variable
Shape	Round, smooth	Irregular	Round, clear margins	Irregular
Texture	Homogeneous	Heterogeneous	Heterogeneous, cystic areas (necrosis)	Heterogeneous
Laterality	Unilateral, solitary	Unilateral, solitary	Unilateral, solitary	Often bilateral
Unenhanced CT density (HU)	≤10	>10	>10	>10
Contrast-enhanced CT	Not vascular			
Vascularity	≥50%	Vascular	Vascular	Vascular
Washout @ 10 min		<50%	<50%	<50%
MRI ^a	Isointense	Hyperintense	Markedly hyperintense	Hyperintense
Growth rate	Stable or slow (<1 cm/y)	Rapid (>2 cm/y)	Slow (0.5–1.0 cm/y)	Variable

^aRelative to liver on T₂-weighted imaging.
 Modified from Young WF Jr. The incidentally discovered adrenal mass. *N Engl J Med* 2007;356:601–610.

Metastases

Primary cancers that commonly metastasize to the adrenals are carcinomas of the lung, kidney, and gastrointestinal (GI) tract. Metastases tend to cause bilateral adrenal masses, and the primary tumor often has been discovered before the adrenal incidentaloma(s) (Zeiger et al., 2011).

Evaluation for Hyperfunction

Table 12-3 lists the screening procedures and the confirmatory tests for adrenal hyperfunction, i.e., autonomous production by an adrenal tumor of cortisol, catecholamines, or aldosterone. Among 3,868 patients with adrenal incidentaloma in 26 series, biochemical evidence of subclinical Cushing syndrome was found in 7.9%, PHEO in 5.6%, and primary aldosteronism in 1.2% (Barzon et al., 2003). More recent data suggest that some degree of increased cortisol secretion occurs in up to 33% (Kmietowicz, 2014).

One-quarter to three-quarters of adrenocortical carcinomas are hormonally active. Cosecretion of cortisol and androgens is the most common pattern and is highly suggestive of adrenocortical carcinoma (Libe et al., 2007).

Subclinical Cushing Syndrome

Subclinical Cushing syndrome needs to be considered when an adrenal incidentaloma is accompanied by subtle clinical signs of hypercortisolism. Patients can have hypertension, central obesity, diabetes, fatigue, and easy bruising; however, they do not have the wide nonblanching purple striae or other signs of full-blown Cushing syndrome (Terzolo et al., 2011; Zeiger et al., 2011). Thus, the clinical picture is hard to distinguish

from the garden-variety metabolic syndrome—except imaging studies have uncovered an adrenal mass.

To improve the sensitivity of the 1 mg overnight dexamethasone suppression test, a lower-than-standard cutoff—1.8 mg/dL rather than 5 mg/dL—should be used for an abnormally elevated 8 a.m. cortisol value; to avoid false positives, the minimally elevated value should be confirmed repeatedly and accompanied by feedback suppression of adrenocorticotrophic hormone (ACTH), additional evidence for autonomous adrenal overproduction of cortisol (Terzolo et al., 2011; Zeiger et al., 2011).

Subclinical Cushing syndrome constitutes a novel cardiovascular risk factor as shown by a recent retrospective study of 198 patients with an incidental adrenal mass and no overt disease were followed for an average of 7.5 years with cortisol levels measured after 1 mg dexamethasone suppression testing (Di Dalmazi et al., 2014). Of these, 114 patients (58%) had stable nonsecreting adrenal masses (postdexamethasone plasma [cortisol] < 50 nmol/L), 61 patients (30%) had either a stable intermediate phenotype ([cortisol] 50 to 138 nmol/L) or subclinical Cushing syndrome ([cortisol] > 138 nmol/L), and 23 patients (12%) who had a progressive pattern of increasing cortisol secretion. Compared with patients with stable nonsecreting masses, the rate of cardiovascular events and death was higher in patients with intermediate disease or subclinical Cushing syndrome (6.7% vs. 16.7%) and those with worsening secretion (6.7% vs. 28.4%). An increase in cortisol secretion during the study was an independent risk factor for having a new cardiovascular event.

Subclinical Cushing's syndrome is particularly common with adrenal incidentalomas larger than 2.4 cm (Morelli et al., 2014) and with bilateral adrenal incidentalomas, where the prevalence is (35% vs. 18% with unilateral incidentaloma) (Vassilatou et al., 2014).

TABLE 12-3

Laboratory Evaluation of an Incidental Adrenal Mass

Adrenal Disorder	Screening Tests	Confirmatory Tests
Subclinical Cushing syndrome	Overnight dexamethasone (1 mg) suppression test	Serum corticotrophin, 24-h urine cortisol; midnight salivary cortisol; 2-d high-dose dexamethasone suppression test
Pheochromocytoma	Fractionated plasma or urine metanephrines	Contrast-enhanced CT, gadolinium-enhanced MRI, consider ¹²³ I MIBG scan
Primary aldosteronism	Plasma renin and serum aldosterone; 24-h urine potassium excretion	Aldosterone suppression testing with salt loading; adrenal vein sampling after proving nonsuppressible hyperaldosteronism; CT scan

Modified from Young WF Jr. Clinical practice: The incidentally discovered adrenal mass. *N Engl J Med* 2007;356:601-610.

Clinically Silent PHEO

In the Mayo Clinic series, approximately 5% of adrenal incidentalomas turned out to be PHEOs (Young, 2007b). The likelihood of discovering a PHEO is approximately 25-fold higher when hypertension is accompanied by an adrenal incidentaloma than in the general hypertensive population. Currently, more than half of all PHEOs are discovered incidentally; of these, one-half are accompanied by neither hypertension nor other classical clinical features (Zeiger et al., 2011). The diagnosis is based on biochemistry, i.e., demonstration of catecholamine oversecretion by the adrenal chromaffin cells (see below).

Primary Aldosteronism

In the Mayo Clinic series, 1% of incidentalomas turned out to be aldosterone-producing adenomas (Young, 2007b). The best screening test is a blood

sample for an elevated serum aldosterone level and suppressed plasma renin activity (see Chapter 11).

Management

Figure 12-1 is an algorithm for evaluating the patient with an adrenal incidentaloma.

Initial hormonal evaluation should include the following three screening tests: (a) an overnight dexamethasone (1 mg) suppression test for subclinical Cushing syndrome, (b) measurement of plasma free metanephrines or of fractionated metanephrines and catecholamines in a 24-hour urine specimen for PHEO, and (c) measurement of serum aldosterone and plasma renin activity for primary aldosteronism.

Even clinically silent PHEOs can trigger lethal hypertensive crisis and therefore should be resected after preoperative adrenergic blockade. Aldosterone-producing adenoma is an indication for laparoscopic

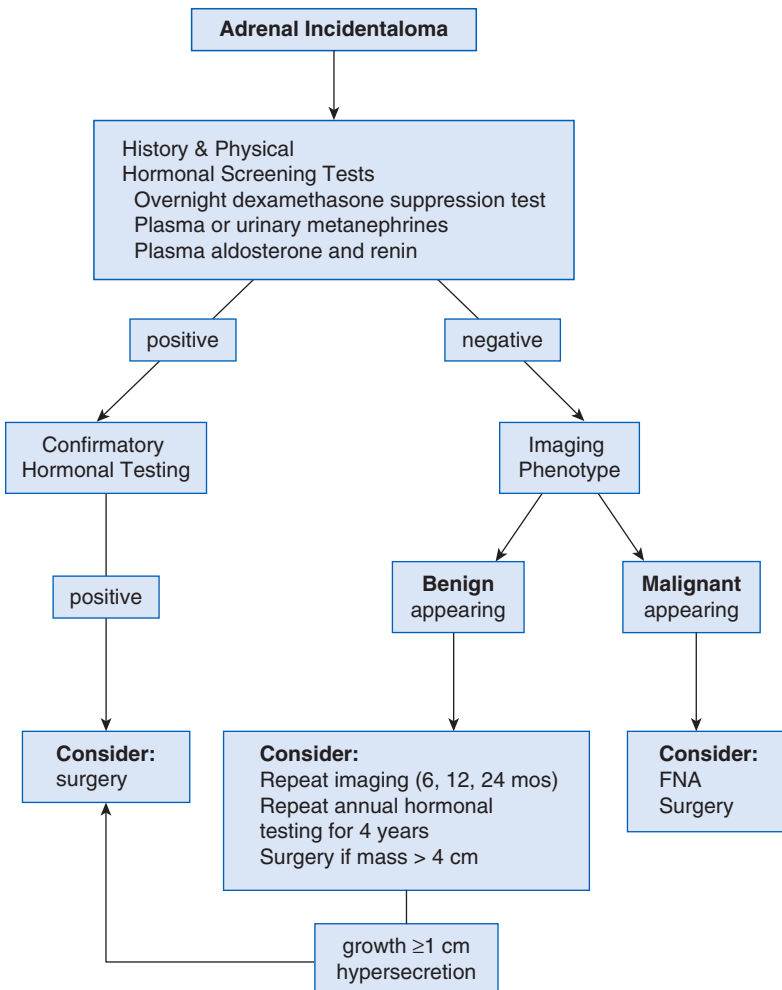


FIGURE 12-1 • Algorithm for diagnostic evaluation of an incidental adrenal mass. FNA, fine needle aspiration. (Modified from Young WF Jr. Clinical practice: The incidentally discovered adrenal mass. *N Engl J Med* 2007b;356:601–610.)

adrenalectomy if accompanied by hypertension or hypokalemia.

The approach to subclinical Cushing syndrome is a work in progress. In an uncontrolled study of nine patients with this diagnosis, unilateral adrenalectomy ameliorated hypertension in six patients and reduced supraclavicular fat pads and other clinical features in all nine (Mitchell et al., 2007). These provocative findings indicate the need for a large multicenter trial.

For now, adrenalectomy for subclinical Cushing syndrome should be considered in younger patients (under age 40) with recent onset or deterioration of hypertension, diabetes, and other clinical features of hypercortisolism. In middle-aged or older patients, a large adrenal mass favors resection. Most cortisol-producing adenomas are 2.5 cm or larger. If surgery is undertaken, glucocorticoid therapy should be administered to avoid perioperative adrenal crisis.

Adrenalectomy is indicated when the radiologic appearance is suspicious for adrenal carcinoma, unless there are extenuating clinical circumstances related to advanced age and comorbidity. If an adrenal mass is ≥ 6 m in diameter, it needs to be resected. If an adrenal mass is 4 to 6 cm in diameter, the patient's age and imaging phenotype should be considered. Before age 30, adrenal incidentalomas are so rare that even a mass ≤ 4 cm merits consideration for resection, particularly if the imaging phenotype is suspicious (Young, 2007b).

Fine needle aspiration (FNA) biopsy is rarely needed to exclude malignancy because the imaging characteristics are much more predictive (Terzolo et al., 2011). FNA is used mainly to exclude metastatic disease or infection (e.g., adrenal TB). A PHEO must be excluded first by biochemistry because FNA of a PHEO can trigger hypertensive crisis.

If the mass has a benign appearance on CT or MRI and the initial hormonal studies are negative, imaging studies should be repeated every 6 months for up to 2 years and adrenal function studies should be repeated yearly for up to 4 years (Terzolo et al., 2011). Only then can the patient be reassured that there is little chance of further trouble.

OVERVIEW OF ADRENAL HYPERTENSION

As stated above, every hypertensive patient with an incidental adrenal mass will merit a workup for adrenal hypertension. Indeed, all hypertensive patients merit *consideration* of a potential adrenal cause but, without a known adrenal mass, only a small percentage

will need an *evaluation*. These adrenal diseases are rare and produce nonspecific signs and symptoms. Many patients with primary hypertension have recurrent spells suggesting PHEO, hypokalemia suggesting primary aldosteronism, and central obesity suggesting subclinical Cushing syndrome. Most will turn out to have normal adrenal function.

Although uncommon, the diagnosis of adrenal hypertension can lead to surgical cure or highly effective targeted drug therapy. Removing a hyperfunctioning adrenal tumor or blocking the effects of hormonal excess on target tissues may be the only way to adequately control the hypertension and protect the patient from rampant target organ damage and premature death. This is particularly the case with PHEO.

PHEOCHROMOCYTOMA AND PARAGANGLIOMA

PHEOs are catecholamine-secreting tumors of adrenal chromaffin cells. *Paragangliomas* are extra-adrenal tumors of sympathetic or vagal ganglion cells. The odds that a paraganglioma will secrete catecholamines vary by location, as shown in Table 12-4. Catecholamine-secreting paragangliomas—often called “extra-adrenal PHEOs”—are located mainly in the abdomen or pelvis. Nonsecreting vagal paragangliomas are located mainly in the head and neck, most frequently involving the glomus cells of the carotid body. While the term PHEO often is used to include adrenal PHEOs and extra-adrenal paragangliomas, they differ not only in location but also in clinical presentation, genetic underpinning, and malignant potential (Waguespack et al., 2010).

TABLE 12-4

Location of Paraganglioma

Location	Percentage
Parasympathetic (nonsecretory)	95
Head and neck	
Catecholamine secreting	
Abdominal para-aortic	75
Urinary bladder	10
Thorax	10
Head and neck	3
Pelvis	2

Modified from Young WF Jr, Abboud AL. Editorial: Paraganglioma—all in the family. *J Clin Endocrinol Metab* 2006;91:790-792.

Most PHEOs and paragangliomas secrete both norepinephrine (NE) and epinephrine (EPI), with NE predominating. Some primarily secrete EPI, and an occasional tumor will secrete only dopamine. When correctly diagnosed and treated, most PHEOs are curable. When undiagnosed or improperly treated, they can be fatal.

PHEOs often go unrecognized (Jones et al., 2012). In an autopsy series at Mayo Clinic, only 13 of 54 autopsy-proven PHEOs had been diagnosed during life (Young, 2007a). The remaining 41 undiagnosed PHEOs caused 30 deaths. They also are overdiagnosed due to false-positive test results (Yu & Wei, 2010). In contrast, when PHEO is diagnosed and managed by a

highly experienced clinical team, the tumors can be successfully resected with minimal perioperative mortality (Darr et al., 2012; Young, 2007a).

Prevalence

PHEOs are rare. The estimated prevalence is less than 0.2% among unselected patients with hypertension but 5% among those with adrenal incidentaloma (Barzon et al., 2003; Young, 2007a). Because PHEOs are so rare and can cause lethal paroxysms, the clinician needs a high index of suspicion and a systematic approach to screening, localization, and surgery (Fig. 12-2).

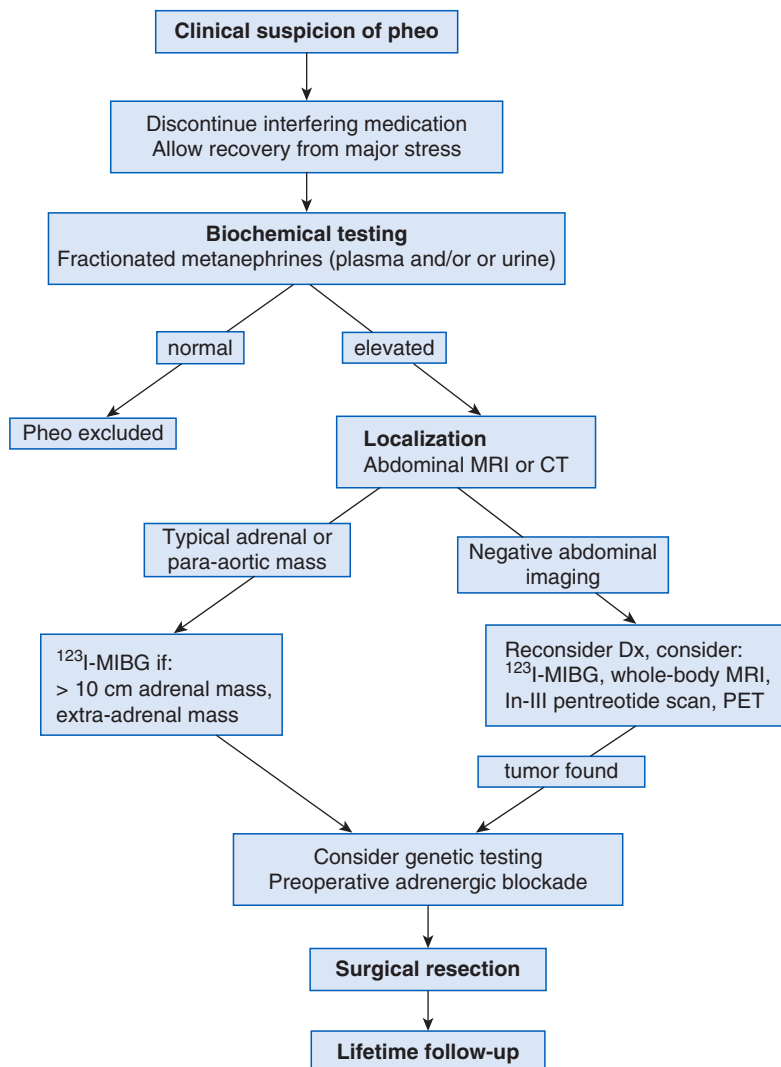


FIGURE 12-2 • Algorithm for diagnostic evaluation of a suspected pheochromocytoma. PHEO, adrenal pheochromocytoma or extra-adrenal paraganglioma; In, indium. (Modified from Young WF Jr. Adrenal causes of hypertension: Pheochromocytoma and primary aldosteronism. *Rev Endocr Metab Disord* 2007a;8:309–320.)

Clinical Features

Table 12-5 lists the varied clinical features of PHEO. Table 12-6 lists the long differential diagnosis.

Hyperadrenergic spells are the classic clinical presentation of PHEO. Excessive α - and β -adrenergic stimulation of the cardiovascular system produces the five “Ps” of the paroxysm (Young WF Jr, *Personal communication*, 2007c):

- Paroxysmal hypertension
- Pounding headache
- Perspiration (often diffuse)
- Palpitations
- Pallor (not flushing)

Flushing is less common than pallor because NE—the dominant catecholamine—is a potent vasoconstrictor. Diabetes and weight loss are other signs of the hyperadrenergic state. Some patients are asymptomatic, some are normotensive, and others have symptoms due to concomitant conditions.

Paroxysmal Hypertension

The paroxysms represent the classic picture of the disease, but exclusively paroxysmal hypertension with intervening normotension is rare. Patients can have sustained hypertension with or without superimposed paroxysms. The paroxysms can be triggered by mechanical com-

TABLE 12-5

Signs and Symptoms of PHEO

More Common	Less Common
Hypertension (sustained or paroxysmal)	Postural hypotension
Excessive sweating	Flushing
Headaches	Weight loss
Palpitations	Decreased GI motility
Tachycardia	Increased respiratory rate
Anxiety/nervousness	Nausea/vomiting
Pallor	Pain in chest/abdomen
Tremulousness	Cardiomyopathy
Fasting hyperglycemia	Dizziness
Weakness, fatigue	Paresthesias
	Constipation (rarely diarrhea)
	Visual disturbances

Modified from Pacak K. Preoperative management of the PHEO patient. *J Clin Endocrinol Metab* 2007;92:4069–4079.

TABLE 12-6

Differential Diagnosis of PHEO-Like Spells

- Cardiovascular
 - Labile primary hypertension
 - Paroxysmal tachycardia
 - Angina
 - Acute pulmonary edema
 - Eclampsia
 - Hypertensive crisis during or after surgery
 - Orthostatic hypotension
 - Renovascular hypertension
- Psychological
 - Anxiety with hyperventilation
 - Panic disorder
- Neurologic
 - Autonomic neuropathy
 - Migraine and cluster headaches
 - Stroke
 - Brain tumor
 - Diencephalic seizures
 - Autonomic hyperreflexia, as with quadriplegia
 - Baroreceptor dysfunction
 - Postural orthostatic tachycardia syndrome (POTS)
- Endocrine
 - Carbohydrate intolerance
 - Thyrotoxicosis
 - Insulinoma and hypoglycemia
 - Medullary thyroid carcinoma
 - Menopausal syndrome
 - Carcinoid
 - Mastocytosis
- Pharmacologic
 - Clonidine rebound
 - Sympathomimetic drug ingestion (phenylephrine-containing cold remedies, cocaine, methamphetamines, Adderall)
 - Chlorpropamide–alcohol flush
 - Monoamine oxidase inhibitor and decongestant
 - Vancomycin “red man syndrome”
- Factitious
 - Ingestion of sympathomimetics

pression of the tumor (by exercise, upright posture, bending over, urination, defecation, an enema, palpation of the abdomen, or a pregnant uterus), injection of chemicals (anesthetic agents or radiology contrast material), drugs that stimulate catecholamine synthesis (glucocorticoids) and secretion (histamine, opiates, or nicotine), psychiatric drugs that inhibit biogenic amine reuptake transporters (tricyclic antidepressants, selective NE reuptake blockers, etc.), and β -blockers, which leave α -adrenergic receptors relatively unopposed.

PHEO crisis can be induced by glucocorticoids, including ACTH, methylprednisolone, and high-dose (but not 1-mg low-dose) dexamethasone suppression testing (Rosas et al., 2008). The paroxysm does not occur immediately but rather 5 to 36 hours after the glucocorticoid administration and is caused by tumor necrosis. Paroxysms also may occur without provocation from spontaneous tumor necrosis.

Among individual patients, paroxysms vary in frequency, duration, severity, and associated symptoms. They may occur many times per day or only every few months. PHEO paroxysms often are misdiagnosed as panic attacks. Patients may describe tightness in the abdomen rising into the chest or head, anxiety, tremors, sweating, palpitations, and weakness.

Cardiac Manifestations of PHEO

In the Cedars-Sinai series, 12% of PHEOs presented without paroxysmal hypertension but rather with acute coronary syndrome or catecholamine-induced cardiomyopathy with acute heart failure (inverted Takotsubo cardiomyopathy) (Yu et al., 2012a). PHEO also may present as monomorphic ventricular tachycardia (Park et al., 2012). A high index of suspicion is needed to make the diagnosis because PHEO is far rarer than the

common forms of adult heart disease it mimics. Failure to consider PHEO or especially paraganglioma in the differential diagnosis can lead to unnecessary invasive procedures, including cardiac transplantation (Yu et al., 2012a). Compared with PHEO patients presenting with either adrenal incidentaloma or paroxysmal hypertension but without cardiac manifestations, those presenting with cardiac complications have large tumors (often >6 cm), markedly elevated plasma normetanephrine (NMN) levels, mildly depressed left ventricular ejection fractions (LVEFs), and prolonged QT intervals (Table 12-7) (Yu et al., 2012a). They may also present with an embolic stroke due to left ventricular thrombus (Buchbinder et al., 2009). Thus, in the absence of paroxysmal hypertension, PHEO should be considered in an adult with no convincing etiology of heart failure, acute coronary syndrome, or tachyarrhythmia with or without an adrenal mass (the latter due to paraganglioma). Spot plasma metanephrines will make the biochemical diagnosis.

Hypotension

Predominantly EPI-secreting PHEOs can present as hypotension, as cyclic attacks of hypertension alternating with hypotension, and as acute coronary syndromes:

TABLE 12-7

Characteristics of Patients with PHEO Presenting with or without Cardiac Complications

Characteristic	Cardiac Complications		P value
	With (n = 9)	Without (n = 67)	
Demographics			
Age, yrs	50	51	NS
Female, %	55	60	NS
PHEO			
Sporadic, %	100	81	NS
Adrenal location, %	78	91	NS
Biochemical marker levels, fold increase	24	11	0.08
Tumor size, cm	6.7	4.4	0.02
Cardiac risk factors	55	59	NS
EKG changes			
ST-T changes, %	67	15	0.05
QTc, ms	473	443	0.02
Echo LVEF, %	43	66	0.002

Modified from Yu R, Nissen NN, Bannykh SI. Cardiac complications as initial manifestation of pheochromocytoma: Frequency, outcome, and predictors. *Endocr Pract* 2012;18:483–492.

diffuse ST-segment depression, chest pain, nausea/vomiting, and diaphoresis (Darr et al., 2012). They can cause cardiogenic shock from catecholamine-induced cardiomyopathy. Profound hypotension may occur with spontaneous tumor necrosis or with α -blocker administration during the preoperative preparation for PHEO surgery. More commonly, patients have modest postural hypotension with tachycardia and dizziness. The postural hypotension indicates hypovolemia, which is a characteristic of PHEO that has never been adequately explained. In an untreated young hypertensive, postural hypotension and tachycardia may be a clue to the presence of a PHEO.

Less Common Presentations

PHEOs also can present as an acute abdomen (from spontaneous tumor rupture), sudden death after minor abdominal trauma, lactic acidosis, or high fever and encephalopathy. Paragangliomas of the urinary bladder can paroxysmal attacks of micturition syncope or painless hematuria (Beilan et al., 2013); they tend to occur in rather young adults and most can be cured by partial cystectomy.

The Revised Rule of 10s

Conventional teaching was that 10% of PHEOs are extra-adrenal (i.e., secretory paragangliomas), 10% occur in children, 10% are bilateral, 10% recur, 10% are malignant, 10% are discovered incidentally, and 10% are familial. Now, up to 70% are discovered incidentally (Darr et al., 2012; Yu et al., 2009) and over 30% are due to inherited germ line mutations (i.e., mutations occurring in all the cells of the body) (Karasek et al., 2013).

Familial PHEO and Paraganglioma

PHEOs and paragangliomas can occur sporadically or they can be inherited as autosomal dominant traits alone or as part of one of several syndromes listed below. As recently reviewed by Karasek and coworkers at the NIH (Karasek et al., 2013), the known disease-causing genes are as follows:

- **RET** (rearranged during transfection), a protooncogene associated with Multiple Endocrine Neoplasia (MEN) type 2A (PHEO, medullary carcinoma of the thyroid, hyperparathyroidism) or type 2B (PHEO, medullary carcinoma of the thyroid, mucosal

neuromas, thickened corneal nerves, intestinal ganglioneuromatosis, slender facies).

- **VHL**, a tumor suppressor gene associated with von Hippel-Lindau disease of PHEO (often bilateral), retinal and cerebellar angiomas, renal and pancreatic cysts, and renal cell carcinoma.
- **NF-1**, associated with neurofibromatosis.
- **SDHD**, succinate dehydrogenase (mitochondrial complex II) gene subunit D that predisposes to familial paraganglioma.
- **SDHB**, succinate dehydrogenase gene subunit B that also predisposes to familial paraganglioma.
- **SDHC**, succinate dehydrogenase gene subunit C that mainly predisposes to nonsecretory vagal paragangliomas of the head and the neck.
- **SDHA**, succinate dehydrogenase A subunit, mutations are associated mainly with abdominal paragangliomas (rarely adrenal PHEOs).
- **SDHAF2**, succinate dehydrogenase A F2 subunit, mutations are associated with head and neck paragangliomas and paternal transmission.
- **TMEM-127**, transmembrane protein 127 gene mutations are associated with mainly nonmalignant adrenal PHEOs.
- **MAX**, protein MAX (also known as MYC-associated factor X), interacts with other transcription factors forming a network that regulates cell proliferation, differentiation, and apoptosis. MAX behaves as a tumor suppressor gene; thus, 2/3 of MAX-associated PHEOs are often bilateral and 25% are malignant.

Differing Phenotypes of MEN2 and VHL Syndrome

Patients with MEN2 are more likely to suffer from paroxysmal hypertension because MEN2 tumors mainly secrete NE whereas VHL tumors mainly secrete EPI. Compared with VHL tumors, MEN2 tumors have higher expression of both tyrosine hydroxylase, the rate-limiting enzyme in catecholamine synthesis, and phenylethanolamine *N*-methyltransferase (PNMT), the enzyme that converts NE to EPI.

The first description of PHEO from 1886 was, in fact, a case of MEN2 syndrome (Neumann et al., 2007). The patient, an 18-year-old German girl named Mina Roll, presented with classic symptoms of PHEO crisis and, at autopsy, was found to have vascular bilateral adrenal tumors that stained brown with chromate fixative (hence the name “PHEO chrom” which means “chromate brown”). With a careful piece of

detective work 120 years later, the geneticists searched the European-American Pheochromocytoma Registry to find four living family members with a germ line mutation in the *RET* gene, thus establishing the diagnosis of MEN2. These and other family members had PHEOs and/or medullary carcinoma of the thyroid, the latter explaining the goiter in Mina Roll's original autopsy report (Neumann et al., 2007). Early clinical recognition of MEN2 syndrome is particularly important because medullary carcinoma of the thyroid—present in most of these patients—poses a major cause of death and thus merits immediate surgical removal.

Neurofibromatosis

PHEO occurs in only 1% of patients with neurofibromatosis type 1. As of 2006, neurofibromatosis accounted for only 25 cases of the 565 total PHEO cases in the European-American Pheochromocytoma Registry (Bausch et al., 2006). By comparison, von Hippel-Lindau syndrome accounted for 75 cases, paraganglioma syndromes for 54 cases, and sporadic PHEO for 380 cases. All 25 of 25 patients with neurofibromatosis had adrenal PHEOs and, of these, three (12%) had metastatic disease.

Familial Paraganglioma

Discovered only in 2000, the familial paraganglioma syndromes are inherited as autosomal dominant traits (Darr et al., 2012; Karasek et al., 2013). Of note, the *SDHD* mutation is characterized by *maternal imprinting*, meaning that the disease can only be inherited from one's father, emphasizing the importance of a detailed family history. The *SDHB* mutation is characterized by a high risk of malignancy including metastatic paraganglioma, renal cell carcinoma, and papillary carcinoma of the thyroid. The *SDHC* mutation is mainly associated with nonsecreting vagal paragangliomas (most often carotid body tumors) of the head and neck. Production of 3-methoxytyramine is associated with the presence of an underlying *SDHB* mutation and may be a viable biomarker of malignancy (van Berkel et al., 2014).

Tumorigenesis may involve (a) the failure of developmental apoptosis and/or (b) pseudohypoxic drive (Karasek et al., 2013). Extra-adrenal chromaffin tissue normally plays an important role in catecholamine production in the developing fetus, but the tissue degenerates shortly after birth. Abnormal persistence of the fetal tissue may give rise to paraganglioma. The most common form of head and neck

paraganglioma involves the hypoxia-sensing cells of the carotid body. Under hypoxic conditions, a hypoxia-inducible factor (HIF) normally translates from the cytosol to the nucleus, causing compensatory activation of the genes involved in angiogenesis, erythropoiesis, extracellular matrix turnover, and many other processes that defend against tissue hypoxia. In patients with familial paraganglioma, HIF remains activated—not by tissue hypoxia but rather by the abnormal accumulation of succinate. Such pseudohypoxic drive is also implicated in the molecular pathogenesis of tumorigenesis in VHL syndrome, as the VHL gene product normally is involved in the tonic restraint of HIF (Kaelin, 2007; Karasek et al., 2013).

Other Associated Conditions

PHEO is a great mimicker being associated with the following conditions:

- *Carney Triad* of secretory paraganglioma, GI stromal tumors, and pulmonary chondroma. Carney triad does not appear to be inherited, and the molecular basis for the association is unknown.
- *Cholelithiasis*, seen in up to 30% of PHEO patients.
- *Diabetes*, especially in young, lean patients (Darr et al., 2012).
- *Hypercalcemia* in the absence of hyperparathyroidism (Kimura et al., 1990).
- *Polycythemia* due to increased erythropoietin production. More frequently, a high hematocrit is related to a contracted plasma volume.
- *Renovascular hypertension*, likely caused by external compression of a renal artery by a paraganglioma or NE-induced vasospasm causing fibromuscular dysplasia (Sarathi et al., 2012).
- *Adrenocortical hyperfunction* may arise from ACTH secretion from the PHEO, a coincidental cortisol-secreting adenoma in the other adrenal, or bilateral adrenal hyperplasia (Ghander et al., 2012).
- *Rhabdomyolysis*, which has occurred with renal failure (Anafiroglu et al., 2008).
- *Megacolon*, reported in 17 cases (Sweeney et al., 2000).

Conditions Simulating PHEO

Most patients with hypertension and one or more of the manifestations of PHEO turn out *not* to have that diagnosis. Table 12-6 lists the many conditions that can mimic a PHEO. The most common are panic disorder and labile primary hypertension. Other common

PHEO mimics are rebound hypertension from clonidine withdrawal—especially with PRN dosing—obstructive sleep apnea (Chapters 3 and 14), and baroreflex failure (Chapters 3 and 14). The latter is suggested by a remote history of the head and neck surgery with mantle field radiation therapy, recent carotid endarterectomy, or surgical excision of bilateral carotid body tumors (i.e., vagal paragangliomas).

Pseudopheochromocytoma is a vague term often used as a diagnosis of exclusion for patients with extremely labile hypertension and symptoms indistinguishable from a true PHEO but negative biochemical testing (typically on multiple occasions) (Hunt & Lin, 2008; Mann, 2008; Sharabi et al., 2007). An emotional trigger may not be apparent and yet the paroxysms can become disabling. Excessive adrenomedullary secretion of EPI has been implicated, but larger studies are needed (Hunt & Lin, 2008; Sharabi et al., 2007).

An iatrogenic form of pseudopheochromocytoma has been described in psychiatric patients treated with clozapine, a tricyclic dibenzodiazepine with complex pharmacologic actions involving α -adrenergic and serotonin receptors (Sara et al., 2013). We have seen such labile hypertension in hospitalized patients treated with third-generation antidepressant medication plus clonidine (Victor, unpublished observations, 2014).

Death from PHEO

Most deaths are related to failure to consider PHEO in patients undergoing severe stress such as nonadrenal surgery or obstetric delivery. Many deaths are unexpected and sudden; this is likely related to catecholamine-induced effects on the cardiac muscle and conduction system. Death has followed acute hemorrhagic necrosis of a PHEO after β -blocker administration. PHEO should be considered before giving a β -blocker to control thyrotoxic symptoms, as this can precipitate a PHEO crisis.

Evaluation

When and How to Screen?

The majority of hypertensive patients do *not* require screening for PHEO. Screening indications are listed in Table 12-8. Many are derived from the patient's history. Screening is indicated in all patients with adrenal incidentaloma, even if the blood pressure is normal.

TABLE 12-8

When to Screen for PHEO/ Paraganglioma?

Hyperadrenergic spells
Resistant hypertension
Family history of pheochromocytoma or paraganglioma
Familial syndrome (e.g., MEN2, VHL)
Hypertensive response to anesthesia
Onset of hypertension before the age of 20 y
Hypertension with dilated cardiomyopathy
Adrenal incidentaloma
New onset of cardiomyopathy without a clear etiology

A systematic approach, such as outlined in Figure 12-2, will help to avoid missing the diagnosis and to avoid unnecessary—and expensive—laboratory testing (Yu et al., 2011). There are two steps to the diagnosis: (1) biochemical determination of autonomous catecholamine hypersecretion and (2) tumor localization.

Biochemical Diagnosis

Scientific breakthroughs in our understanding of the catecholamine metabolism and technical advances in the measurement of catecholamine metabolites have greatly improved the biochemical detection of PHEO (Darr et al., 2012).

Scientific Rationale

Figure 12-3 depicts the clear view of catecholamine secretion, uptake, and metabolism by the work of Eisenhofer and coworkers at the NIH (Darr et al., 2012; Eisenhofer et al., 2004, 2008; Goldstein et al., 2006).

PHEOs contain large amounts of the enzyme catechol-*O*-methyltransferase (COMT), which converts NE and EPI to *O*-methylated derivatives, normetanephrine (NMN), and metanephrine (MN), which collectively are termed *metanephrines* (*met*s). The metanephrines circulate free in the plasma and are sulfated as they pass through the GI circulation. The conjugated sulfates are filtered by the kidneys and excreted in the urine. Measurement of metanephrines either in a plasma sample or in a 24-hour urine sample is far superior to the measurement of the parent

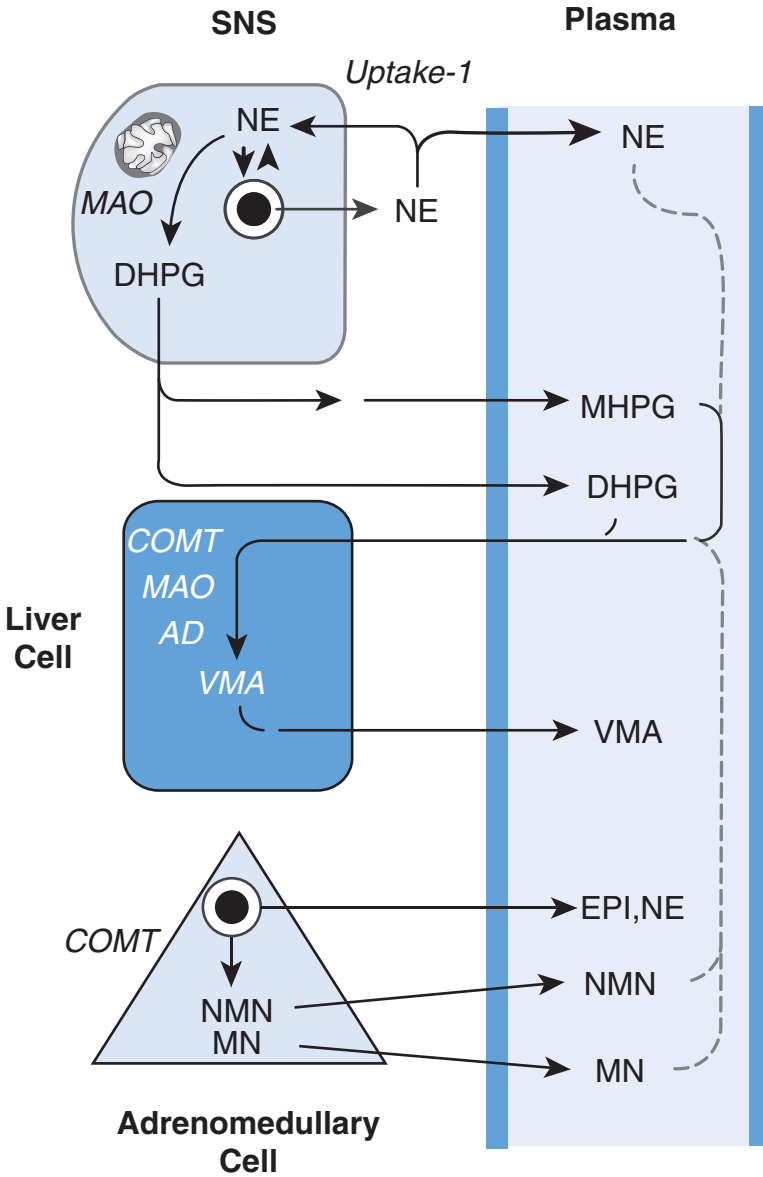


FIGURE 12-3 • Catecholamine secretion, uptake, and metabolism. SNS, sympathetic nervous system; NE, norepinephrine; EPI, epinephrine; MAO, monoamine oxidase; DHPG, 3,4-dihydroxyphenylglycol; MHPG, 3-methoxy-4-hydroxyphenylglycol; COMT, catecholamine-O-methyltransferase; AD, aldehyde dehydrogenase; VMA, vanillylmandelic acid; NMN, normetanephrine; MN, metanephrine. (Modified from Goldstein DS, Eisenhofer G, Kopin IJ. Clinical catecholamine neurochemistry: A legacy of Julius Axelrod. *Cell Mol Neurobiol* 2006;26:695–702.)

catecholamines and has revolutionized the diagnosis of PHEO.

Elevated plasma or urine levels of metanephrines are highly sensitive diagnostic indicators of PHEO for several reasons. Plasma levels of NMN and MN normally are very low. They are produced mainly within adrenal chromaffin cells and are not produced within the sympathetic nerves (as with the parent catecholamines) or within the liver (as with vanillylmandelic acid [VMA]). There is no COMT in peripheral sympathetic nerve terminals. As a result, most

NMN and MN are generated within the adrenal chromaffin cells before being secreted into the circulation. In patients with PHEO, metanephrines are continuously produced within the tumor and continuously secreted into the plasma by an autonomous process that is independent of vesicular catecholamine release, which is episodic (Goldstein et al., 2006). Whereas spikes in plasma NE and EPI may be missed between the PHEO spells, plasma metanephrines are continuously elevated and therefore provide greater diagnostic sensitivity. A twofold

elevation in plasma NE is associated with a sixfold elevation in plasma NMN (Eisenhofer et al., 2008). Metanephrines can be measured either in the plasma (as free metanephrines) or in a 24-hour urine specimen as the sulfate conjugates.

Which Test Is Best: Plasma or Urine Metanephrines?

Plasma metanephrines are more convenient for the patient and have a high degree of sensitivity. Normal spot plasma metanephrine values virtually exclude the diagnosis of catecholamine-secreting tumor (except for the rare case of dopamine-secreting paraganglioma). However, the specificity is not ideal, with an overall false-positive rate of 15% in some series (Young, 2007a). The false-positive rate increases to approximately 25% in patients over age 60, because plasma catecholamine and metanephrine levels normally rise with age (Singh, 2004). Urinary measurements require an inconvenient 24-hour specimen collection, but they have a lower false-positive rate of only 2% to 3% (Darr et al., 2012; Young, 2007a).

Either plasma or urinary metanephrines—or both—can be recommended as the initial screening test (Darr et al., 2012). Either test is far superior to the measurement of parent catecholamines alone. The biochemical diagnosis should be compelling before ordering imaging tests to localize the tumor; thus, additional biochemical testing is needed when the initial biochemical results are equivocal.

If plasma metanephrines are normal, typically no further evaluation is needed. A fourfold or greater elevation in plasma-free NMN is almost 100% diagnostic of a catecholamine-secreting tumor; imaging studies are indicated without further biochemical testing (Darr et al., 2012).

However, gray zone results (e.g., twofold elevations above the reference values) are often encountered in clinical practice and necessitate additional biochemical testing. A retrospective study of 140 patients evaluated for PHEO at the Mayo Clinic suggested that follow-up testing with either urine-fractionated metanephrines or plasma chromogranin A (another protein released by chromaffin cells) improves the diagnostic accuracy of plasma metanephrines (Algeciras-Schimmich et al., 2008). Whatever analytical method is used, careful attention to the technique can reduce false-positive testing, as discussed below.

Technique

To minimize acute stress reactions, ideally blood samples be taken only after the patient has been supine for at least 20 minutes after the insertion of an indwelling venous cannula.

Urinary VMA assays are no longer routinely performed because of their poor sensitivity (Darr et al., 2012). About 20% of VMA comes from hepatic metabolism of circulating catecholamines and metanephrines, with the remaining 80% from metabolites of neutrally released NE (Fig. 12-2). Thus, large increases in adrenal catecholamine secretion by a PHEO must occur before an increase in urinary VMA will be detected.

Increasingly, the measurement of total urinary metanephrines by spectrophotometry is being replaced by liquid chromatography–tandem mass spectrometry, which provides superior detection of total and fractionated metanephrines and avoids false-positive results from interference by sotalol, labetalol, acetaminophen, and other medications with structural similarity to metanephrines (Darr et al., 2012). Figure 12-4 shows that tandem mass spectrometry provides an excellent resolution of elevated urine total metanephrine values in PHEO patients from normal values in non-PHEO patients and normal volunteers (Perry et al., 2007). However, the ordering physician needs to know the expertise of their particular lab, as standards can vary. Except for α -blockers, most antihypertensives no longer need to be discontinued.

Table 12-9 lists the various tests and clinical cutoff values from the Mayo Clinic Laboratory.

Table 12-10 lists the common conditions that can elevate metanephrines, leading to a false-positive diagnosis of PHEO. The most frequent are antidepressant medication, α -blockers, and sympathomimetics. Perioperative stress, acute myocardial infarction, and heart failure exacerbation can cause transient elevations in catecholamines, and biochemical testing for PHEO should be delayed until the stress has subsided for 1 to 2 weeks (Fig. 12-2).

Patients with End-Stage Renal Disease

PHEO presents a particular diagnostic challenge in patients with renal failure. Urinary metanephrines are invalid, even in patients who are not anuric, because of an impaired renal excretion. Plasma metanephrines

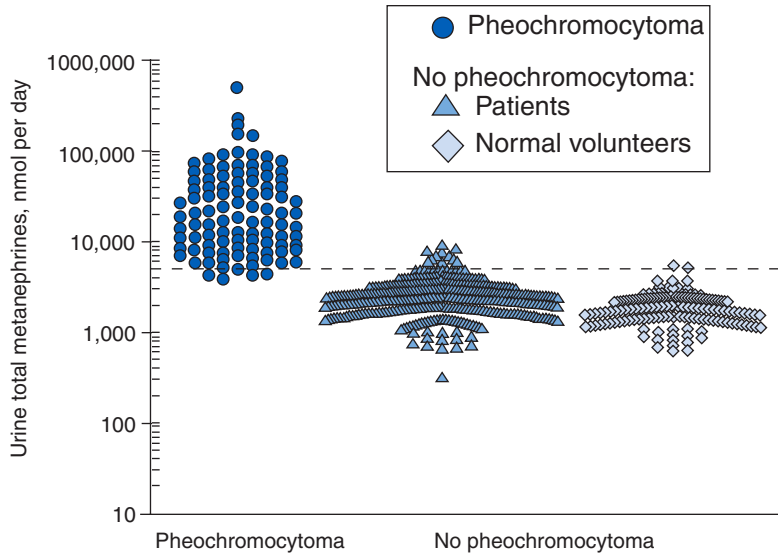


FIGURE 12-4 • Comparison of 24-hour urinary excretion of total metanephrines by tandem mass spectrometry in patients with histology-proven pheochromocytoma or paraganglioma (circles, $n = 102$), patients suspected of PHEO but with a negative workup (triangles, $n = 404$), and normotensive healthy volunteers (diamonds, $n = 221$). The dashed line is the diagnostic cutoff value. (Modified from Perry CG, Sawka AM, Singh R, et al. The diagnostic efficacy of urinary fractionated metanephrines measured by tandem mass spectrometry in detection of pheochromocytoma. *Clin Endocrinol (Oxf)* 2007;66:703–708.)

are the only option but the false-positive rate is as high as 25% (Eisenhofer et al., 2005) because renal failure itself—either ESRD or moderate CKD—is characterized by sympathetic overactivity and impaired catecholamine clearance (Chapter 3). There is considerable overlap between elevated MN values in dialysis patients without PHEO and those in PHEO patients with normal renal function (Fig. 12-5) (Niculescu et al., 2013); fortunately, there is less overlap with elevated NMN values such that higher-than-usual

cutoff values of plasma NMN > 410 pg/mL are recommended for biochemical evidence of PHEO in the setting of CKD or ESRD (Eisenhofer et al., 2005).

Dopamine-Secreting Paraganglioma

An occasional tumor will exclusively secrete dopamine because the tumor cells lack the enzyme dopamine- β -hydroxylase that converts dopamine to EPI and NE. These tumors are extremely rare and are extra-adrenal *SDHx*-mediated paragangliomas (Waguespack et al., 2010). The diagnosis is easily missed because of the normal blood pressure and the normal plasma and urinary metanephrines. Rather than hyperadrenergic

TABLE 12-9

Biochemical Diagnosis of Catecholamine Secreting Tumor

Test	Cutoff Value ^a
Blood test	
Plasma free normetanephrine	0.9 nmol/L
Plasma free metanephrine	0.5 nmol/L
Plasma norepinephrine	750 pg/mL
Plasma epinephrine	110 pg/mL
Plasma dopamine	30 pg/mL
Urine test	
Total metanephrines	1,300 μ g/24 h
Normetanephrine	900 μ g/24 h
Metanephrine	400 μ g/24 h
Norepinephrine	170 μ g/24 h
Epinephrine	300 μ g/24 h
Dopamine	50 μ g/24 h

^aSupine values from the Mayo Clinic Laboratory. Modified from Singh RJ. Advances in metanephrine testing for the diagnosis of PHEO. *Clin Lab Med* 2004;24:85–103.

TABLE 12-10

Causes of False-Positive Metanephrines

- Medications that increase catecholamines
 - Antidepressants
 - Levodopa
 - Clonidine withdrawal (PRN dosing)
 - Antipsychotics
 - α -Blockers
- Conditions that increase catecholamines
 - Major physical stress (surgery, stroke, MI, etc.)
 - Obstructive sleep apnea
 - End-stage renal disease

Modified from Young WF Jr. Pheochromocytoma. In: *ASH Clinical Hypertension Review Course Syllabus*. American Society of Hypertension; 2007:481–494.)

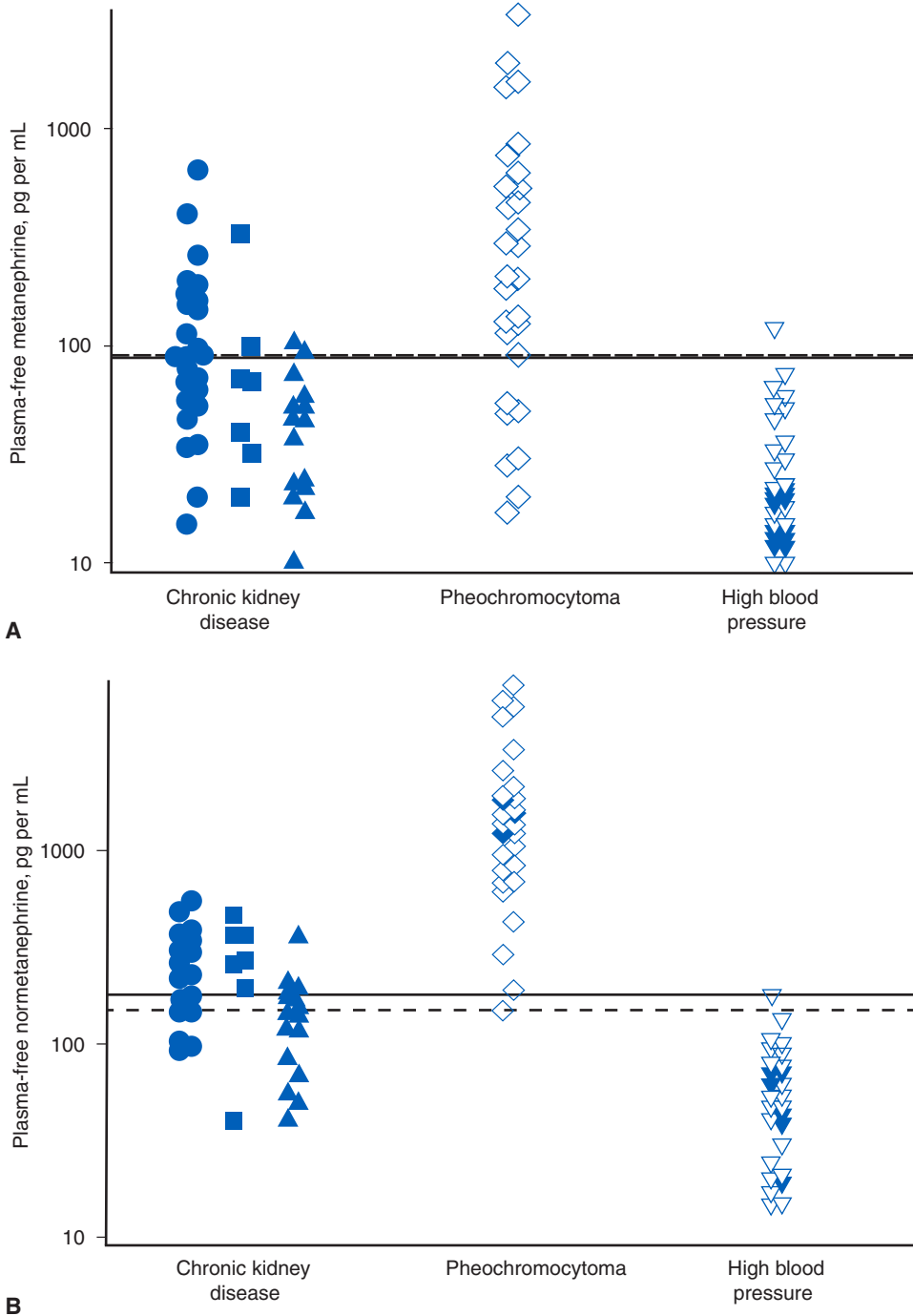


FIGURE 12-5 • Plasma free metanephrine levels (A) and normetanephrine levels (B) in patients with chronic kidney disease (end-stage renal disease), pheochromocytoma, and high blood pressure with normal renal function. (Modified from Niculescu DA, Ismail G, Polana C. Plasma free metanephrines and renal failure. *Endocr Pract* 2014;20(2):139–144.)

spells, the presenting symptoms are nausea, vomiting, or psychosis (due to excessive dopamine production) or an inflammatory syndrome of fever, weight loss,

and an elevated sedimentation rate. Most are discovered incidentally on an abdominal CT or MRI for evaluation of abdominal pain. These paragangliomas are

often large and metastatic by the time they are discovered, causing a poor prognosis. The diagnosis is made by an elevated 24-hour urinary dopamine level, which is usually dramatic (several fold the upper limit of normal of 3,300 nmol/24 hours).

Pharmacologic Testing

With the improvement and widespread availability of metanephrine measurements, hazardous provocative tests (e.g., glucagon injection) have become obsolete. The clonidine suppression test, while safe, also is rarely needed to distinguish false-positive from true-positive elevations in metanephrines (Lee et al., 2011; Sartori et al., 2008). Plasma catecholamines and metanephrines are measured before and 3 hours after a single oral 0.3-mg dose of clonidine (Eisenhofer et al., 2008). The principle is that clonidine, a central sympatholytic, should cause a greater fall in plasma catecholamines and metanephrines when elevated plasma levels are due to sympathetic neural overactivity than from an autonomously secreting tumor. However, false negatives can occur in patients with PHEO and milder elevations in plasma catecholamines and metanephrines because much of the plasma NE and NMN is derived from sympathetic nerves, which continue to function normally and remain responsive to clonidine (Sartori et al., 2008). The test cannot distinguish false-positive from true-positive elevations in MN, and it is not needed to confirm the diagnosis of PHEO when urine or plasma metanephrines are unequivocally elevated.

Localizing the Tumor

Abdominal CT and MRI

Once the biochemical diagnosis of autonomous catecholamine hypersecretion is certain, the next step is tumor localization in preparation for curative surgery (Fig. 12-2). Abdominal and pelvic MRI or CT is the initial imaging procedure, as 90% of catecholamine-secreting tumors are adrenal PHEOs and 98% are located in the abdomen or pelvis (Young, 2007a).

Nevertheless, the diagnosis of PHEO is not always straightforward. Figure 12-6 shows four different clinical scenarios to illustrate the importance of considering the imaging phenotype, the patient's symptoms, and the degree of biochemical abnormality (Young, 2007c). Patient 1 and Patient 3 had no symptoms and both presented with adrenal incidentalomas. In Patient 1, the imaging phenotype was suspicious for

PHEO and the fivefold elevation in plasma NMN—in the absence of recent stress or confounding medication—confirmed the diagnosis. In Patient 3, the imaging phenotype was not suspicious for PHEO and the normal plasma metanephrines excluded the diagnosis; no further evaluation was needed. Patient 2 presented with classic PHEO symptoms and a classic imaging phenotype of a 3 to 10 cm cystic hyperintense adrenal mass with necrotic centers; the 20-fold elevation in plasma NMN confirmed the diagnosis. Patient 4 depicts a common clinical scenario of a gray-zone elevation in the plasma NMN ordered because of episodes of labile hypertension with flushing; subsequently, normal 24-hour urine metanephrine and catecholamine levels were sufficient to exclude the diagnosis without ordering the imaging studies.

In patients with suspected PHEO, adrenergic blockade may not be necessary prior to contrast-enhanced imaging to prevent a hypertensive crisis during intravenous administration of the contrast material. No PHEO paroxysms were observed in 17 patients with PHEO who received nonionic contrast material (Bessell-Browne & O'Malley, 2007). According to Pacak (2007), "Nonionic CT contrast does not have any appreciable effect on NE and EPI release in various types of PHEO patients; therefore, adrenergic blockade does not seem to be necessary as a specific precautionary measure before i.v. nonionic contrast."

While the results of this one small study await confirmation, gadolinium clearly does not stimulate PHEOs, thus eliminating the need for adrenergic blockade prior to gadolinium-enhanced MRI. Both MRI and CT have similar sensitivities (90% to 100%) and specificities (70% to 80%) for adrenal PHEO, whereas MRI may detect pelvic paragangliomas that are missed by CT or ¹³¹I-metaiodobenzylguanidine (MIBG) (Garovic et al., 2004). Thus, gadolinium-enhanced MRI is the preferred technique if available.

Additional Imaging Studies

If abdominal imaging is negative, ¹²³I-MIBG scintigraphy can be used to localize the tumor (Fig. 12-2). The radiopharmaceutical is taken up selectively by the NE transporter in catecholamine-secreting tumors but has a false-negative rate of 15% (Young, 2007c). Before MIBG scanning, calcium channel blockades (CCBs) as well as vasodilating β -blockers such as labetalol and nasal decongestants should be withheld as they can interfere with MIBG uptake (Waguespack et al., 2010).

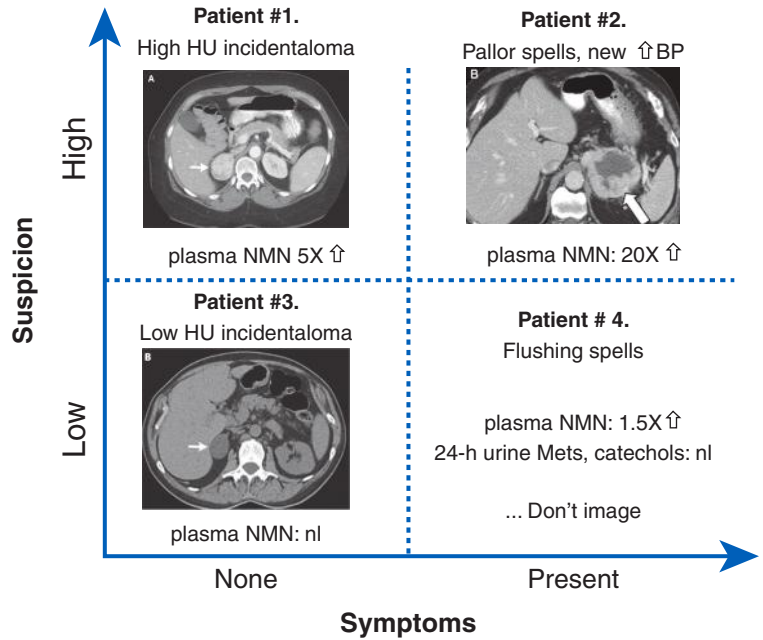


FIGURE 12-6 • Examples of four patients in whom a PHEO was suspected based on either symptoms or CT imaging studies. HU, Hounsfield units; NMN, normetanephrine; Mets, metanephrines. (Modified from Young WF Jr. Pheochromocytoma. In: *ASH Clinical Hypertension Review Course Syllabus*. American Society of Hypertension; 2007:481–494.)

Some experts recommend confirmatory MIBG scanning before all PHEO surgeries (Pacak, 2007); others believe this is unnecessary as MIBG can produce both false-positive and false-negative results (Garovic et al., 2004). Additional localizing procedures include whole-body MRI, In-III pentretotide scanning, and PET scanning with ^{18}F -fluorodeoxyglucose is superior to MIBG scanning for detection of metastatic PHEO (Timmers et al., 2009) ^{11}C -hydroxyephedrine, or 6- ^{18}F fluorodopamine (Young, 2007a).

The 2012 European Association of Nuclear Medicine guidelines for radionuclide imaging of PHEO and paraganglioma emphasize the increasing importance of PET scanning (Taieb et al., 2012). For apparently sporadic nonmetastatic PHEO, ^{123}I -MIBG is as sensitive as PET imaging and superior to ^{111}In -pentretotide SPECT/CT in tumor localization. PET scanning should be reserved for:

- MIBG-negative cases
- Multifocal tumors on MIBG scintigraphy
- Patients in whom it is unsafe to hold drugs that interfere with the accuracy of ^{123}I -MIBG. These include CCBs, β -blockers, and nasal decongestants as mentioned above, as well as opioids, tricyclic antidepressants, and antipsychotics. Labetalol would need to be held for 10 days to avoid a false-negative MIBG scan (Taieb et al., 2012).

Genetic Testing

The goal of genetic testing is to identify individuals at high risk for developing new or recurrent catecholamine-secreting tumors. In such individuals, frequent biochemical screening and imaging may detect early tumors that have not yet metastasized, increasing the chance of surgical cure.

Some experts recommend genetic testing for all patients with catecholamine-secreting tumors and their first-degree relatives (Gimenez-Roqueplo et al., 2006; Pacak et al., 2007) while others recommend a more selective, cost-effective approach (Erlic & Neumann, 2009; Young, 2007a). The exact rate of familial inheritance is unknown due to missed diagnoses outside of academic centers and referral bias at academic centers conducting the research. Current estimates are that over 30% of all PHEOs and paragangliomas are inherited, with germ line mutations being found in 5% to 27% of apparently sporadic tumors, i.e., those without the evidence of associated syndromes or family history after thorough evaluation (Moraitis et al., 2014; Muth et al., 2012).

However, in the United States, the yield of routine genetic testing in patients with sporadic adrenal PHEO—defined by unilateral disease, a negative family history, and no syndromic signs or symptoms—is low (Young & Abboud, 2006). Nevertheless, all patients should be monitored for findings of one of the familial syndromes, some of which can be detected

on physical examination. These include retinal angiomas in VHL syndrome, a thyroid mass in MEN2, café au lait spots in neurofibromatosis type 1, and a neck mass in paraganglioma syndromes. Evaluation and monitoring of first-degree relatives is also important since each of these disorders is transmitted as an autosomal dominant trait.

Who Should be Tested?

Genetic testing has a higher yield and should be considered in patients with one or more of the following: (a) paraganglioma, (b) bilateral adrenal PHEOs, (c) unilateral adrenal PHEO and a family history of PHEO/paraganglioma, (d) unilateral adrenal PHEO before the age of 40 years, and clinical findings suggestive of a syndromic disorder (Erlic & Neumann, 2009; Young & Abboud, 2006), and (e) all pediatric PHEOs because the majority will have a germ line mutation (Waguespack et al., 2010). Informed consent must be obtained and all family members should be offered genetic counseling. A list of clinically approved molecular genetic diagnostic laboratories is available at www.genetests.org.

Which Genes Should be Tested?

To eliminate the unneeded (and often nonreimbursable) expense of genetic testing for all known germ line mutations causing PHEO or paraganglioma, genes should be tested sequentially with the order being driven by the clinical scenario (Erlic & Neumann, 2009; Young & Abboud, 2006). For example, a patient with a catecholamine-secreting abdominal paraganglioma is most likely to have a mutation in *SDHB*, *SDHD*, or *VHL*—in that order. Thus, the *SDHB* gene should be tested first and no further testing would be needed if a mutation were identified. A patient with bilateral adrenal PHEOs—but without medullary carcinoma of the thyroid—is most likely to have mutations in *VHL* followed by *RET*; if a *VHL* mutation is identified, *RET* does not need to be tested. Referral to a specialized center is key.

Management

Surgical resection is the treatment of choice. Most PHEOs are benign and can be excised with high cure rates. Operative mortality is less than 3% when patients are managed by an experienced medical team (Darr et al., 2012; Young, 2007a). Thus, referral to an experienced center is strongly recommended for any patient in which there is a high suspicion of PHEO (Moraitis et al., 2014).

Preoperative Management

Preoperative management of PHEO involves α -adrenergic blockade followed by β -adrenergic blockade and plasma volume expansion. α - and β -adrenergic blockades are needed to prevent a PHEO crisis in the operating room. Liberal salt intake is needed to prevent postoperative hypotension. Preoperative management should begin 10 days before surgery to ensure effective adrenergic blockade and volume expansion. In the absence of randomized controlled trials, the following approach is recommended by most experts (Darr et al., 2012; Young, 2007a).

α -Blockade

Phenoxybenzamine is an irreversible α -blocker that produces more complete and more sustained α -adrenergic blockade than doxazosin or other α -blockers commonly used in general practice. Accordingly, side effects include orthostatic hypotension and reflex tachycardia, miosis, nasal congestion, ejaculation failure, diarrhea, and fatigue. Side effects are less severe with doxazosin, prazosin, or terazosin, which therefore are preferred for long-term palliative management of catecholamine excess in the setting of metastatic PHEO for which surgical cure is not an option. For short-term preoperative preparation for PHEO excision, phenoxybenzamine is preferred because the α -blockade is of a longer duration. This also provides adequate time to reexpand a contracted plasma volume before surgery.

The Mayo Clinic protocol is as follows (Young, 2007a). The initial dose of phenoxybenzamine is 10 mg BID. The dose is increased by 10 to 20 mg every 2 to 3 days as needed to control the blood pressure and the symptoms of catecholamine excess. The average final dosage is 20 to 100 mg/day. The target seated BP is less than 120/80 mm Hg. Orthostatic hypotension is very common when α -blockade is superimposed on a contracted plasma volume, which typically accompanies chronic catecholamine excess. Thus, the patient should be carefully instructed to liberalize salt intake to achieve a standing systolic BP greater than 90 mm Hg.

β -Blockade

Except for β -blocker-intolerant patients, β -blockade is indicated to control sinus tachycardia and other catecholamine-induced tachyarrhythmias but *only*

after an effective α -blockade has been achieved (which usually takes several days). If inadvertently used alone, β -blockers may exacerbate the hypertension by leaving α -mediated vasoconstriction unopposed. β -Blockers also can precipitate pulmonary edema if there is a catecholamine-induced cardiomyopathy. Thus, the β -blocker should be started at a low dose and titrated carefully. The Mayo Clinic protocol uses short-acting propranolol, with a starting dose of 10 mg every 6 hours (Young, 2007a). Over the next 3 to 5 days, the dose is increased gradually and converted to a long-acting formulation to eliminate tachycardia prior to surgery.

The NIH protocol is similar (Pacak, 2007). β -Blockade and liberal salt intake are added to phenoxybenzamine. The recommended end points are seated BP less than 130/80 mm Hg, standing systolic BP greater than 100 mm Hg, seated heart rate 60 to 70 bpm, and standing heart rate 70 to 80 bpm.

Calcium Channel Blockade

CCBs have been used effectively and safely both as an adjunct to α -/ β -blockade and as an alternative form of primary therapy for preoperative and intraoperative management of PHEO (Bravo & Tagle, 2003; Darr et al., 2012). These drugs block the intracellular calcium signal that produces α -adrenergic vasoconstriction in response to NE. According to Bravo (2004) at the Cleveland Clinic:

These agents [CCBs] do not produce hypotension and therefore may be used safely in patients who are normotensive but have occasional episodes of paroxysmal hypertension.

The CCBs also may be useful in preventing catecholamine-induced coronary artery spasm that occasionally occurs in patients with PHEO.

Nicardipine is the CCB most commonly used to manage PHEO (Young, 2007a). Nicardipine can be given orally (30 to 60 mg BID) to control the blood pressure before surgery and intravenously (5 to 15 mg/hour) to control the blood pressure in the operating room.

Catecholamine Synthesis Inhibition

α -Methyl-paratyrosine (metyrosine) inhibits tyrosine hydroxylase, which catalyzes the initial step in catecholamine synthesis. The side effects can be disabling, particularly when used for more than 1 week. They include sedation, depression, anxiety, nightmares,

uroolithiasis, diarrhea, galactorrhea, and extrapyramidal signs. According to Young (2007a):

Although some centers advocate that this agent should be used routinely preoperatively, most reserve it primarily for patients who cannot be treated with the typical combined α - and β -adrenergic blockade protocol because of cardiopulmonary reasons [e.g., bronchospasm]. α -Methyl-paratyrosine (metyrosine) should be used with caution and only when other agents have been ineffective or [in addition to α - and β -blockade] in patients where tumor manipulation or destruction (e.g., radiofrequency ablation of metastatic sites) will be marked.

The Mayo Clinic protocol is as follows (Young, 2007a): metyrosine 250 mg q6h on day 1, 1,500 mg q6h on day 2, 750 mg q6h on day 3, and 1,000 mg q6h on the day before the procedure (day 4) with the last dose on the morning of the procedure (day 5). With this “short course,” the main side effect is hypersomnolence.

Acute Hypertensive Crisis

Acute hypertensive crises can occur before or during surgery and should be treated with intravenous therapy (also see Chapter 8). Options include sodium nitroprusside, nicardipine, or phentolamine. Nitroprusside is the most commonly used therapy for all forms of hypertensive crisis, including PHEO. Nitroprusside should be avoided in pregnancy and in patients with renal failure because of thiocyanate toxicity. Nicardipine is a good alternative; an intravenous infusion is started at 5 mg/hour, and the infusion rate can be increased by 2.5 mg/hour every 15 minutes to a maximum dose of 15 mg/hour. Phentolamine is rarely used anymore and may not be readily available; the protocol is a 1-mg test dose followed by repeated 5-mg boluses.

Surgery and Anesthesia

PHEO surgery is a high-risk procedure, but 98% to 100% survival rates can be achieved at experienced centers (Darr et al., 2012; Young, 2007a). Most experts recommend hospital admission the day before surgery to ensure adequate volume expansion (intravenous saline with 5% dextrose) and administration of the final preoperative dose of blocking agents on the morning of surgery.

Most anesthetics can be used if the patient has been properly prepared, but several agents (including fentanyl, ketamine, and morphine) should be avoided

because they can potentially stimulate the PHEO to secrete catecholamines. Atropine should be avoided to prevent tachycardia from vagal withdrawal. Hemodynamic parameters must be closely monitored during surgery.

With accurate preoperative tumor localization, laparoscopic adrenalectomy is the procedure of choice for the excision of a unilateral PHEO less than 8 to 10 cm in diameter. With the retroperitoneal surgical approach, hospital stay is as short as 2 days (Young, 2007a). Larger tumors require open adrenalectomy. An anterior midline surgical approach is needed for abdominal paragangliomas, whereas specialized surgical approaches are needed to excise paragangliomas in the neck, chest, and urinary bladder. Cortical-sparing procedures (partial adrenalectomies) have been advocated for patients with bilateral PHEOs in the setting of VHL or MEN2 syndromes.

After surgery, patients require close monitoring in an ICU for the first 24 hours. Hypotension and hypoglycemia are the two main postoperative complications and can occur suddenly despite careful preoperative preparation (Lenders et al., 2005). Hypotension is mainly due to hypovolemia and should be treated with intravenous fluids and, if needed, pressor agents. Hypotension also can be caused by transient adrenocortical insufficiency, particularly if both the adrenal glands were manipulated during surgery. Blood glucose levels should be carefully monitored, and intravenous fluids should contain 5% dextrose as a countermeasure to hypoglycemia resulting from sudden withdrawal of catecholamines and a rebound increase in insulin secretion (Lenders et al., 2005).

Blood pressure is often normalized by the time of hospital discharge but may remain elevated for several weeks after successful surgery. Almost 50% of patients remain hypertensive to some degree due to persistent vascular remodeling and associated hypertensive target organ damage or coexisting primary hypertension.

Postoperative Follow-up

Early Postoperative Follow-up

Plasma and urinary-fractionated metanephrines should be measured 1 to 2 weeks after surgery. If the levels are completely normalized, surgery is considered successful. Elevated levels indicate a residual tumor, a second PHEO or paraganglioma, or metastases.

Long-Term Follow-up

After successful adrenalectomy, patients should undergo annual biochemical testing for the rest of their lives to detect recurrent tumors, new tumors, or metastatic diseases. Imaging studies are not needed unless metanephrine levels become elevated. The lifetime risk of recurrence varies by genotype.

PHEO During Pregnancy

PHEO is a rare but important cause of maternal–fetal mortality. The diagnosis is often missed because the estimated prevalence is only 1 per 143,000 pregnancies, symptoms can be nonspecific, and the PHEO can be asymptomatic until delivery (Biggar & Lennard, 2013). Pregnancy may precipitate PHEO crisis due to fetal movement, uterine growth, or delivery. Maternal and fetal mortality exceeds 50% if undiagnosed. With antenatal diagnosis and appropriate management, maternal mortality approaches zero and fetal mortality falls below 15%. If diagnosed in the first or second trimester (before 23 weeks of gestation), the PHEO should be surgically removed (laparoscopically) after preoperative adrenergic blockage. If diagnosed in the third trimester, medical management should be used as a bridge to PHEO surgery performed during C-section, the latter to minimize the stress of labor and delivery (Biggar & Lennard, 2013). CT and MIBG scintigraphy are contraindicated in pregnancy while MRI is considered safe. Extra-adrenal and bilateral tumors are more common in pregnant women because syndromic germ line mutations are present in younger adults.

PHEO in Children

Up to one in five PHEOs occurs in children (Waguespack et al., 2010). A retrospective chart review of the Mayo Clinic database from 1975 to 2005 identified 30 patients less than 18 years of age with histology-proven PHEO or paraganglioma (Pham et al., 2006). Most were teenagers. The proportion of paraganglioma (60%), metastatic disease (47%), or a genetic mutation or family history of PHEO/paraganglioma (30%) was considerably higher in these children than in the adult series from the same institution. Other series indicate that in children, over 40% of PHEOs are associated with known genetic mutations (Havekes et al., 2008). Metastatic disease was more likely in those with apparently sporadic disease,

paraganglioma, and tumor diameter greater than 6 cm. It is essential to differentiate paraganglioma (with fractionated metanephrines and dopamine) from retroperitoneal neuroblastomas, which are much more common in children and do not require preoperative adrenergic blockade. In children, it also is essential to differentiate PHEO from attention deficit hyperactivity disorder (ADHD) (Havekes et al., 2008).

Small PHEOs

While PHEOs are typically large, small PHEOs (<3 cm) are being diagnosed more commonly due to wide availability of abdominal imaging with CT/MRI. A retrospective series of 24 patients at Cedars-Sinai indicates that small PHEOs can be accompanied by minimally (i.e., proportionately) elevated or normal metanephrine levels requiring a high index of suspicion and imaging phenotype to make the diagnosis (Yu et al., 2012b). They can contribute to hypertensive crisis during unrelated medical procedures but rarely contribute to chronic hypertension (Yu et al., 2012b).

Malignant PHEO

Malignancy is defined only by the presence of distal metastases as no molecular or histologic markers currently exist (Jimenez et al., 2013). The most common sites for metastases are to lymph ganglia, bone, liver, and lungs. Three clinical predictors of metastatic PHEO or sympathetic paraganglioma are

- Tumor size greater than 5 cm
- Extra-adrenal location in the abdomen, pelvis, or chest
- Germ line mutation in the *SDHB* gene

At least 50% of all metastatic cases have a *SDHB* mutation. Rapid growth is another hallmark of malignancy. Whereas malignant PHEOs grow at a rate of approximately 2 cm/year, sporadic PHEOs grow very slowly, with almost no change in size over 3 years (Yu & Phillips, 2012).

The presence of distant metastases greatly reduces the possibility of surgical cure. Overall, the 5-year survival rate is only 60% (Jimenez et al., 2013). Long-term survival is more likely with bony metastases, which may be solitary, than with metastases to the liver, lung, and lymph nodes. However, bony metastases can be extensive (Fig. 12-7).

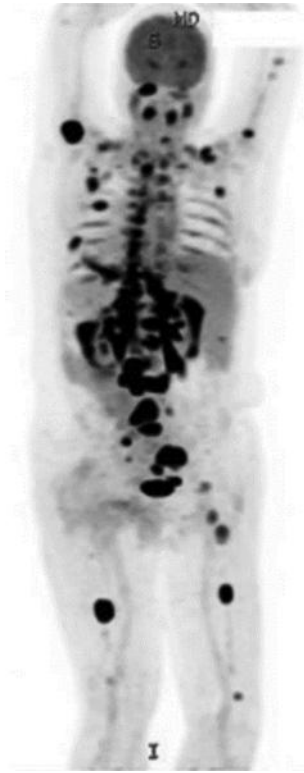


FIGURE 12-7 • Extensive bony metastases by ^{123}I MIBG scanning in a patient with metastatic paraganglioma of the organ of Zuckerkandl. (From Jimenez C, Rohren E, Habra MA, et al. Current and future treatments for malignant pheochromocytoma and sympathetic paraganglioma. *Curr Oncol Rep* 2013;15:356–371.)

Current therapeutic options are limited. These include (a) surgery to reduce tumor burden, (b) external beam irradiation for solitary bony metastases, (c) radiofrequency ablation for solitary liver metastases less than 4 cm in diameter, (d) systemic ^{131}I -MIBG radiotherapy for patients with strongly positive ^{123}I -diagnostic MIBG imaging, (e) octreotide or other somatostatin analogs for rare patients with strongly positive diagnostic octreotide imaging, (f) chemotherapy with cyclophosphamide, vincristine, and dacarbazine, and (g) sunitinib, an oral caprot tyrosine kinase inhibitor (Jimenez et al., 2013). With any of these modalities, responses often are partial and short lived. ^{131}I therapy requires preparation with sodium perchlorate or potassium iodide to protect the thyroid gland and discontinuation of drugs that interfere with MIBG uptake. A recent meta-analysis of 243 patients suggests that treatment with ^{131}I -MIBG suggests can stabilize disease activity (tumor volume, catecholamine

response) in 40% of patients with metastatic PHEO and in 50% of patients with metastatic paraganglioma (van Hulsteijn et al., 2013). Prolonged treatment with α - and β -blockers and sometimes metyrosine may be needed to palliate the symptoms of catecholamine excess, which can be severe.

Next, we will examine excess of cortisol or deoxycorticosterone as other adrenal causes of hypertension.

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Hypertension Induced by Cortisol or Deoxycorticosterone

The preceding chapters described the syndromes of hypertension induced by catecholamine or aldosterone excess. This chapter covers syndromes in which hypertension is induced by other adrenal steroids: *cortisol*, either in excess (Cushing syndrome) or with increased exposure to mineralocorticoid receptors (MCRs) (apparent mineralocorticoid excess [AME] and licorice ingestion); or *deoxycorticosterone* (DOC) (congenital adrenal hyperplasias [CAHs]). Subclinical Cushing syndrome is the most common hormonal disturbance arising from adrenal incidentalomas found by adrenal scans (Starker et al., 2014) as discussed in Chapter 12.

CUSHING SYNDROME

Significance

Although overt Cushing syndrome is rare, it often must be suspected in the growing number of patients with the metabolic syndrome (Prague et al., 2013). Moreover, as milder and cyclical forms of Cushing syndrome have been recognized (Manenschijn et al., 2012), the laboratory confirmation of the diagnosis has become more difficult despite the availability of better hormonal assays (Newell-Price et al., 2006; Nieman et al., 2008).

When present, Cushing syndrome is a serious disease. Hypertension is present in more than 75% of patients with Cushing syndrome (Feelders et al., 2012) and is often difficult to treat and, if the syndrome is incompletely controlled, contributes to a four-fold excess mortality (Yaneva et al., 2013).

Pathophysiology

Cushing syndrome is caused by either excess endogenous cortisol with the idiopathic form or excess exogenous steroids in the more common iatrogenic form

which may result even from use of steroid-containing cosmetic creams (Druce et al., 2008). The idiopathic disease may be either ACTH dependent or independent (Table 13-1; Fig. 13-1). The most common type, termed Cushing disease, is due to overproduction of ACTH from a pituitary microadenoma with resultant diffuse bilateral adrenal hyperplasia. Ectopic ACTH production may come from multiple types of tumors, the largest number being malignant small cell carcinomas of the lung (Boscaro et al., 2001). In addition, adrenocortical cells may harbor “illegitimate” receptors, responding to unusual ligands (Bertherat et al., 2005).

ACTH-independent forms are mostly benign adrenal adenomas or malignant carcinomas, but various forms of hyperplasia may pose diagnostic difficulty. As noted in Chapter 12, the number of adrenal tumors found incidentally by abdominal CT or MRI is increasing. As many as 20% of these adrenal incidentalomas when initially recognized secrete cortisol in a partially unregulated manner, often in association with hypertension, diabetes, and generalized obesity (Rossi et al., 2000). Over 5 years, as many as 7% of those with initially normal cortisol regulation develop subclinical hyperfunction (Barzon et al., 2002). Adrenalectomy may be indicated for some with clinical features but “subclinical” hormonal tests (Mitchell et al., 2007).

A number of interesting variants have been reported, including

- Spontaneously remitting disease (Ishibashi et al., 1993)
- Cyclic or periodic disease (Manenschijn et al., 2012)
- Association with overt hypothalamic disorders (Dubois et al., 2007)
- Transition from pituitary-dependent to pituitary-independent disease (Hermus et al., 1988)
- ACTH-independent bilateral macronodular hyperplasia, which is often massive (Doppman et al., 2000),

TABLE 13-1

Prevalence of Various Types of Cushing Syndrome in Three Separate Series (in Percentages)

Reference	Orth (1995)	Boscaro et al. (2000)	Valassi et al. (2011)
Number of Patients	630	302	481
ACTH dependent			
Pituitary ACTH (Cushing disease)	68	66	66
Ectopic ACTH syndrome	12	7	5
Ectopic CRH syndrome	<1	<1	
Macronodular adrenal hyperplasia		2	
ACTH independent			
Adrenal adenoma	10	18	27
Adrenal carcinoma	8	6	
Micronodular hyperplasia	1	<1	
Adrenal hyperplasia from other stimuli (e.g., GIP)	<1	<1	
Exogenous glucocorticoid intake			

may be genetic (Beuschlein et al., 2014; Faucz et al., 2014), and associated with the expression of ectopic receptors for various hormones including the gastric inhibitory polypeptide (GIP), vasopressin, β -adrenergic agonists, LH/human CG or serotonin 5-HT₄ (Bertherat et al., 2005; Lacroix et al., 2001). Such receptors are occasionally found in adrenal adenomas as well

- ▶ Pigmented micronodular dysplasia, in most cases as part of the autosomal dominant familial syndrome with cardiac and skin myxomas, the Carney complex (Bram et al., 2014)
- ▶ Association with pheochromocytoma (Lee et al., 2008), chemodectoma, carcinoid tumors (Corsello et al., 2014) and multiple endocrine neoplasia type 1 (Simonds et al., 2012).
- ▶ Increased sensitivity of peripheral glucocorticoid receptors without increased levels of cortisol (van Rossum & Lamberts, 2004)

Hypertension with Glucocorticoid Excess

Hypertension is present in about 75% of patients with Cushing syndrome. The severity of the hypertension may be related to the abolition of the normal nocturnal fall in BP seen after exogenous glucocorticoid administration and in patients with Cushing syndrome (Zelinka et al., 2004). The longer the duration of hypertension,

the greater the likelihood that it will persist after relief of the syndrome (Suzuki et al., 2000).

Hypertension is relatively rare in patients who take exogenous glucocorticoids because of the use of steroid derivatives with less mineralocorticoid activity than cortisol. However, significant rises of BP can occur within 5 days of the administration of cortisol in fairly high doses (Whitworth et al., 2000).

Mechanisms for the Hypertension

Multiple mechanisms may be responsible for the hypertension so common in Cushing syndrome. The mechanisms may include the following:

- ▶ A sodium-retaining action of the high levels of cortisol. Although cortisol is 300 times less potent a mineralocorticoid than is aldosterone, 200 times more cortisol is normally secreted; this level is increased by two times or more in Cushing syndrome. With high levels of cortisol, the 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) capacity to convert cortisol to cortisone is overwhelmed, allowing cortisol to act on MCRs (Quinkler & Stewart, 2003; Ulick et al., 1992b).
- ▶ Glucocorticoids directly activate glucocorticoid receptors on vascular smooth muscle to raise blood pressure in knockout mice (Goodwin et al., 2008) and stimulate mineralocorticoid signaling in vascular smooth muscle cells in vitro, independent of aldosterone levels (Molnar et al., 2008).

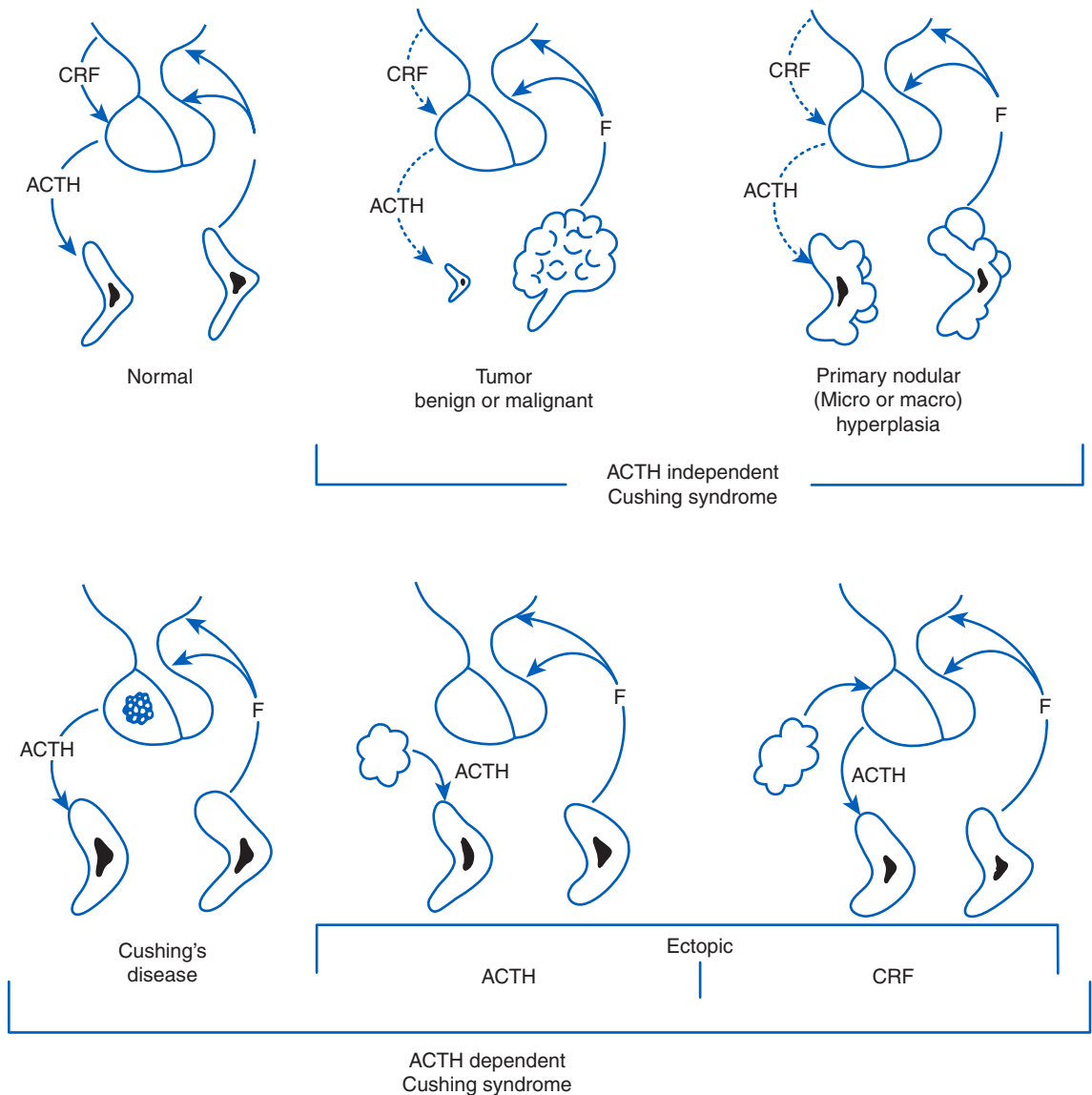


FIGURE 13-1 • Causes of endogenous Cushing syndrome. The lesions on the top arise within the adrenal. Those in the bottom arise within the pituitary (Cushing disease) or from ectopic production of ACTH or corticotropin-releasing factor (CRF). F, cortisol. (Modified from Carpenter PC. Diagnostic evaluation of Cushing syndrome. *Endocrinol Metab Clin NA* 1988;17:445–472.)

- Increased production of *mineralocorticoids*. Though usually noted only in patients with adrenal tumors, increased levels of 19-nor-DOC (Ehlers et al., 1987), DOC, and less commonly, aldosterone (Cassar et al., 1980) have been found in patients with all forms of the syndrome.
- Stimulation of glucocorticoid receptors in the dorsal hindbrain (Scheuer et al., 2004).
- Reduced activity of various vasodepressor mechanisms (Saruta, 1996) in particular endothelial nitric oxide (Mangos et al., 2000).
- Increased levels of renin substrate and an increased responsiveness to various *pressors* (van der Pas et al., 2014).
- Other mechanisms may also be involved including an increase in erythropoietin (Whitworth et al., 2000) or endothelin (Kirilov et al., 2003).

Clinical Features

Many more patients with cushingoid features are seen than the relatively few who have the syndrome. The

TABLE 13-2

Clinical Features of Cushing Syndrome

Clinical Features	Approximate Incidence (%)
General	
Obesity	80–95
Truncal	45–95 ^a
Hypertension	70–90
Headache	10–50
Skin	
Facial plethora	70–90
Hirsutism	70–80
Purple striae	50–70 ^a
Bruising	30–70 ^a
Neuropsychiatric	60–95
Gonadal dysfunction	
Menstrual disorders	75–95
Impotence or decreased libido	65–95
Musculoskeletal	
Osteopenia	75–85
Weakness from myopathy	30–90 ^a
Metabolic	
Glucose intolerance/diabetes	40–90
Kidney stones	15–20

^aMost discriminatory features.

Modified from Nieman LK et al. The diagnosis of Cushing's syndrome. *J Clin Endocrinol Metab* 2008;93(5):1526–1540.

syndrome is more likely in patients with the clinical features shown in Table 13-2 (Prague et al., 2013) along with a hypercoaguable state (van der Pas et al., 2012). Significant hypokalemia is usually seen with the ectopic ACTH syndrome (Torpy et al., 2002). Significant hypokalemia is usually noted with the ectopic ACTH syndrome (Torpy et al., 2002).

Cushing syndrome in children is usually manifested by weight gain and growth retardation, with systolic hypertension noted in 93% of 63 young patients (Magiakou et al., 1997). Fortunately, they usually become normotensive within a few months of surgical cure, but may have residual hypertension-related adverse effects (Lodish et al., 2009).

Pseudo-Cushing Syndrome

As many as 50% to 80% of patients with Cushing syndrome meet the criteria for major depression and may have persistent psychological and cognitive problems

even after surgical remission (Resmini et al., 2012). On the other hand, patients with endogenous depression without Cushing syndrome may have poorly suppressible hypercortisolism related to increased ACTH pulse frequency (Mortola et al., 1987), but their basal cortisol levels are usually normal and they do not hyperrespond to corticotrophin-releasing hormone (CRH) (Yanovski et al., 1998).

Alcoholics often display numerous features suggestive of Cushing syndrome, including hypertension and elevated cortisol secretion (Badrack et al., 2008), which likely reflects increased secretion of corticotrophin-releasing factor (Groote Veldman & Meinders, 1996). On the other hand, 20% of patients with Cushing syndrome have hepatic steatosis by CT scans (Rockall et al., 2003).

Pregnant women often have features suggestive of Cushing syndrome; the rare appearance of Cushing syndrome during pregnancy may pose diagnostic dilemmas (Solomon & Seely, 2006).

Laboratory Diagnosis

Two somewhat contradictory scenarios exist in relation to the diagnosis of Cushing syndrome. First, the disease is being looked for in more patients with suggestive clinical features such as poorly controlled obese diabetics; in one study, 5.5% were found to have Cushing syndrome (Tabarin and Perez, 2011). This scenario requires screening tests with high specificity, i.e., few false positives—so that fewer suspects will have to be put through extensive confirmatory testing (Newell-Price, 2008).

The second scenario relates to the usually long duration between onset of symptoms and the time of diagnosis, averaging 6.0 years from one center (Psaras et al., 2011). This scenario requires confirmatory tests with high sensitivity, i.e., few false negatives—so that all patients can be correctly identified as early as possible. In view of the serious nature and the often irreversibility of the complications of the disease, the best balance is likely to be with a number of tests done over a short interval to achieve maximal predictive power (Findling & Raff, 2006). Nonetheless, controversy persists as to the appropriate cutoff values for different tests to provide the best balance (Newell-Price, 2008).

Screening Tests

For interpretation of cortisol levels, 1 µg/dL = 27 mmol/L.

The extent of the workup of patients suspected of having Cushing syndrome varies with the clinical situation. An overnight 1-mg dexamethasone suppression

TABLE 13-3

Tests to Determine the Anatomical Cause of Cushing Syndrome

	Adrenal	Pituitary	Ectopic
ACTH	Low	Normal/high	Normal/very high
CRH test	No response	Response	Rare response
DEX, 8 mg	No suppression	Suppression	Rare suppression
CT/MRI adrenal	Mass(es)	Normal/hyperplasia ^a	Normal/hyperplasia ^a
MRI pituitary	Normal	Tumor (60%)	Normal
BIPSS	Not applicable	Gradient (pit/periph)	No gradient (pit/periph)

^aNodules.

DEX, dexamethasone; DST, dexamethasone suppression test; BIPSS, bilateral inferior petrosal sinus sampling.

Data from Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing's syndrome: A consensus statement. *J Clin Endocrinol Metab* 2003;88(12):5593–5602.

test (OST) will be adequate for most patients with only minimally suggestive features; patients with highly suggestive features should have repeated measurement of 24-hour urinary free cortisol (UFC) and midnight serum or salivary cortisol (Arnaldi et al., 2003; Findling & Raff, 2006; Nieman et al., 2008) (Table 13-3). In data from 4,126 patients, (Pecori et al., 2007) found the midnight serum cortisol, using a 1.8 $\mu\text{g}/\text{dL}$ (50 nmol/L) cutoff, to provide only a 20% specificity whereas both the UFC and OST had 91% specificities. Nonetheless, the ease of obtaining the sample and the high sensitivity of the late-night salivary control lead Elias et al. (2014) to recommend it as the best screening study. The Endocrine Society recommends any one of the three screening tests: urine cortisol, late-night salivary cortisol, or 1-mg overnight dexamethasone suppression (Nieman et al., 2008) in keeping with their overall similar accuracy (Elamin et al., 2008).

Urinary Free Cortisol

The 24-hour UFC provides an integrated measure of the unbound circulating cortisol. High-performance liquid chromatography coupled with mass spectrometry provides better specificity than do immunoassays. The upper range of normal is 40 to 50 $\mu\text{g}/24$ hours (1,100 to 1,380 nmol/L) and a value four times greater is usually diagnostic (Findling & Raff, 2006). The level may be lowered in patients with renal damage or raised with increased urinary volumes by reducing the fraction of filtered cortisol that is metabolized to cortisone or reabsorbed. Since the level is variable, three daily specimens are usually assayed.

Overnight Plasma Suppression

For screening, the single bedtime 1-mg dose dexamethasone suppression test (OST), measuring the plasma cortisol at 8 a.m. the next morning, has worked well but, to provide adequate sensitivity, the cutoff value should be 1.8 $\mu\text{g}/\text{dL}$, rather than the previously recommended 5 $\mu\text{g}/\text{dL}$ (Findling et al., 2004). However, at the lower level, false-positive results are seen in about 10% of non-Cushing patients and false-negative results are seen in about 20% of patients with Cushing disease (Findling & Raff, 2006).

Late-Night Salivary Cortisol

An elevated late-night serum or salivary cortisol level is the earliest and most sensitive marker for Cushing syndrome (Elias et al., 2014). Rather than the inconvenience of obtaining blood samples, measurement of salivary cortisol levels in easily obtained samples has rapidly been accepted as a valid screening test including in children (Batista et al., 2007). Levels above 0.3 $\mu\text{g}/\text{dL}$ (8.6 nmol/L) are abnormal (Findling & Raff, 2006).

Low-Dose Dexamethasone Suppression Test and Combined DST-CRH

DSTs may give anomalous results because hormone hypersecretion may be cyclic or variable. Pseudo-Cushing's states, including depression, may be more accurately excluded by adding a CRH stimulation test after completion of the low-dose dexamethasone test (Yanovski et al., 1998). However, Gatta et al. (2007)

found no additional diagnostic accuracy by the addition of CRH stimulation to the DST using a cutoff of plasma cortisol 15 minutes after CRH of 4 $\mu\text{g/dL}$ (110 nmol/L). The plasma cortisol level value 15 minutes after CRH (1 $\mu\text{g/kg}$) is above 1.4 $\mu\text{g/dL}$ (40 nmol/L) in patients with Cushing syndrome but remains suppressed in normals and patients with pseudo-Cushing's.

Establishing the Cause of Cushing Syndrome

Once Cushing syndrome has been diagnosed, the anatomic cause needs to be accurately determined to guide therapy (see Table 13-3). In view of all the clinical vagaries and laboratory pitfalls that often confuse the differential diagnosis of the etiology of Cushing syndrome, referral to a medical facility with experience in dealing with such patients is almost always appropriate.

Corticotropin (ACTH) Assay

Measurement of plasma ACTH is the first step, using two-site immunometric assays that are sensitive, specific, and reliable, able to reliably detect values below 10 pg/mL (2 pmol/L). A suppressed ACTH concentration, below 5 pg/mL, indicates adrenal-independent Cushing syndrome usually from an adrenal tumor. However, other stimuli of adrenocortical receptors, such as insulinotropic peptide and vasopressin, may induce bilateral nodular adrenal hyperplasia with suppressed plasma ACTH levels. Normal or elevated plasma ACTH, above 20 pg/mL, indicate ACTH-dependent Cushing syndrome from either a pituitary or ectopic tumor. When values are between 10 and 20 pg/mL, a CRH stimulation test is indicated (Arnaldi et al., 2003).

Corticotrophin-Releasing Hormone Stimulation Test

Most pituitary tumors respond to IV CRH (1 $\mu\text{g/kg}$) with a release of plasma ACTH whereas adrenal tumors do not. Unfortunately, some ectopic ACTH-secreting tumors express the CRH receptor and also respond. Findling and Raff (2006) recommend a CRH test in patients with Cushing syndrome whose plasma ACTH levels are at the low end. The ACTH response is usually exaggerated if the pituitary tumor expresses the CRH receptor but blunted with adrenal tumors.

High-Dose Dexamethasone Suppression

Using the criterion of suppression of UFC to less than 10% of baseline for the diagnosis of pituitary-dependent Cushing disease, the high-dose (2 mg four times a day for 2 days) DST provides 70% to 80% sensitivity and close to 100% specificity (Boscaro et al., 2001). However, the results do not clearly separate ectopic ACTH from pituitary tumors, and this test is no longer recommended (Findling & Raff, 2006).

Pituitary MRI

In most patients, the measurement of plasma ACTH will be followed by a pituitary MRI with gadolinium enhancement (Lonser et al., 2013). Thereby, a discrete pituitary adenoma will be seen in about 60% of patients; if the tumor is greater than 6 mm in size, no further studies are required and the patients may be referred to a pituitary neurosurgeon (Arnaldi et al., 2003). It should be remembered that almost 15% of the general population harbor incidental pituitary tumors, although most are below 5 mm in diameter (Karavitaki, 2007). Since some patients with an ectopic ACTH-secreting tumor have abnormal pituitary MRI findings, bilateral inferior petrosal sinus sampling is indicated in those with clinical features suggesting an ectopic tumor, such as rapid onset of symptoms or hypokalemia (Findling & Raff, 2006).

Inferior Petrosal Sinus Sampling

Bilateral simultaneous sampling of the inferior petrosal sinuses (IPSS) is a powerful means of confirming whether or not the source of corticotropin is the pituitary, especially if imaging is negative. Ratio of central to peripheral ACTH of greater than 3 after CRH stimulation provides a sensitivity of 95% to 97% and specificity of 100% in diagnosing pituitary-dependent Cushing disease (Arnaldi et al., 2003). Less discrimination was found in a series of 185 IPSS procedures with a 99% positive predictive power but only a 20% negative predictive power (Swearingen et al., 2004). In view of the technical difficulty with IPSS, sampling of the internal jugular vein may be performed and only patients with a negative result referred for IPSS (Ilias et al., 2004).

If clinical and lab data point to an ectopic ACTH-secreting tumor, CT and/or MRI of the neck, thorax, and abdomen and, for occult tumors, scintigraphy with the somatostatin analog, ^{111}In -pentetreotide, are currently used to locate the tumor (De Herder & Lamberts, 1999). Positron emission tomography with

other labeled precursors has identified ACTH-secreting carcinoid tumors (Dubois et al., 2007).

Treatment

Treatment of the Hypertension

Until definitive therapy is provided, the hypertension that accompanies Cushing syndrome can temporarily be treated with the usual antihypertensive agents described in Chapter 7. Since excess fluid volume is likely involved, a diuretic, perhaps in combination with an aldosterone antagonist, spironolactone or eplerenone, is an appropriate initial choice. After definitive therapy, hypertension usually improves but coronary disease risk factors often persist, likely because of residual abdominal obesity and insulin resistance (Barahona et al., 2013).

Treatment of the Syndrome in General

In view of the long-term morbidity associated with Cushing syndrome, the condition must be treated as rapidly as possible after the diagnosis has been

established (Pulse et al., 2013). The choice of definitive therapy depends on the cause of the syndrome (Table 13-4).

- In the majority of patients who have ACTH-dependent Cushing disease with a pituitary tumor, transsphenoidal microsurgical removal is the treatment of choice (Hassan-Smith et al., 2012; Wagenmakers et al., 2013). In some circumstances, bilateral adrenalectomy or stereotactic radiotherapy (Petit et al., 2008) may be used if pituitary surgery is unsuccessful or when no pituitary tumor is found (Pouratian et al., 2007).
- Benign adrenal tumors should be surgically removed, increasingly by laparoscopy (Conzo et al., 2014).
- For adrenal cancers and ectopic ACTH tumors that cannot be resected, removal of the adrenal may be helpful, but chemotherapy is usually needed (Pozza et al., 2012).
- The drugs listed in Table 13-4 are mainly used to quickly overcome severe complications, either in preparation for surgery or whenever definitive treatment must be delayed (Trainer, 2014).

TABLE 13-4
Therapies for Cushing Syndrome

Class	Site	Therapy
Surgery	Pituitary	Transsphenoidal microsection; transfrontal hypophysectomy
	Adrenal	Unilateral adrenalectomy; bilateral adrenalectomy
Radiation		Fractionated x-ray (4–6 wk) Single dose Gamma knife Linear acceleration Heavy charged proton
Drugs	Acting at hypothalamic–pituitary	Serotonin antagonists (cyproheptadine, ritanserin) Dopamine agonists (bromocriptine, lisuride) GABA agonists (sodium valproate) Somatostatin analogs (octreotide); pasireotide
	Inhibitors of adrenocortical steroid synthesis	PPAR γ -agonist Mitotane Metyrapone Aminoglutethimide Ketoconazole
	Glucocorticoid antagonist	Etomidate Mifepristone

Follow-up

With definitive therapy, remission rates of 70% to 80%—defined as normal plasma and urinary cortisol levels and resolution of clinical stigmata—have been noted (Arnaldi et al., 2003; Hassan-Smith et al., 2012). However, as many as 25% of pituitary-dependent Cushing's patients have recurrences at 5 years after initially successful transsphenoidal surgery, so close and long-term follow-up is necessary (Alexandraki et al., 2013).

SYNDROMES WITH INCREASED ACCESS OF CORTISOL TO MINERALOCORTICOID RECEPTORS

Less common than Cushing syndrome caused by cortisol excess are a variety of fascinating syndromes wherein normal or increased levels of cortisol exert a mineralocorticoid effect by binding to the renal MCRs. As depicted in Figure 13-2, the normal renal MCR is as receptive to glucocorticoids as it is to mineralocorticoids. The 11β -hydroxysteroid dehydrogenase type 2 isoform (11β -HSD2) enzyme in the renal tubules upstream to these receptors normally converts the large amounts of fully active cortisol to the inactive cortisone, thereby leaving the MCRs open to the effects of aldosterone (Quinkler & Stewart, 2003).

However, there are both congenital and acquired deficiencies of the 11β -HSD2 enzyme, so that the normal levels of cortisol remain fully active, flooding the MCR

and inducing the full syndrome of mineralocorticoid excess: Sodium retention, potassium wastage, and hypertension with virtually complete suppression of renin and aldosterone secretion (Stewart, 2003).

11β -HSD2 Deficiency: Apparent Mineralocorticoid Excess

Apparent mineralocorticoid excess (AME) is an autosomal recessive disorder that has now been identified in about 100 patients. The syndrome clinically is characterized by familial consanguinity, low birth weight, failure to thrive, onset of severe hypertension in early childhood with extensive target organ damage, hypercalciuria, nephrocalcinosis, and renal failure (Chemaitilly et al., 2003). As noted, sodium retention, hypokalemia, low aldosterone, and low renin levels are present.

Genetics

Soon after the first case was described (Werder et al., 1974), Ulick et al. (1979) recognized that these children did not metabolize cortisol normally. Some years later, Stewart et al. (1988), in studies on a 20-year-old with the syndrome, recognized a defect in the renal cortisol–cortisone shuttle and demonstrated the deficiency of the 11β -HSD2 enzyme. A number of mutations in the 11β -HSD gene have now been identified in patients with AME (Carvajal et al., 2003; Friso et al., 2008).

Some of these mutations result in only partial inhibition of the 11β -HSD2 enzyme as evidenced by a higher ratio of urinary cortisone to cortisol metabolites

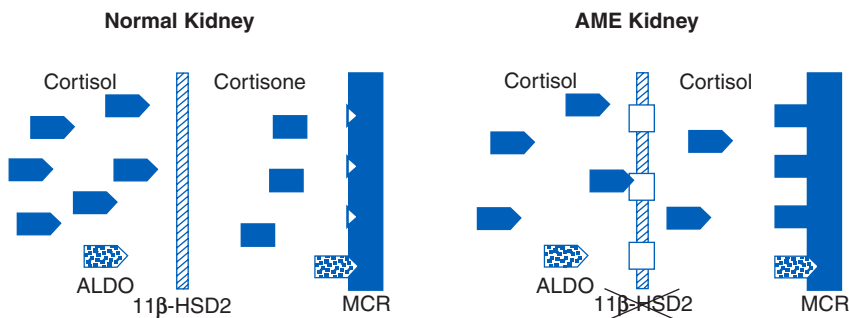


FIGURE 13-2 • Enzyme-mediated receptor protection. Normally, 11β -dehydrogenase (11β -HSD2) converts cortisol to inactive cortisone in the more proximal nephron, protecting mineralocorticoid receptors (MCRs) from cortisol and allowing selective access for aldosterone. When 11β -HSD2 is defective, e.g., in congenital deficiency (AME kidney) or after licorice administration, cortisol gains inappropriate access to mineralocorticoid receptors, resulting in sodium retention and potassium wasting. (Modified from Cerame BI, New MI. Hormonal hypertension in children: 11β -Hydroxylase deficiency and apparent mineralocorticoid excess. *J Ped Endocrinol Metab* 2000;13:1537–1547.)

and a milder clinical course with larger birth weight, later age of presentation (Nunez et al., 1999), and in at least one patient, only mild low-renin hypertension (Wilson et al., 1998). Not surprisingly, mutations resulting in less inhibition of the enzyme have been sought in patients with “essential” hypertension. Some have found them but most have not (Quinkler & Stewart, 2003). A role of impaired 11β -HSD2 activity has also been proposed for sodium sensitivity (Ferrari et al., 2001), intrauterine growth retardation (McTernan et al., 2001), and preeclampsia (Schoof et al., 2001).

An intriguing prospect has been proposed that decreased 11β -HSD2 activity may occur with aging and thereby may be involved in hypertension in the elderly (Campino et al., 2013).

Variant

A few patients with the features of AME have a defect not in the cortisol to cortisone shuttle but in the ring A reduction of cortisol to inactive metabolites because of a deficiency of the 5β -reductase enzyme (Ulick et al., 1992a). The resultant high levels of cortisol keep the MCRs flooded in the same manner as when 11β -HSD2 is deficient.

Therapy

Therapy is usually based on competitive blockade of the MCR with spironolactone (Dave-Sharma et al., 1998) or eplerenone (Funder, 2000). Suppression of endogenous cortisol with dexamethasone has also been used (Quinkler & Stewart, 2003). Cure has been reported on one patient after transplantation of a kidney with normal 11β -HSD2 activity (Palermo et al., 1998).

11 β -HSD2 Inhibition: Glycyrrhetic Acid (Licorice)

Since the early 1950s, glycyrrhizin acid, the active ingredient in licorice extract, has been known to cause hypertension, sodium retention, and potassium wastage. Stewart et al. (1987) and Edwards et al. (1988) recognized the similarities between the syndrome induced by licorice and the syndrome of AME and documented that licorice inhibited the same renal 11β -HSD2 enzyme that was deficient in AME. These effects are accompanied by a fall in cortisone and a rise in cortisol excretion, reflecting the inhibition of renal 11β -HSD2 activity.

Relatively small amounts of confectionary licorice, as little as 50 g daily for 2 weeks, produce a rise

in BP in normal people (Sigurjonsdottir et al., 2001). The syndrome also has been induced by the licorice extracts in chewing tobacco and candy and herbal remedies (Sontia et al., 2008). Not surprisingly, aldosterone receptor blockers (spironolactone and eplerenone) have been shown to relieve all of the effects of licorice-induced hypertension (Quaschnig et al., 2001). Even better is to recognize and stop the habit.

Massive Cortisol Excess

The capacity of the 11β -HSD-directed cortisol-cortisone shuttle and of 5β -reductase inactivation may be overcome by massive amounts of cortisol. Ulick et al. (1992b) have shown this to be the mechanism responsible for the significant features of mineralocorticoid excess—profound hypokalemia and hypertension—that are seen in patients with ectopic ACTH tumors wherein cortisol levels are much higher than in other causes of Cushing syndrome (Torpy et al., 2002).

Glucocorticoid Resistance

Both sporadic and familial forms of glucocorticoid receptor resistance, ascribed to various mutations in the receptor gene (Nicolaidis et al., 2014), have increased levels of circulating cortisol but without typical Cushing stigmata (Kino et al., 2002). Many of these patients have hypertension that may mimic mineralocorticoid excess. Moreover, among 60 hypertensive patients under age 36, 45 had increased levels of urinary glucocorticoid metabolites, suggesting partial resistance of glucocorticoid receptors with subsequent increased mineralocorticoid effects (Shamim et al., 2001).

DEOXYCORTICOSTERONE EXCESS: CONGENITAL ADRENAL HYPERPLASIA

Excessive amounts of the mineralocorticoid DOC may cause hypertension (Ferrari & Bonny, 2003), arising either from hyperplastic adrenals with enzymatic deficiencies or from rare DOC-secreting tumors (Gröndal et al., 1990).

Defects in all of the enzymes involved in adrenal steroid synthesis have been recognized (Fig. 13-3). These defects are inherited in an autosomal recessive manner, and their manifestations result from inadequate levels of the end products of steroid synthesis—in

particular, cortisol. The low levels of cortisol call forth increased secretion of ACTH, further increasing the accumulation of the precursor steroids proximal to the enzymatic block and stimulating steroidogenesis in pathways that are not blocked (Table 13-5).

The clinical manifestations of CAH, often obvious at birth, vary with the degree of enzymatic deficiency and the mix of steroids secreted by the hyperplastic adrenal glands. The most common type, the 21-hydroxylase deficiency, responsible for perhaps 90% of all CAH, which can now be recognized in maternal blood (New et al., 2014), is not associated with hypertension.

The two forms of CAH in which hypertension occurs are caused by deficiency of the 11 β -hydroxylase (CYP11 β) or 17-hydroxylase (CYP17A) enzymes. Though these are rare causes of hypertension, partial enzymatic deficiencies have been observed in hirsute women (Lucky et al., 1986), so some hypertensive adults may have unrecognized, subtle forms of CAH.

11-Hydroxylase Deficiency

Much less common than 21-hydroxylase deficiency in hyperandrogenized adults (Escobar-Morreale et al., 2008), this is the second most common form of CAH and is usually recognized in infancy because, as shown in Figure 13-3, the defect sets off production of

excessive androgens. The enzyme deficiency prevents the hydroxylation of 11-deoxycortisol, resulting in cortisol deficiency and prevents the conversion of DOC to corticosterone and aldosterone. The high levels of DOC induce hypertension and hypokalemia, the expected features of mineralocorticoid excess. Thus, the syndrome features virilization of the infant, hypertension, and hypokalemia.

The enzyme deficiency has been attributed to various mutations in the *CYP 11B1* gene (Polat et al., 2014). The syndrome is diagnosed by finding high levels of 11-deoxycortisol and DOC in urine and plasma. Treatment, as for all of the syndromes of CAH, is with glucocorticoid, which should relieve the hypertension and hypokalemia and allow the child to develop normally. Prenatal diagnosis and treatment have been shown to prevent virilization (Cerame et al., 1999).

17-Hydroxylase Deficiency

Unlike the 21-hydroxylase and 11-hydroxylase deficiencies, CAH caused by a 17-hydroxylase deficiency is typically associated with an absence of sex hormones, leading to incomplete masculinization in males and primary amenorrhea in females in addition to hypertension and hypokalemia (Fig. 13-3; Table 13-5). This is the first hypertensive disorder of steroidogenesis that

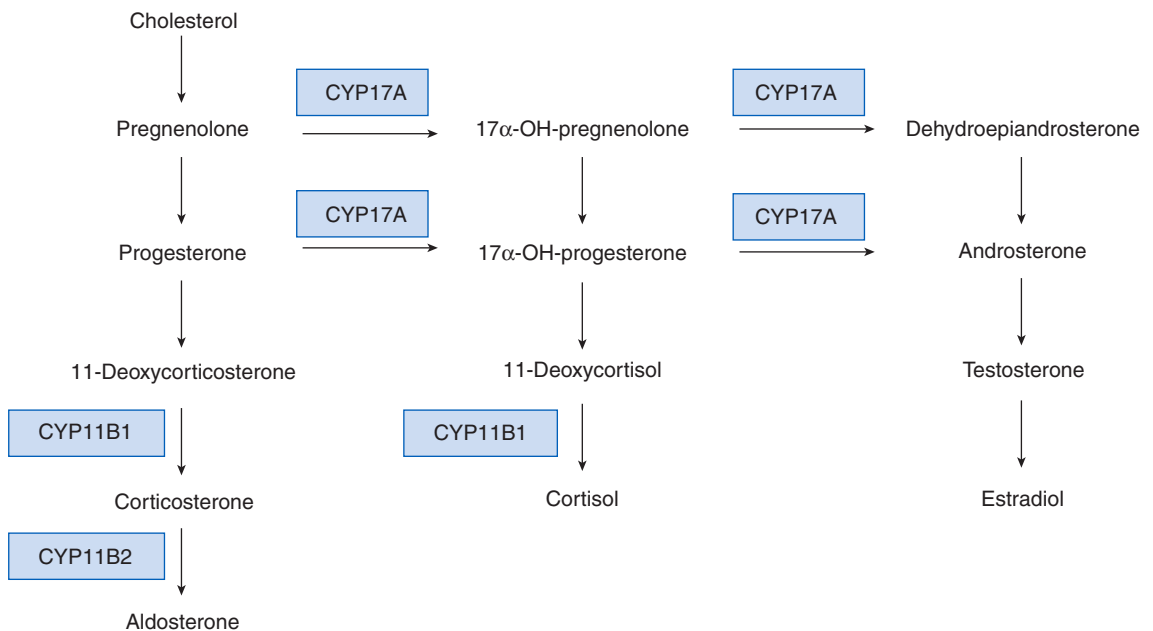


FIGURE 13-3 • The adrenal steroid pathway.

TABLE 13-5

Syndromes of Congenital Adrenal Hyperplasia

Enzyme	Site of Defect		Steroid Levels			Clinical Features	
	Increased Precursor	Decreased Product	17-OH-P or P' triol	DOC	Aldo	Virilization	Hypertension
21-Hydroxylase							
Nonsalt wasting	17-Hydroxyprogesterone	11-Deoxycortisol, cortisol	↑↑↑	N	N	Marked	No
Salt wasting	Progesterone	11-DOC, cortisol	↑↑↑	↓	↓↓	Marked	No
11-Hydroxylase							
Nonsalt wasting	11-Deoxycortisol	Cortisol	N, ↑	↑↑	↓↓, N	Marked	Yes
Salt wasting	11-Deoxycorticosteroid	Corticosterone					
17-Hydroxylase							
Nonsalt wasting	Progesterone	Cortisol	↓↓	↑↑	↓, N, ↑	Absent	Yes
Salt wasting	Pregnenolone	17-Hydroxypregnenolone					
3β-ol-Dehydrogenase	Pregnenolone	Progesterone, cortisol	N, ↑	N, ↓	↓, N	Sight	No
STAR protein	Cholesterol	All steroids	↓↓	↓↓	↓↓	Absent	No

17-OH-P, 17-hydroxyprogesterone; P' triol, pregnanetriol; Aldo, aldosterone; N, normal; ↑, increased by varying degrees; ↓, decreased by varying degrees.

has been identified (Biglieri et al., 1966). Nearly 40 different mutations in CYP17 have now been described, and there is considerable variability in the clinical and hormonal features (Rosa et al., 2007).

Now that the various renal and adrenal causes of hypertension have been covered, we shall turn to an even larger variety of less common forms.

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Other Forms of Identifiable Hypertension

As described in Chapter 3, the pathogenesis of primary (essential) hypertension likely involves multiple mechanisms. Beyond the involvement of obvious players such as renal sodium handling, renin–angiotensin, and the sympathetic nervous system—whose altered roles may be genetically determined—lurk a number of environmental factors. Of those factors, sodium and potassium intake, weight gain, and stress most likely are causal. Others, such as smoking and alcohol, may raise the blood pressure (BP), but they are generally considered to be contributory rather than causal, since, when discontinued, their pressor effect disappears.

As described in Chapters 9 through 16, a number of secondary or identifiable causes of hypertension have been characterized. In addition to those, which primarily reflect renal and adrenal hormonal abnormalities, a number of other, generally less common forms of hypertension have been identified and are covered in this chapter. Additional coverage of hypertension in childhood is provided in Chapter 16.

COARCTATION OF THE AORTA

Constriction of the lumen of the aorta is seen most commonly just beyond the origin of the left subclavian artery, at or below the insertion of the ligamentum arteriosum. This lesion makes up approximately 7% of all congenital heart diseases. Hypertension in the right upper extremity with diminished or absent femoral pulses is the usual presentation (Table 14-1).

Most other cases are identified at routine medical examination. Otherwise, age at presentation is related to the severity rather than the site of obstruction, as a result of cardiac failure or occasionally

cerebrovascular accident (CVA), aortic dissection, or endocarditis. Adults with coarctation repaired in infancy are more likely to have associated bicuspid aortic valve, subaortic stenosis, ventricular septal defect (VSD), and hypoplastic aortic arch (Warnes et al., 2008). There also is an important association with circle of Willis aneurysms, which can rupture.

Pathophysiology

If the coarctation is proximal to the ductus arteriosus, pulmonary hypertension, congestive failure, and cyanosis of the lower half of the body occur early in life. Before surgery was possible, 45% to 84% of infants found to have coarctation died during their 1st year of life (Campbell, 1970).

Patients with less severe postductal lesions may have no difficulties during childhood. However, they almost always develop premature cardiovascular disease; in the two largest series of autopsied cases seen before the advent of effective surgery, the mean age of death was 34 years (Campbell, 1970). The causes of death reflected the pressure load on the heart and the associated cardiac and cerebral lesions.

In addition to the mechanical stimulus of high BP, coarctation somehow induces structural and functional abnormalities in arterial segments proximal to the constriction that persist after successful repair and thus may contribute to the late development of hypertension and an excessive arteriosclerotic cardiovascular disease (ASCVD) risk (Brili et al., 2005). These abnormalities—which include endothelial dysfunction in the right forearm vessels and impaired elasticity of the carotid artery but not of the femoral artery—are accompanied by increased circulating levels of proinflammatory cytokines and adhesion molecules, all of which can be

TABLE 14-1

Symptoms and Signs of Coarctation**Symptoms**

- Headache
- Cold feet
- Pain in legs with exercise

Signs

- Hypertension
- Hyperdynamic apical impulse
- Murmurs in front or back of the chest
- Pulsations in neck
- Weak femoral pulse

improved by treatment with an angiotensin converting enzyme inhibitor (ACEI) (Brili et al., 2008). In a rabbit model of coarctation, complete correction of the pressure gradient has absolutely no effect on endothelial dysfunction and abnormal protein expression (decreased smooth muscle myosin and increased nonmuscle myosin) in the walls of the proximal aorta, coronary arteries, or cerebral vessels (Menon et al., 2012). Progressive weight gain and obesity, possibly from restricted exercise, is increasingly recognized after coarct repair and may contribute to the late onset of hypertension and ASCVD risk (Smith-Parrish et al., 2014).

Recognition of Coarctation

Hypertension in the right arm with weak femoral pulses in a young adult strongly suggests coarctation. Patients may complain of exertional headaches and/or intermittent claudication. Detection of a murmur of a bicuspid aortic valve (crescendo–decrescendo murmur of aortic stenosis with or without a diastolic murmur of aortic regurgitation), VSD (harsh systolic murmur), or collaterals (a continuous murmur over the parasternal area and left scapula) may lead to the diagnosis (Warnes et al., 2008). Coarctation is present in 12% of young women with Turner syndrome, which is 400 times higher than in the general population (Wong et al., 2014). With minimal constriction, symptoms may not appear until later in life. Often the heart is large and shows LVH with strain on the electrocardiogram. The chest radiograph can be diagnostic, demonstrating the “three” sign from dilation of the aorta above and below the constriction and notching of the ribs by enlarged collateral vessels (Fig. 14-1) (Quiros-Lopez & Garcia-Alegria, 2007). The diagnosis

is now usually made by suprasternal notch echocardiography with color Doppler flow imaging and confirmed by cardiac magnetic resonance imaging (MRI) or computerized tomography (CT) (Fig. 14-1) (Quiros-Lopez & Garcia-Alegria, 2007). Exercise testing with a supine bicycle ergometer is important to determine the responses of BP and echocardiographic Doppler gradient to exercise, which estimate the coarctation gradient (Warnes et al., 2008).

Atypical aortic coarctation in adults most likely represents Takayasu arteritis, or pulseless disease—a giant cell arteritis occurring mainly in young women in their 20s or 30s and causing stenosis and occasionally aneurysm formation of the aorta and its major branches (Fig. 14-2) (Clifford & Hoffman, 2014). While corticosteroids are first-line therapy, early results with anti-TNF biologics, mainly etanercept or infliximab, are promising (Clifford & Hoffman, 2014).

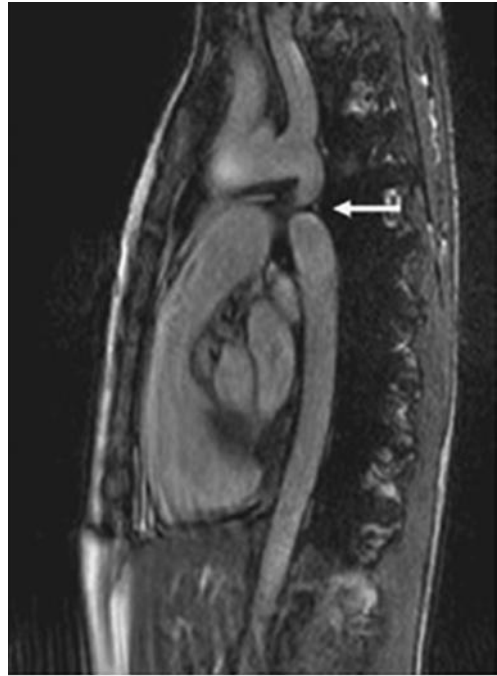
Management

Prior to repair, hypertension should be controlled with an ACEI or angiotensin receptor blocker (ARB) as first-line therapy. Add-on therapy may include a beta-blocker if the aortic root is large to minimize the risk of aneurysmal rupture or a vasodilator if there is associated aortic insufficiency that would be exacerbated by bradycardia from beta-blockade. According to the 2008 American College of Cardiology/American Heart Association Guidelines, (Warnes et al., 2008) intervention is recommended if peak-to-peak coarctation gradient is ≥ 20 mm Hg or the gradient is less than 20 mm Hg in the presence of anatomic imaging evidence of significant coarct with radiologic evidence of significant collateral flow. Early repair is recommended with very low rates of recoarctation being encountered but nonetheless with high rates of late postoperative hypertension and ASCVD. Percutaneous catheter intervention with stenting is indicated for recurrent discrete coarctation whereas surgical repair is indicated for previously repaired coarct with a long recoarctation segment or concomitant hypoplasia of the aortic arch and women of childbearing age to assure removal of the pre-coarct segment. If repair is delayed until adulthood, there is a greater likelihood of persistent hypertension, which may be severe. Even in those with normal resting BPs, there may be an exaggerated BP response to exercise (Warnes et al., 2008).

Obviously, patients after repair need to be followed at least annually with stress testing, and any degree of resting or exercise-induced hypertension needs to be



A



B



C

FIGURE 14-1 • Coarctation of the aorta in a young woman. A chest radiograph shows classical changes associated with coarctation of the aorta (**A**, arrows). Magnetic resonance imaging shows constriction of the lumen of the aorta (**B**, arrow). A chest radiograph shows endovascular repair with stent placement (**C**, arrow). (From Quiros-Lopez R, Garcia-Alegria J. A medical mystery—High blood pressure. *N Engl J Med* 2007;356:2630.)

intensively treated (Gurvitz et al., 2013). Despite improvements in surgical technique and earlier age of operation, long-term survival has not improved as much as expected: up to 75% of patients develop lifelong

postoperative hypertension if repaired after age 15 and still 40% if before age 15 (Brown et al., 2013). Thus, lifelong medical follow-up with intensive management of hypertension and ASCVD risk factors is essential.

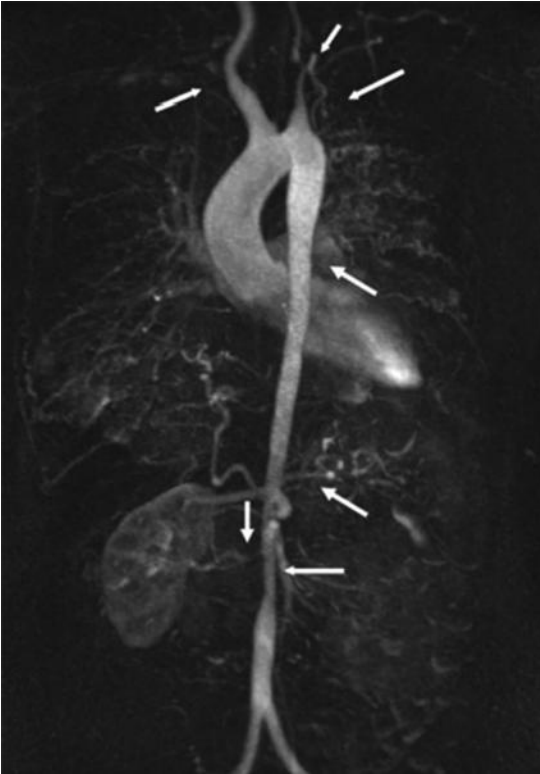


FIGURE 14-2 • Vascular lesions in Takayasu arteritis. MR imaging of the entire aorta in a 33-year-old woman with Takayasu arteritis. Arrows indicate multiple stenotic or occluded lesions. The left common carotid and both subclavian arteries are occluded, resulting in antegrade flow through the vertebral arteries. The right renal artery is stenotic and the left is occluded, resulting in an atrophic left kidney. There are also areas of stenosis in the descending and abdominal aorta. Presenting features were syncope, transient ischemic attack, and severe hypertension. (From Clifford A, Hoffman GS. Recent advances in the medical management of Takayasu arteritis: An update on use of biologic therapies. *Curr Opin Rheumatol* 2014;26(1):7–15.)

HORMONAL DISTURBANCES

Hypothyroidism

Hypertension, particularly diastolic, may be more common in hypothyroid patients. Among 40 patients prospectively followed over the time they became hypothyroid after radioiodine therapy for thyrotoxicosis, 16 (40%) developed a diastolic BP higher than 90 mm Hg (Streeten et al., 1988). Hypothyroid patients tend to have a low cardiac output with a decrease in contractility and impaired diastolic relaxation (Danzi & Klein, 2003). To maintain tissue perfusion, peripheral resistance increases, from a combination of increased responsiveness of α -adrenergic receptors, increased

levels of sympathetic nervous activity (Fletcher & Weetman, 1998), and aldosterone (Fommei & Iervasi, 2002). These would tend to raise diastolic BPs more than systolic BPs, the usual pattern seen in hypothyroidism (Saito & Saruta, 1994).

Subclinical hypothyroidism, defined as an elevated thyrotropin-stimulating hormone but normal free thyroxine levels, was associated with marginally higher BP in a meta-analysis of 50,147 individuals in 20 studies (Ye et al., 2014). A meta-analysis of 10 population-based studies found a 51% higher relative risk of coronary disease in such patients under age 65 (Gencer et al., 2013).

Hyperthyroidism

An elevated systolic but lowered diastolic BP is usual in patients with hyperthyroidism, associated with a high cardiac output and reduced peripheral resistance. Even after successful therapy, cardiovascular disease (CVD) morbidity persists (Metso et al., 2008).

Hyperparathyroidism

Primary hyperparathyroidism is common, accounting for 80% to 90% of hypercalcemia in asymptomatic outpatients. Calcium elevation is typically mild (10.5 to 11.5 mg/dL) and often noted only after thiazide therapy for hypertension. Only half of those with hyperparathyroidism have high parathyroid hormone (PTH) levels, and the others have inappropriately “normal” PTH levels with high serum calcium (Adami et al., 2002). The incidence of primary hyperparathyroidism is highest among Blacks, followed by Whites, with lower rates for Asians and Hispanics (Yeh et al., 2013). Consensus guidelines on indications for parathyroid surgery have been published (Bilezikian et al., 2009).

Several recent studies indicate that hyperparathyroidism is a cardiac risk factor. Irrespective of the serum level of 25OHD, increased levels of PTH are associated with higher BP in older patients with isolated systolic hypertension (Mateus-Hamdan et al., 2013). The Parathyroid Epidemiology and Audit Research Study (PEARS), an observational cohort study of 2,097 patients with untreated primary hyperparathyroidism (mean age 68, 70% women), found that serum PTH—not serum calcium—was the best predictor of fatal and nonfatal CVD (Yu et al., 2013). Patients with primary hyperparathyroidism are predisposed not only to hypertension but also to hypertensive heart disease, which regresses after parathyroidectomy (Agarwal et al., 2013).

Aldosterone may link elevated PTH with hypertension. Parathyroidectomy lowers serum aldosterone and improves cardiovascular outcomes (Tomaschitz et al., 2014). PTH induces aldosterone secretion both directly by binding to PTH receptors on adrenal zona glomerulosa and indirectly by potentiating Ang II effects. These effects of PTH on aldosterone and the cardiovascular system may warrant parathyroidectomy, even in the elderly (Oltmann et al., 2013). Among patients with primary aldosteronism, elevated serum PTH levels favor the diagnosis of aldosterone producing adenoma rather than bilateral adrenal hyperplasia and thus may be useful for selecting those patients to be submitted to adrenal vein sampling (Rossi et al., 2012).

Vitamin D Deficiency

Chronic vitamin D deficiency increases levels of PTH and can cause secondary hyperparathyroidism, which may increase cardiovascular risk, especially in patients with chronic kidney disease (CKD) (Lavie et al., 2013). Epidemiologic studies, such as the Copenhagen City Heart Study (Brondum-Jacobsen et al., 2012) and the Whitehall study (Tomson et al., 2013), continue to show that lower levels of plasma 25-hydroxyvitamin D associate with nonfatal and fatal CVD events. However, as discussed in Chapter 3, proper randomized clinical trials (RCTs) show that Vitamin D supplementation has no effect on BP either in patients with difficult hypertension and LVH (Witham et al., 2014) or in older patients with ISH (Witham et al., 2013).

Acromegaly

Acromegaly affects 20% of patients with McCune-Albright Syndrome, which refers to the triad of bone (often skull-based) fibrous dysplasia, cafe-au-lait spots, and hyperfunctioning endocrinopathy (Salenave et al., 2014). In a recent series, the mean age of diagnosis of acromegaly was 24 years of age and a pituitary adenoma was seen in over half (Salenave et al., 2014). Hypertension is found in approximately 35% of patients with acromegaly and is a risk factor for their increased rate of mortality (Dekkers et al., 2008). The hypertension is related to a number of factors: Sodium retention, neurogenic vasoconstriction, endothelial dysfunction, and hypertrophic remodeling of resistance arteries (Rizzoni et al., 2004). LVH and impaired systolic function are usual (Bogazzi et al., 2008). Guidelines for management are available (Melmed et al., 2009). When the condition is controlled, hypertension usually improves (Melmed, 2009).

OBSTRUCTIVE SLEEP APNEA

Obstructive sleep apnea (OSA) has been implicated as the most common form of identifiable hypertension in the United States (U.S.), as BP tracks with OSA in epidemiologic studies and OSA is present in 50% of hypertensive patients (Konecny et al., 2014). Still, clear proof of causality is lacking. One challenge is how to clearly separate an independent effect of OSA from associated problems such as obesity and troubled sleep. Most troubling is that continuous positive airway pressure (CPAP) produces a trivial improvement in BP despite a large improvement in OSA (Montesi et al., 2012).

Clinical Features and Diagnosis

OSA should be considered in patients with the clinical features of increasing obesity, loud snoring, fitful sleep, and daytime sleepiness (Table 14-2). Although OSA is common in patients who are morbidly obese, most afflicted are not “pickwickian.” A 10% increase

TABLE 14-2

Clinical Features of OSA

History

- Snoring^a
- Apnea during sleep
- Arousals or awakenings
- Choking spells
- Nocturnal diaphoresis or enuresis
- Abnormal motor activity during sleep
- Excessive daytime sleepiness^a
- Headaches
- Loss of memory and concentration
- Personality changes, depression
- Angina
- Diminished libido, impotence

Physical Examination

- Hypertension^a
- Overweight, particularly visceral^a

Oral Cavity Abnormalities

- Enlarged tonsils
- Thickened uvula
- Long and redundant soft palate

Cardiovascular Findings

- Increased heart rate variability
- Left ventricular hypertrophy
- Arrhythmias
- Conduction disturbances

^aMost useful in considering diagnosis.

in weight was associated with a sixfold increased risk of developing OSA among subjects initially free of OSA (Peppard et al., 2000b). Virtually all with OSA will snore, but only approximately half of people who snore for more than half the night have sleep apnea (Konecny et al., 2014). The diagnosis can be made by a sleep study at home (Tishler et al., 2003) but with more certainty by overnight polysomnography in a sleep laboratory, with continuous recordings of respiration, electroencephalogram, electromyogram, eye movements, electrocardiogram, O₂ saturation, and BP.

Association with Hypertension

Incidence

Multiple cross-sectional and observational studies have unequivocally shown a higher prevalence and incidence of systemic hypertension in direct proportion to the severity of sleep apnea (Hiestand et al., 2006) (Fig. 14-3). Lavie et al. (2000) found that each apneic event per hour of sleep increased the odds for hypertension by 1%, whereas each 10% decrease in O₂ saturation increased the odds by 13%.

A history of snoring, by itself, has been associated with an increased incidence of hypertension. Among 73,000 U.S. female nurses followed for 8 years, the risk of developing hypertension increased by 29% in

those who snored occasionally and by 55% in those who snored regularly as compared to those who said they did not snore (Hu et al., 1999). The association was independent of age, body mass index, waist circumference, and other lifestyle factors.

The risk of hypertension is greater for younger subjects than for those older than 60 years (Konecny et al., 2014). Moreover, the prevalence of sleep apnea is even higher both in patients with uncontrolled hypertension and in patients with stroke. Typically, patients with OSA have nondipping BP during sleep and accentuated morning surge of BP when monitored by ambulatory BP monitoring (Amin et al., 2008).

Mechanisms of Hypertension

A number of possible mechanisms for persistent hypertension as a consequence of OSA have been proposed (Konecny et al., 2014). These include: increased carotid chemoreceptor drive both night and day driving sympathetic neural activation, vascular inflammation, increased cortisol, increased erythropoietin, arterial stiffness, and, most recently, central fluid shift during nocturnal recumbency. In support of the last mechanism, graded lower body positive pressure—used experimentally to displace venous blood from the lower body to the cardiopulmonary region—triggered a greater degree of upper airway constriction in patients

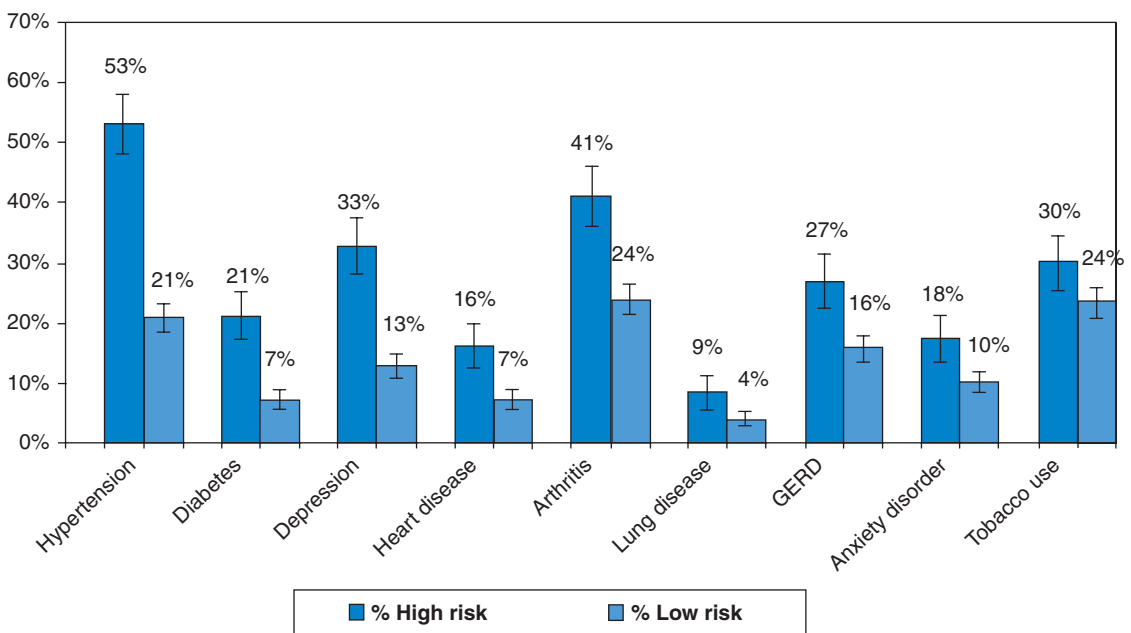


FIGURE 14-3 • Prevalence of chronic illness among individuals with either high or low risk for sleep apnea by the Berlin questionnaire. (Data from Hiestand DM, Britz P, Goldman M, et al. Prevalence of symptoms and risk of sleep apnea in the US population: Results from the national sleep foundation sleep in America 2005. *Chest* 2006;130:780–786.)

with resistant hypertension than in those with well-controlled hypertension (Friedman et al., 2013). Moreover, high serum aldosterone levels with low plasma renin activity have been found in over half of patients with OSA, suggesting that aldosterone contributes to OSA by shifting fluid from the plasma to the extracellular space surrounding the airway (Clark et al., 2012).

Treatment

Weight loss—even as little as 10% of body weight—will help over the long term (Peppard et al., 2000a); avoiding the supine position during sleep may help in the short term (Kuhlmann et al., 2009). However, among a group of 60 obese patients with OSA, the use of bariatric surgery compared with conventional weight loss therapy did not result in a greater reduction in apnea–hypopnea index, despite the much greater weight loss with surgery (Dixon et al., 2012). The best relief is by nasal continuous positive airway pressure (CPAP), but dental appliances (mandibular advancement devices) are better tolerated and gaining popularity. In a recent RCT of 126 patients with moderate–severe OSA, CPAP was more efficacious than the mandibular device in reducing the apnea–hypopnea index but compliance was better with the latter (Phillips et al., 2013). However, in that study, neither approach improved BP by 24-hour ambulatory monitoring. A recent meta-analysis including 1,948 patients in 28 trials has confirmed several older studies showing that CPAP only lowers office BP by approximately 3/2 mm Hg (Montesi et al., 2012).

The conclusion is obvious: Neither CPAP nor dental appliances alone will be sufficient to control hypertension in patients with OSA. Proper RCTs are needed to determine if diuretic-based therapy, perhaps with a combination of an aldosterone blocker and a potent thiazide, would be highly effective therapy both for the OSA and the associated hypertension. In the meantime, weight loss and standard antihypertensive therapy are needed to control BP, while CPAP or a dental appliance is needed to improve the OSA and thus daytime sleepiness. By reducing transthoracic transmural pressure, CPAP may reduce the risk of LVH and atrial fibrillation (less atrial stretch) even if it does little to improve BP (Naughton et al., 1995).

NEUROLOGIC DISORDERS

Beyond stroke, a number of seemingly different disorders of the central and peripheral nervous system may cause hypertension. Many may do so by a common

mechanism involving sympathetic nervous system discharge from the vasomotor centers in response to an increased intracranial pressure. The rise in systemic pressure is necessary to restore cerebral perfusion.

As noted in Chapters 4 and 7, patients with acute stroke may have transient marked elevations in BP. Rarely, episodic hypertension suggestive of a pheochromocytoma may occur after cerebral infarction (Manger, 2008).

Alzheimer Disease

According to the American Heart Association/American Stroke Association (Gorelick et al., 2011),

“Midlife hypertension ranks as an important modifiable risk factor for late-life cognitive decline, mild cognitive impairment, and vascular dementia. In longitudinal cohort studies, higher systolic BP has been associated with greater late-life cognitive decline, although some studies have reported a J- or U-shaped relation. The data on the role of blood pressure and hypertension in later life are not consistent, leaving open the issue of blood pressure treatment in older people.”

The existing RCTs have produced inconsistent results as to whether antihypertensive therapy reduces cognitive decline, which has never been the primary end point. The most compelling data are from the Syst-Eur trial in which the onset of Alzheimer disease was reduced by 50% with calcium channel blocker (CCB)-based therapy versus placebo (Forette et al., 1998). Provocative observational data from the Cardiovascular Heart Study indicate that cognitive decline in older hypertensives is slowed by centrally acting ACEIs that cross the blood–brain barrier such as ramipril, perindopril, and lisinopril but not by other ACEIs that do not cross such as benazepril, enalapril, and quinapril (Sink et al., 2009). Perindopril treatment showed a positive signal for reduced cognitive decline in PROGRESS (Tzourio et al., 2003) but not in the HYVET-COG study (Peters et al., 2008).

Brain Tumors

Intracranial tumors, especially those arising in the posterior fossa, may cause hypertension (Pallini et al., 1995). In some patients, paroxysmal hypertension and other features that suggest catecholamine excess may point mistakenly to the diagnosis of pheochromocytoma. The problem may be confounded by the increased incidence of neuroectodermal tumors, some within the central nervous system, in patients with pheochromocytoma. Unlike patients with a

pheochromocytoma who always have high catechol levels, patients with a brain tumor may have increased catecholamine levels during a paroxysm of hypertension but normal levels at other times (Manger, 2008).

Quadriplegia

Patients with transverse lesions of the cervical spinal cord above the origins of the thoracolumbar sympathetic neurons lose central control of their sympathetic outflow. Stimulation of nerves below the injury, as with bladder or bowel distension, may cause reflex sympathetic activity via the isolated spinal cord, inducing hypertension, sweating, flushing, piloerection, and headache, a syndrome described as *autonomic hyperreflexia*. Such patients have markedly exaggerated pressor responses to various stimuli (Krum et al., 1992). The hypertension may be severe and persistent enough to cause cerebrovascular accidents (CVAs) and death. An α -blocker effectively controlled the syndrome (Chancellor et al., 1994).

Severe Head Injury

Immediately after severe head injury, the BP may rise because of a hyperdynamic state mediated by excessive sympathetic nervous activity (Simard & Bellefleur, 1989). If the hypertension is persistent and severe, a short-acting β -blocker (e.g., esmolol) should be given. Caution is needed in the use of vasodilators such as hydralazine and nitroprusside, which may increase cerebral blood flow and intracranial pressure. Moreover, hypotension is an even greater threat (Fuller et al., 2014). Both high and low prehospital systolic BP (and heart rate) predict mortality after traumatic brain injury (Reisner et al., 2014).

Other Neurologic Disorders

Hypertension may be seen with:

- Guillain-Barré syndrome (Watson et al., 2014)
- Fatal familial insomnia, a prion disease with severe atrophy of the thalamus (Portaluppi et al., 1994)
- Baroreceptor failure (Heusser et al., 2005)
- Autonomic failure with orthostatic hypotension and supine hypertension, often helped by a bedtime ARB (Arnold et al., 2013).
- Parkinson disease, wherein severe postural hypotension and exercise-induced hypotension (Low et al., 2014) may also be accompanied by nocturnal hypertension, indicating the importance of

ambulatory BP monitoring to manage BP in this patient population (Tsukamoto et al., 2013)

FUNCTIONAL SOMATIC DISORDERS

Anxiety and depression are common in the general population and even more prevalent in patients with hypertension or cardiovascular disease (Davies et al., 2004). In the U.S., terrorism is taking its toll. Using health data on a representative national sample collected before 9/11 as a baseline, acute stress response to the terrorist attacks predicted increased reports of physician-diagnosed hypertension and other cardiovascular ailments over 3 years following the attacks (Holman et al., 2008). An anxiety disorder was found in 19.5% of consecutive patients seen in 15 U.S. primary care clinics in 2005 (Kroenke et al., 2007).

Anxious patients are more likely to have white-coat reactions that may persist over many office visits (Pickering & Clemow, 2008). Such patients obviously will be more anxious unless their excessive altering reaction is recognized and their anxiety over their BP relieved.

As common as it is, anxiety and its manifestations are often not recognized as being responsible for a variety of symptoms (Pickering & Clemow, 2008). Because of the common failure to recognize the underlying nature of various functional syndromes (Wessely et al., 1999) (Table 14-3), patients and their physicians often enter into a vicious cycle: More and more testing, often with false-positive results; more and more incorrect “organic” disease diagnoses; more and more ineffective therapy; more and more anxiety; and more and more functional symptoms.

Anxiety-Induced Hyperventilation

The problem is often encountered with hypertensive patients, either because of their concern over having “the silent killer” or because of their poor response to antihypertensive therapies. In 300 consecutive patients referred to me, usually because of hypertension that was difficult to control, 104 had symptoms attributable to anxiety-induced hyperventilation (Kaplan, 1997) (Fig. 14-4). The symptoms and signs of panic attack encompass all these same manifestations but go beyond them to include fears of falling apart, losing control, or even more acute anxiety and are associated with increased reactivity of vasoconstricting sympathetic nerves (Katon, 2006). Among 351 hypertensive patients

TABLE 14-3

Functional Somatic Syndromes by Specialty

Specialty	Syndrome
Gastroenterology	Irritable bowel syndrome, nonulcer dyspepsia
Gynecology	Premenstrual syndrome, chronic pelvic pain
Rheumatology	Fibromyalgia
Cardiology	Atypical or noncardiac chest pain
Respiratory medicine	Hyperventilation syndrome
Infectious diseases	Chronic (postviral) fatigue syndrome
Neurology	Tension headache
Dentistry	Temporomandibular joint dysfunction, atypical facial pain
Ear, nose, and throat	Globus syndrome
Allergy	Multiple chemical sensitivity

Modified from Wessely S, Nimnuan C, Sharpe N. Functional somatic syndromes: One or many? *Lancet* 1999;354:936-939.

randomly selected from one primary care practice in Sheffield, United Kingdom, panic attacks had occurred in 18% during the previous 6 months and in 37% over their lifetime (Davies et al., 1999). The reported diagnosis of hypertension usually antedated the onset of panic attacks. Anxiety and panic attacks were even more

common among their patients who had nonspecific intolerance to multiple antihypertensive drugs (Davies et al., 2003). These patients are extremely difficult to help.

Many of these patients had been subjected to intensive workup for dizziness, headaches, chest pain, fatigue, and the like (Newman-Toker et al., 2008). When the symptoms are reproduced by voluntary overbreathing and relieved by rebreathing into a paper sack, the patient's recognition of the mechanism often provides immediate relief and opens the way to the appropriate use of rebreathing exercises, other cognitive therapy, or, if needed, anti-anxiety medications.

Mechanistic Underpinnings of the Heart/Brain Connection

Depression may not be more common in uncomplicated hypertension (Lenoir et al., 2008). Antidepressants can raise the risk of hypertension (Licht et al., 2009). Hypertension has been linked to anger, with rumination about previous anger-provoking events being both common and a strong predictor of daytime BP and heart rate during ambulatory BP monitoring (Ottaviani et al., 2011).

In patients with panic attacks, brain imaging studies indicate a fundamental down-regulation of the inhibitory neurotransmitters—GABA and serotonin—in patients with panic attacks (Davies et al.,

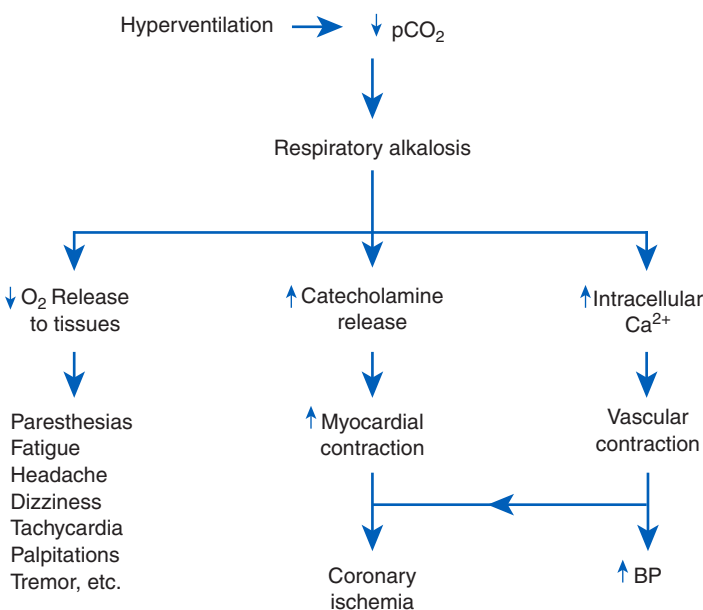


FIGURE 14-4 • The mechanisms by which acute hyperventilation may induce various symptoms, coronary ischemia, and a rise in blood pressure (BP). Ca, calcium; pCO₂, partial pressure of carbon dioxide.

2010). Brain spillover of norepinephrine (NE) is increased and linked to increase NE spillover in the heart and to multiple single unit axon firings per cardiac cycle in muscle sympathetic nerves (Lambert et al., 2011).

ACUTE PHYSICAL STRESS

Hypertension may appear during various acute physical stresses, usually reflecting an intense sympathetic discharge and sometimes the contribution of increased renin–angiotensin from volume contraction.

Surgical Conditions

Perioperative Hypertension

In addition to the reasons mentioned in the coverage of anesthesia and hypertension in Chapter 7, for numerous reasons, hypertension may be a problem during and soon after surgery. Elevated postoperative readings can be related to pain, hypoxia and hypercapnia, and physical and emotional excitement. These causes should be managed rather than treating the elevated BP with antihypertensives.

Marked rises in BP have been measured when pneumoperitoneum is performed for abdominal laparoscopic surgery (Joris et al., 1998). The rise in BP was accompanied by increases in blood catecholamines, cortisol, and vasopressin and was blunted by preoperative clonidine.

Cardiovascular Surgery

Table 14-4 summarizes the causes of hypertension associated with surgery in a temporal fashion (Vuylsteke et al., 2000).

Coronary Bypass

Approximately one-third of patients will have hypertension after coronary artery bypass grafting, usually starting within the first 2 hours after surgery and lasting 4 to 6 hours. Immediate therapy may be important to prevent postoperative heart failure or myocardial infarction. In addition to deepening of anesthesia, various parenteral antihypertensives have been used, including nitroprusside and nitroglycerin (Vuylsteke et al., 2000).

TABLE 14-4

Hypertension Associated with Cardiac Surgery

Preoperative

- Anxiety, angina
- Discontinuation of antihypertensive therapy
- Rebound from β -blockers in patients with coronary artery disease

Intraoperative

- Induction of anesthesia: Tracheal intubation; nasopharyngeal, urethral, or rectal manipulation
- Before cardiopulmonary bypass (during sternotomy and chest retraction)
- Cardiopulmonary bypass
- After cardiopulmonary bypass (during surgery)

Postoperative

- Early (within 2 h)
 - Obvious cause: Hypoxia, hypercapnia, ventilatory difficulties, hypothermia, shivering, arousal from anesthesia
 - With no obvious cause: After myocardial revascularization; less frequently after valve replacement; after resection of aortic coarctation
- Late (weeks to months)
 - After aortic valve replacement by homografts

Modified from Estafanous FG, Tarazi RC. Systemic arterial hypertension associated with cardiac surgery. *Am J Cardiol* 1980;46:685–694.

Other Cardiac Surgery

Hypertension has been reported, although less frequently, after other cardiac surgery. Virtually all patients who undergo orthotopic heart transplantation develop hypertension (Taegtmeyer et al., 2004) and lose the usual nocturnal fall in BP, likely from a combination of effects, including the effects of immunosuppressive agents (see the section on Immunosuppressive Agents, later in this chapter), impaired low-pressure baroreceptor control from cardiac (afferent) denervation (Scherrer et al., 1990), and the inability to excrete sodium normally (Hoorn et al., 2011). The hypertension may be controlled by combination therapy with an ACEI and a DHP-CCB, with monotherapy of each effective in half of patients (Rockx & Haddad, 2007) and, if needed, a thiazide (to counter inhibition of the thiazide-sensitive Na–Cl transporter by the calcineurin inhibitors), and a central sympatholytic (to counter the sympathetic neural activation).

Carotid Endarterectomy

Postoperative hypertension may be particularly serious in patients with cerebrovascular disease who have carotid endarterectomy (Demirel et al., 2012a), because of altered carotid baroreceptor activity (Demirel et al., 2012b). The acute neurogenic hypertension is worse with eversion carotid endarterectomy, which requires the surgeon to transect the carotid sinus nerve than with the conventional longitudinal incision (Demirel et al., 2012a). Perioperative control of hypertension is important because severe postoperative hypertension can lead to cerebral hyperperfusion syndrome, which is a form of hypertensive encephalopathy often leading to cerebral hemorrhage with a mortality rate of 67% (Stoneham & Thompson, 2009). With unilateral carotid disease, the hypertension typically is self-limited. Short-term BP management most logically should be with labetalol (α,β -blocker) rather than with a vasodilator such as nitroprusside or nifedipine that would further increase cerebral blood flow.

INCREASED INTRAVASCULAR VOLUME

If vascular volume is raised a significant degree over a short period, the renal natriuretic response may not be able to excrete the excess volume, particularly if renal function is also impaired. Cell-free, hemoglobin-based oxygen carriers (HBOCs) cause hypertension by vasoconstriction secondary to scavenging of nitric oxide (NO). Both inhaled NO and intravenous sodium nitrite given before the infusion of HBOC prevent subsequent hypertension in mice and lambs (Yu et al., 2008). The same benefit is seen with direct soluble guanylate cyclase (sGC) activators in rats (Raaf et al., 2013). Clinical trials are needed.

Erythropoietin Therapy

Correcting anemia with erythropoietin (EPO) administration in patients with advanced CKD can exacerbate hypertension. As the hematocrit rises, so do blood viscosity and BP. The mechanism may be more complicated than simply increasing viscosity as EPO may stimulate production of both endothelin and reactive oxygen species (Rancourt et al., 2010). Nearly one-third of patients developed clinically important hypertension (Luft, 2000). This may add to

the currently recognized danger of treating the anemia of chronic renal disease (Vaziri & Zhou, 2009), leading to a recent modest decrease in EPO use (Winkelmayer et al., 2014).

Polycythemia and Hyperviscosity

Patients with primary polycythemia are often hypertensive, and some hypertensives have a relative polycythemia that may resolve when the BP is lowered. The hypertension seen in polycythemic states could also reflect increased blood viscosity. Significant falls in BP were seen in 12 hypertensive patients with polycythemia when blood viscosity was reduced without changing the blood volume (Bertinieri et al., 1998).

CHEMICAL AGENTS THAT CAUSE HYPERTENSION

Table 14-5 lists various chemical agents that may cause hypertension, indicating their mechanism if known. Some of these substances, such as sodium-containing antacids, alcohol, insulin, licorice, oral contraceptives, and monoamine oxidase inhibitors, are covered elsewhere in this book because of their frequency or special features.

Caffeine and Coffee

Caffeine is likely the most widely consumed drug in the world, and its use will almost certainly increase with the amazing proliferation of Starbucks and its clones. Coffee consumption causes an acute increase in BP lasting about 3 hours (Mesas et al., 2011) due to central sympathetic activation and vascular adenosine receptor blockade (Vlachopoulos et al., 2007). Although tolerance to this pressor effect has been widely assumed, such tolerance was found in only half of regular consumers (Lovallo et al., 2004). However, habitual coffee intake was not associated with an increased incidence of hypertension in two separate meta-analyses (Mesas et al., 2011; Steffen et al., 2012).

Thus, the effects of caffeine on hypertension may, over the long term, be neutral but, at least acutely, a pressor effect may be noted. Perhaps the wisest course is to order an ambulatory BP monitor or simply have patients check their home BPs before and within an hour after drinking their coffee, tea, or caffeinated soft drink. Those who experience a large pressor effect

TABLE 14-5

Hypertension Induced by Chemical Agents

Mechanism	Examples
Expansion of Fluid Volume	
Increased sodium intake	Antacids; processed foods (Chapter 6)
Mineralocorticoid effects	Licorice (Chapter 13); cortisone (Chapter 14); anabolic steroids (Owens et al., 1998)
Stimulation of renin–angiotensin	Estrogens (oral contraceptives; Chapter 11)
Inhibition of prostaglandins	NSAIDs (Solomon et al. 2008)
Stimulation of Sympathetic Nervous Activity	
Sympathomimetic agents	Caffeine (Lovallo et al., 2004); cocaine (Tuncel et al., 2002); ephedrine (Bent, 2008); methylenedioxymethamphetamine (MDMA, “ecstasy”) (Lester et al., 2000); methylphenidate (Ritalin) (Ballard et al., 1976); nicotine (Halimi et al., 2002); phencyclidine (Sernulan) (Eastman & Cohen, 1975); phenylpropranolamine (Kernan et al., 2000)
Interactions with monoamine oxidase inhibitors	Foods with high tyramine content (e.g., red wines, aged cheese) (Liu & Rustgi, 1987)
Anesthetics	Ketamine (Broughton Pipkin & Waldron, 1983)
Ergot alkaloids	Ergotamine (Joyce & Gubbay, 1986)
Dopamine receptor agonist	Bromocriptine (Bakht et al., 1990)
Antidopaminergic	Metoclopramide (Roche et al., 1985)
Sandostatin analogue	Sandostatin LAR (Pop-Busui et al., 2000)
Interference with Antihypertensive Drugs	
Inhibition of prostaglandin synthesis	NSAIDs (Izhar, 2004)
Inhibition of neuronal uptake	Tricyclic antidepressants (Walsh et al., 1992); sibutramine (Bray, 2002)
Paradoxical Response to Antihypertensive Drugs	
Withdrawal, followed by ↑ catechols	Clonidine (Metz et al., 1987)
Unopposed α -adrenergic vasoconstriction	β -Blockers (Druyer et al., 1976)
Intrinsic sympathomimetic activity	Pindolol (Collins & King, 1972)
Combination of α - and β -blocker	Propranolol plus clonidine (Warren et al., 1979)
Unknown Mechanisms	
Heavy metal poisoning	Lead (Nash et al., 2003); mercury (Velzeboer et al., 1997); thallium (Bank et al., 1972)
Chemicals	Carbon disulfide (Egeland et al., 1992); arsenic (Rahman et al., 1999); methyl chloride (Scharnweber et al., 1974); polychlorinated biphenyl (Kreiss et al., 1981)
Insecticides	Parathion (Tsachalinas et al., 1971)
Insect bites	Spider (Weitzman et al., 1977); scorpion (Gueron & Yaron, 1970)
Diagnostic agents	Indigo carmine (Merguet et al., 1974); pentagastrin (Merguet et al., 1974)
Therapeutic agents	Thyrotropin-releasing hormone (Rosenthal et al., 1987)
	Cyclosporine (Zhang & Victor, 2000); clozapine (Henderson et al., 2004); disulfiram (Volicer & Nelson, 1984); erythropoietin (Luft, 2000); herbal remedies (De Smet, 2002); indinavir (Cattelan et al., 2000); lithium (Michaeli et al., 1984)
Alcohol	Alcohol (Sierksma et al., 2004)

Adapted from Grossman E, Messerli FH. High blood pressure: Aside effect of drugs, poisons, and food. *Arch Intern Med* 1995;155:450–460.

should be advised to reduce or stop their caffeine consumption, particularly if does not habituate.

Nicotine and Smoking

Among U.S. adults, currently an astounding 32% use one or more tobacco products (Lee et al., 2014). While cigarette smoking rates have stabilized or declined recently in the U.S., both cigar and Hookah (water pipe) smoking are increasing at alarming rates (Lee et al., 2014). Among a representative survey of 3 billion people in 16 low or middle income countries conducted between 2008 and 2010, 49% of men and 11% of women smoked a tobacco product (Giovino et al., 2012). Clearly, the world public health community is waging an uphill battle against *Big Tobacco*.

The next big epidemic is electronic cigarettes, or e-cigarettes, which deliver nicotine but replace combustible smoke with steam (Fairchild et al., 2014). Thus e-cigarettes represent harm reduction rather than abstinence. However, in a randomized trial of 657 cigarette smokers, after 6 months, verified smoking abstinence was only 7% with nicotine e-cigarettes, 6% with nicotine patches, and 4% with nicotine-free placebo e-cigarettes (Bullen et al., 2013). If they are not very effective smoking tobacco aids, could e-cigarettes backfire by encouraging dual cigarette habits or even serve as a bridge to traditional cigarette smoking (Fiore et al., 2014)?

As described in Chapters 3 and 6, even in chronic smokers, each cigarette induces a pressor response (Mahmud & Feely, 2003). Whereas the peripheral BP returns to near baseline within 15 minutes, pressure within the aorta remains higher. Moreover, the indices of large artery stiffness start higher in the chronic smokers and remain higher than in the nonsmokers. These hemodynamic consequences of smoking have been underestimated for two reasons: First, in the smoke-free environment where patients are seen, the BP is usually measured well after the acute effects are over; second, the arm (peripheral) BP is usually deceptively lower in chronic smokers who have reduced aortic-brachial pressure amplification (Mahmud & Feely, 2003). A similar acute increase of larger artery stiffness has been seen with cigar smoking (Vlachopoulos et al., 2004).

Data on prevalence of persistent hypertension among smokers have not been consistent: Most find them to have higher BP recorded by ambulatory monitoring while they continue to smoke (Oncken et al., 2001), but if the BP is taken while subjects are not smoking, little more hypertension is seen (Halimi et al., 2002).

When chronic smokers quit smoking, their BPs tend to rise in large part because of weight gain (Halimi et al., 2002). On the other hand, the data are much clearer that both active cigarette smoking (Hänninen et al., 2014) and passive second-hand smoke (Seki et al., 2010) are a major cause of masked hypertension. Hookah smoking has been identified as a risk factor for hypertension and metabolic syndrome in a Middle Eastern population, where this practice has been endemic for centuries (Shafique et al., 2012).

Smoking has been found to have a profoundly deleterious effect on renal function (Orth & Ritz, 2002), and on cognitive function (Sabia et al., 2008). Moreover, the 2,983 smokers enrolled in the massive Hypertension Optimal Treatment (HOT) trial were the only subgroup to experience an *increased* risk of major cardiovascular events when given more intensive therapy to achieve a lower BP (Zanchetti et al., 2003). As the authors note, these data “strengthen the need for concerted efforts to persuade patients to quit smoking.” This potentially important finding is yet to be confirmed in an independent study. For the majority of patients who do not quit, the general goal of antihypertensive therapy is less than 135/85 mm Hg for their home BP—which will be higher than their BP in the smoke-free physician's office.

Alcohol

Alcohol is a two-edged sword: In excess, it is a major cause of social disorder, trauma, and death; in moderation (one drink per day for women, two for men), it is a protector against heart attack, stroke, diabetes, and heart failure (O'Keefe et al., 2014). Part of its diverse roles involves hypertension: In excess, alcohol raises the BP; in moderation, it may be protective against the development of hypertension (see also Chapters 3 and 6).

The Relation to Hypertension

When consumed in amounts equivalent to three usual portions—a usual portion being 12 oz of beer, 4 oz of wine, or 1.5 oz of whiskey which all contain about 12 g of ethanol—alcohol causes an immediate depressor effect and subsequently a pressor action (Rosito et al., 1999). These changes are reflected in the measurements of arterial stiffness by pulse wave velocity (Sasaki et al., 2013).

In large population studies, the incidence of hypertension is increased among those who drink

more than three drinks per day (Ohira et al., 2009), either in a linear dose–response relationship or with a threshold wherein smaller quantities are associated with a modest decrease (O’Keefe et al., 2014). The cessation of heavy drinking is usually followed by significant falls in BP (Ohira et al., 2009). The mechanism for the pressor effect of large quantities of ethanol is not well defined but may involve central activation of the sympathetic nervous system and release of corticotropin-releasing hormone (Randin et al., 1995).

Relation to Other Diseases

Light to moderate consumption, i.e., less than three drinks per day, has been shown to provide multiple significant benefits as detailed in Chapter 3.

This litany of benefits must be balanced by the potential for encouragement of alcohol abuse and a high prevalence of excessive drinking among the elderly (O’Connell et al., 2003). Among 553 elderly subjects (mean age 71), heavy drinking was associated with higher diastolic BP by 24 hour ambulatory BP monitoring while light drinking was associated with reduced daytime BP variability (Jaubert et al., 2014).

Gout is more common among even light drinkers (Choi et al., 2004). Light to moderate alcohol consumption of three to six drinks per week was found to cause a small increase in the risk of breast cancer in the Nurses’ Health Study (Chen et al., 2011) and a recent review of the literature (Scocciati et al., 2014). Moreover, as described in Chapter 3, a genetic mutation may cause some people to be bothered by even small amounts of alcohol (Tseng et al., 2008).

We have no hesitation in allowing hypertensives to drink in moderation, but others do not believe that drinking any amount of alcohol should be recommended by physicians (O’Keefe et al., 2014).

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) are well known to raise BP, blunt the antihypertensive effect of some antihypertensive agents, and increase the risk of MI and stroke (Patrono & Baigent, 2014). This interference likely reflects an inhibition of prostaglandin-dependent counterregulatory mechanisms in the kidney that have been invoked by the antihypertensive drugs and possibly reduction in endothelial nitric oxide synthase. Reduced generation of NO and inhibition of cyclooxygenase enzymes may

induce renal sodium retention and thereby increase the BP and precipitate hypertension, increasing the risk of stroke (Patrono & Baigent, 2014).

A cohort study of 5,710 hypertensive subjects in the French health insurance system found that ACEIs and ARBs were the only classes of drugs requiring intensification of antihypertensive therapy after the addition of a non-steroidal anti-inflammatory drug (NSAID) (Fournier et al., 2012). Moreover, a recent case–control study of the UK Clinical Practice Research Database found that the addition of a NSAID to combination therapy with ACEI or ARB plus a diuretic is associated with a 31% increase in the risk of acute kidney injury, 82% within the 1st month of therapy (Lapi et al., 2013).

The American College of Rheumatology recommends that acetaminophen should be initial therapy for osteoarthritis (Hochberg et al., 2012). If 4,000 mg/day does not provide symptomatic relief, oral NSAIDs are recommended except for patients aged 75 years or older in whom topical rather than systemic NSAIDs are recommended. A recent systematic review found conflicting and inconclusive evidence as to whether acetaminophen increases BP in patients with or without hypertension (Turtle et al., 2013). Clearly, the risk of increased BP and associated CV events is lowest with acetaminophen and low-dose aspirin (81 mg daily), intermediate with non-COX-2-selective NSAIDs including high-dose aspirin, and highest with COX-2-selective NSAIDs (Antman et al., 2007).

Immunosuppressive Agents

The introduction of the calcineurin inhibitor cyclosporine in 1983 greatly improved the long-term survival after organ transplantation. However, major complications soon became obvious, including nephrotoxicity and hypertension. Similar troubles accompanied the use of another calcineurin inhibitor, tacrolimus. More recently, inhibitors of the mammalian target of rapamycin (mTOR), sirolimus and everolimus, have been introduced with less hypertension and nephrotoxicity but with other serious toxicities (thrombocytopenia, gingival hyperplasia, oral ulceration) (Mourer et al., 2013; Uhlmann et al., 2012).

Heart transplantation is followed by even more hypertension than is renal transplantation. It is seen in about half of recipients and ascribed both to the heavier immunosuppressive regimen usually needed (Roche et al., 2008) and to deafferentation of the donor heart with loss of cardiac vagal afferent restraint

on calcineurin inhibitor–mediated sympathetic activation (Scherrer et al., 1990).

Besides rodent models (Zhang & Victor, 2000), the strongest case for a neurogenic component to clinical cyclosporine/tacrolimus-induced hypertension is hypertensive crisis with cerebral edema and seizures caused by acute overdose, especially iatrogenic overdose during intravenous therapy in pediatric patients (Ceschi et al., 2013). Medical personnel need to be particularly careful measuring noncapsule drug formulations to avoid such potentially fatal errors. Phenytoin or phenobarbital are used to treat the seizures and to enhance calcineurin inhibitor metabolism by induction of CYP3A.

Treatment

The pathogenesis of chronic calcineurin inhibitor–mediated hypertension is multifactorial, and treatment is largely empiric; neural, hormonal, vascular, and renal mechanisms all have been implicated (Hoorn et al., 2012). While DHP-CCBs, central sympatholytics, and ACEIs or ARBs are reasonable, thiazides should be part of the multidrug regimen because recent evidence suggests that tacrolimus activates the thiazide-sensitive renal sodium chloride cotransporter to cause hypertension both in mice and in human renal transplant recipients (Hoorn et al., 2011).

Chemotherapy

As the number, variety, and effectiveness of cancer chemotherapeutic agents increase, long-term cancer survivors are experiencing higher rates of mortality from cardiovascular disease than from recurrent cancer (Steingart et al., 2013). Hypertension has surfaced as the most common comorbid condition that directly shortens the survival and is most common with agents that disrupt angiogenesis by inhibition of vascular endothelial growth factor (VEGF): both anti-VEGF monoclonal antibodies such as bevacizumab and VEGF receptor inhibitors such as sorafenib, sunitinib, and pazopanib (Milan et al., 2014).

In the absence of RCT data, amlodipine has been recommended based on the theory that this is NO-deficient hypertension, but the key issue is to achieve adequate control of hypertension with standard antihypertensive therapy (Mancia et al., 2013). Diltiazem and verapamil should be avoided when using sunitinib and sorafenib because the non-DHP CCBs are potent CYP3A4 inhibitors that will impair anti-VEGF drug metabolism (Milan et al., 2014).

Dietary Supplements

Previously marketed as weight-loss aids and energy boosters, ephedra-containing supplements were removed from the market by the FDA in 2004, because they were linked to heart attacks, strokes, seizures, and psychosis (Bent, 2008). However, ephedra-free dietary supplements such as Zantrex 3, Xenadrine EFX, Metabolift, and Guarana contain large amounts of caffeine and other sympathomimetics that can still cause trouble: With daily use, they increase BP (by 10/5 mm Hg on average) and heart rate and may trigger supraventricular and even ventricular tachycardia (Foster et al., 2013). Although hypertensive patients are often advised to avoid cold remedies containing pseudoephedrine (an α -adrenergic agonist), a meta-analysis shows a trivial effect on BP in adequately treated hypertensives (Salerno et al., 2005a). More pronounced effects may be seen with phenylpropanolamine, which is used for nasal congestion and obesity (Salerno et al., 2005b). However, these α -adrenergic agonists, when swallowed with a glass of water, can trigger huge increases in BP with hypertensive crisis in patients with hypoadrenergic orthostatic hypotension, whose blood vessels have denervation supersensitivity, and in patients with baroreflex failure (Jordan et al., 2004). Perhaps the safest way to prevent these various interactions is to advise hypertensives to avoid all over-the-counter drugs and herbal remedies.

Drugs of Abuse

Marijuana, or δ -9-tetrahydrocannabinol, seems to activate the human sympathetic nervous system, causing a brisk sinus tachycardia and a small increase in seated BP but can rarely cause orthostatic hypotension (Malinowska et al., 2012). Marijuana has been linked to a small but statistically significant increased risk of atrial and ventricular tachyarrhythmia, stroke, and myocardial infarction and increased mortality with these events (Singh et al., 2012). There are no trials investigating effects of the antiobesity cannabinoid type 1 receptor antagonist rimonabant (which has been removed from the market for causing suicidal depression) in hypertensive patients (Siebenhofer et al., 2013).

Cocaine (Kontak et al., 2013) and amphetamines (Rush et al., 2011) activate the sympathetic nervous system and can trigger acute hypertension, stroke, and acute coronary syndrome. Even a small dose of intranasal

cocaine—one-half the conventional dose used for local anesthesia during nasal procedures—triggers acute constriction of human coronary microvessels and decreased myocardial perfusion despite increased BP and heart rate causing increased myocardial oxygen demands (Gurudevan et al., 2013). Based on weak evidence, benzodiazepines and nitrates are recommended as first-line treatment for cocaine-induced acute hypertension and chest pain with labetalol being second-line therapy (McCord et al., 2008). Dexmedetomidine, an intravenous central sympatholytic, could prove helpful as add-on therapy but only at low nonsedating doses as higher doses can cause a paradoxical increase in BP; RCTs are needed (Kontak et al., 2013).

The next chapter addresses hypertension in women who are pregnant or taking estrogen.

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Hypertension with Pregnancy and the Pill

Hypertension occurs in approximately 10% of first pregnancies and 8% of all pregnancies. Preeclampsia (PE), defined as new onset of hypertension with proteinuria after 20 weeks' gestation, is a leading cause of maternal and neonatal mortality worldwide (Abalos et al., 2013). Though maternal mortality from PE has fallen in developed countries, it remains a common cause of preterm delivery of low birth weight babies from intrauterine growth retardation (Sibai, 2008a). As noted later in this chapter and in Chapter 3, when such babies become adults, they have an increased risk of hypertension and cardiovascular disease as well as an increased likelihood of PE in their own pregnancies (Collen et al., 2013). Moreover, the rate of PE is increasing, likely from increasing maternal age and more multiple births (Wallis et al., 2008) while the number of hospitalizations for stroke in the United States (U.S.) among postpartum women has increased (Kuklina et al., 2011).

Special attention will be directed at maternal obesity, which increases the risk for hypertension during pregnancy (Macdonald-Wallis et al., 2013) with resultant increases in large babies and cesarean delivery. Moreover, maternal obesity marks the baby with an increased risk for obesity, hypertension, and premature cardiovascular disease (Gademan et al., 2013; Reynolds et al., 2013).

Hypertension is seen more often in users of oral contraceptives (OCs), although the absolute risk is small (Lidegaard et al., 2012). Although the causes of neither pregnancy-related nor pill-induced hypertension are completely known, if these forms of hypertension are recognized early and handled appropriately, the morbidity and mortality they cause can hopefully be diminished.

TYPES OF HYPERTENSION DURING PREGNANCY

Classification

The classification provided in the 2000 report of the National HBPEP Working Group (2000) is as follows:

- **Chronic hypertension:** Hypertension, defined as a blood pressure (BP) in excess of 140 mm Hg systolic or 90 mm Hg diastolic present before pregnancy or diagnosed before the 20th week of gestation or that persists beyond 6 weeks' postpartum.
- **Gestational hypertension (GH):** Hypertension detected for the first time after the 20th week of gestation, without proteinuria. Some will develop PE; if not, and the BP returns to normal postpartum, the diagnosis of *transient hypertension of pregnancy* can be assigned; if the BP remains elevated postpartum, the diagnosis is *chronic hypertension*.
- **Preeclampsia (PE):** Hypertension detected for the first time after the 20th week of gestation (or earlier with trophoblastic diseases) with proteinuria of at least 300 mg in a 24-hour specimen (Kayatas et al., 2013).
- **Eclampsia:** PE with seizures that cannot be attributed to other causes. Seizures may appear 2 or more days after delivery (Fong et al., 2013).
- **PE superimposed on chronic hypertension:** In a prospective study of 822 women with chronic hypertension, 22% developed PE (Chappell et al., 2008).

The correct diagnosis may not become apparent until 12 weeks postpartum (Garovic, 2012) (Fig. 15-1).

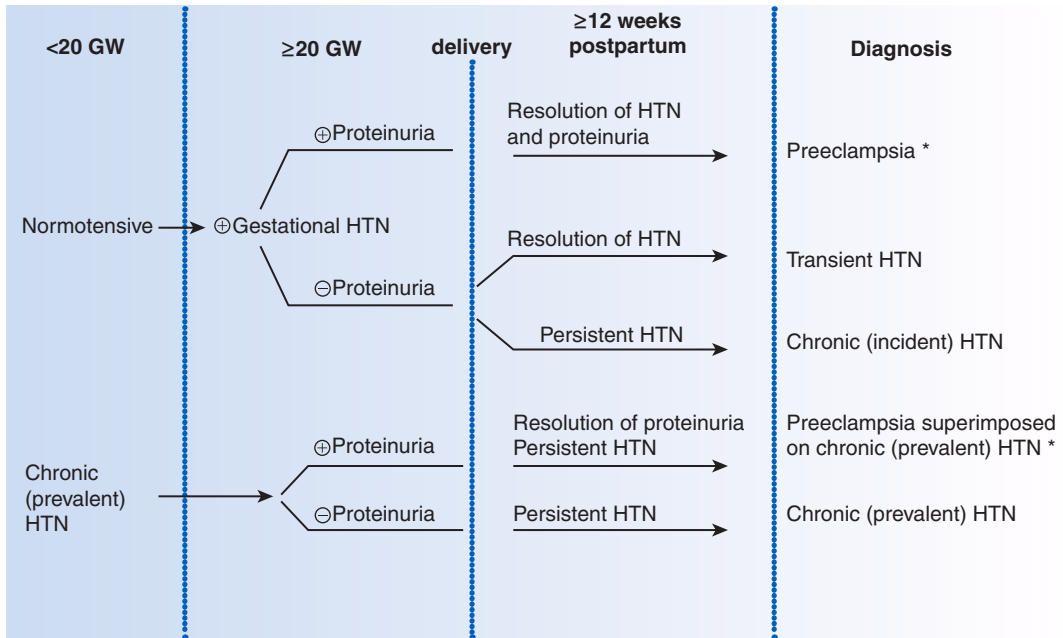


FIGURE 15-1 • Hypertensive pregnancy disorders: classification and diagnostic criteria. (From Garovic VD. The role of angiogenic factors in the prediction and diagnosis of preeclampsia superimposed on chronic hypertension. *Hypertension* 2012;59:555–557.)

BLOOD PRESSURE MONITORING DURING PREGNANCY

Office Readings

The vagaries of office BP readings, noted in Chapter 2, obviously are in play during pregnancy. However, errors in BP measurement have even more immediate importance, possibly leading to overtreatment of some incorrectly diagnosed as hypertensive, but even more harm in those with elevated pressures that presage PE who are not recognized.

The various guidelines described in Chapter 2 should be followed in measuring the BP during pregnancy. Initially, BP should be taken in both arms since a difference of 10 mm Hg or more was found in 8.3% of pregnant women (Poon et al., 2008). The arm with the higher reading should be used.

In a meta-analysis of 34 studies involving 60,599 women, Cnossen et al. (2008) found that the most accurate predictor of PE in those considered to be at low risk was a mean BP of 90 mm Hg, or higher, during either the first or second trimester. For women considered to be at high risk, the best predictor was a diastolic BP of 75 mm Hg, or higher, during weeks 13 to 20 of gestation.

Home Readings

In their review of BP measurements during pregnancy, Chancellor and Thorp (2008) conclude

that pregnant women might benefit from bypassing clinic assessment and its inherent inaccuracies. Home blood pressure recording devices are inexpensive and overcome some of the problems in the clinic setting. In our experience, women are likely to take the time and energy to standardize the environment and follow protocols consistently. Armed with these data, they will be able to provide their clinicians with more accurate information about their trends in blood pressure across pregnancy.

Until home BP monitoring becomes more widely used, most women will be monitored by occasional readings in the office. The definitions given earlier in this chapter are based on office readings, with the caveat that unless the woman is in serious trouble, repeated readings be taken before diagnosing any form of hypertension.

Ambulatory Monitoring

In normal pregnancy, lower pressures are found in the midportion, with rises to nonpregnant levels near term (Macdonald-Wallis et al., 2012) (Fig. 15-2).

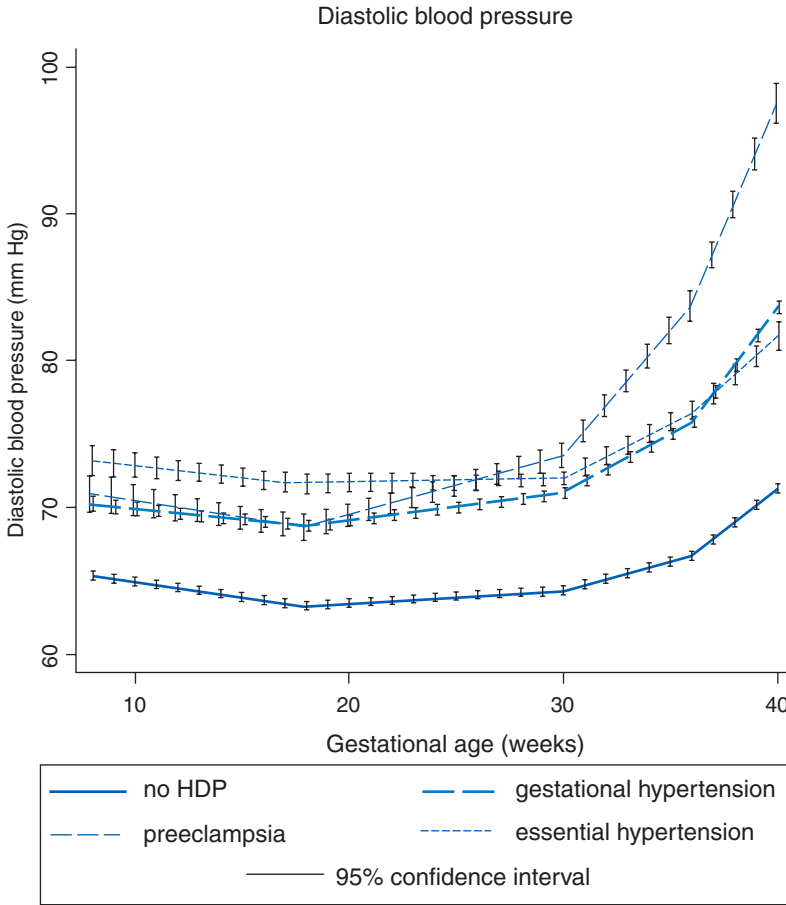


FIGURE 15-2 • Average trajectories of diastolic blood pressures by hypertensive disorders of pregnancy in the unadjusted joint model (N = 13,016). (From Macdonald-Wallis C, Lawlor DA, Fraser A, et al. Blood pressure change in normotensive, gestational hypertensive, preeclamptic, and essential hypertensive pregnancies. *Hypertension* 2012;59:1241–1248.)

The data in Figure 15-2 are from repeated (mean of 14) office readings on 13,016 women followed throughout pregnancy. A longitudinal, prospective study in 403 women who started with normal casual BP during the first trimester and who had repeated ABPM recordings made every 4 weeks found a highly significant higher level of both daytime and sleep BPs was noted *during the first trimester* in the 128 women who later developed GH and the 40 who later developed PE, in comparison to the 235 who remained normotensive (Hermida et al., 2004). These data suggest that ABPM may provide the best tool now available for the early identification of women who are predisposed to GH or PE. Moreover, those who developed PE had a greater blunting of the nighttime dipping of BP during the third trimester as compared to those who only had GH, so the procedure may provide additional warning of the impending development of PE (Ayala & Hermida, 2013).

Pulse Wave Analysis

As described in Chapters 2 and 3, pulse wave analysis is being used increasingly as a noninvasive way to measure arterial compliance and central BP. Unfortunately, the procedure did not prognosticate the development of PE better than brachial blood pressure readings and a maternal risk factor profile (Carty et al., 2013).

CIRCULATORY CHANGES IN NORMAL PREGNANCY

Serial measurements begun before conception have portrayed the evolution of the profound changes of normal pregnancy that are apparent as early as 6 to 7 weeks (Mahendru et al., 2012). In 10 women, 9 nulliparous, who were studied before and repeatedly during pregnancy, significant decreases in systemic vascular resistance resulted in a fall in BP, despite

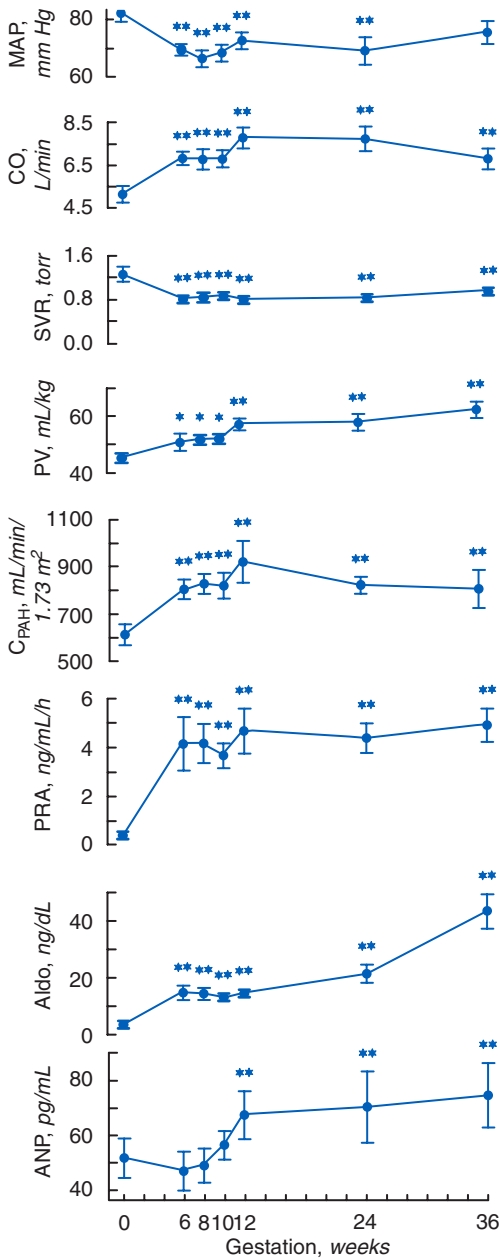


FIGURE 15-3 • Changes in mean arterial pressure (MAP), cardiac output (CO), systemic vascular resistance (SVR), plasma volume (PV), effective renal plasma flow measured by para-aminohippurate clearance (C_{PAH+}), plasma renin activity (PRA), plasma aldosterone (Aldo), and atrial natriuretic peptide (ANP) in 10 women studied in the midfollicular phase of the menstrual cycles and at weeks 6, 8, 10, 12, 24, and 36 of gestation. $p < 0.05$; $**p < 0.01$. (Adapted from Chapman AB, Abraham WT, Zamudio S, et al. Temporal relationships between hormonal and hemodynamic changes in early human pregnancy. *Kidney Int* 1998;54:2056–2063.)

an increase in cardiac output (CO), even before placentation (Chapman et al., 1998) (Fig. 15-3). As the authors note, “Therefore, it is likely that maternal factors, possibly related to changes in ovarian function or extended function of the corpora lutea, are responsible for the initial peripheral vasodilation found in human pregnancy” (Chapman et al., 1998).

The progressive rises in plasma and blood volume are likely adaptations, via renal sodium retention, to the vasodilation and fall in BP. The low pressure and underfilled circulation provoke an increase in renin secretion (Watanabe et al., 2012) and, secondarily, a rise in aldosterone levels aided by stimulation from vascular endothelial growth factor (VEGF) (Gennari-Moser et al., 2013). The somewhat later rise in plasma atrial natriuretic peptide is evidence that, despite the increased blood volume, the central circulation is not overexpanded. As a consequence of renal vasodilation, renal plasma flow and glomerular filtration increase and renal vascular resistance decreases.

At the same time as various forces raise levels of renin–angiotensin–aldosterone, normal pregnancy brings forth numerous mechanisms including nitric oxide, carbon monoxide, and hydrogen sulfide (Holwerda et al., 2013) to protect the circulations of both mother and fetus from the intense vasoconstriction, volume retention, and potassium wastage that high angiotensin II and aldosterone levels would ordinarily engender (Gennari-Moser et al., 2014).

The large amounts of potent mineralocorticoids would be expected to increase sodium reabsorption at the cost of progressive renal wastage of potassium, yet pregnant women are normokalemic, likely the result of the high level of progesterone, which acts as an aldosterone antagonist (Brown et al., 1986).

Rang et al. (2008) showed that normal pregnancy is a low BP state associated with marked vasodilation that reduces peripheral resistance, along with an expanded fluid volume that increases CO. Renal blood flow is markedly increased, and the renin–aldosterone system is activated but with blunted effects. C-type natriuretic peptide levels remain low in normal pregnancies (Reid et al., 2014).

PRECLAMPSIA

Most PE becomes manifest near the end of pregnancy with few severe fetal or maternal complications. In a smaller percentage, 10% to 30%, PE becomes manifest

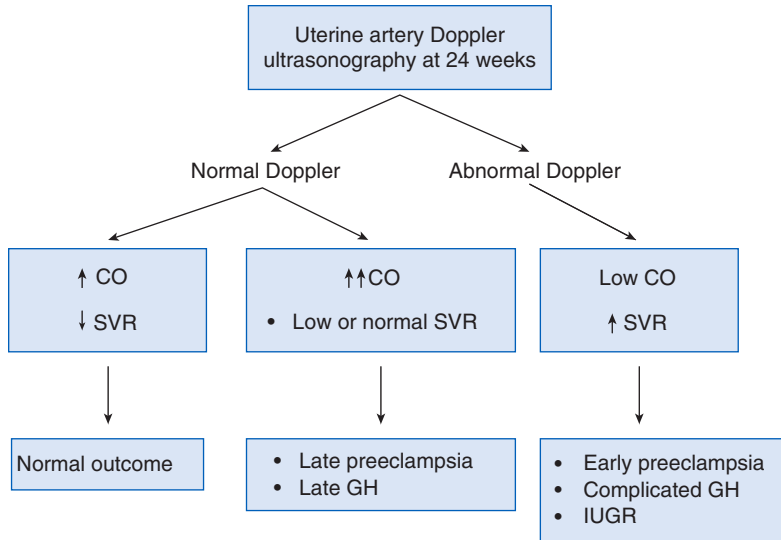


FIGURE 15-4 • Uteroplacental and maternal hemodynamics at 24 weeks and subsequent pregnancy outcome. CO, cardiac output; SVR, systemic vascular resistance; GH, gestational hypertension; IUGR, intrauterine growth restriction. (Modified from Valensise H, Vasapollo B, Gagliardi G, et al. Early and late preeclampsia: Two different maternal hemodynamic states in the latent phase of the disease. *Hypertension* 2008;52:873–880.)

earlier, before the 34th week, with frequent intrauterine growth restriction (IUGR) and more maternal complications (Sibai, 2008b). Valensise et al. (2008) characterized the maternal hemodynamics of 75 women with early PE and 32 with late PE, all initially studied by uterine artery Doppler ultrasonography at 24 weeks' gestation. Figure 15-4 summarizes their findings that have also been observed by other investigators (Khaw et al., 2008; Mei et al., 2008; Rang et al., 2008).

From these studies, Valensise et al. (2008) conclude that “early PE is placental mediated, linked to defective trophoblast invasion with a high percentage of altered uterine artery Doppler.”

Problems in Diagnosing Preeclampsia

There are problems inherent in diagnosing a syndrome of unknown cause on the basis of only highly nonspecific signs. For example, the BP in normal pregnancy usually falls during the first and middle trimesters, only to return toward the prepregnant level during the third trimester. Because women with chronic hypertension have an even greater fall early on, their subsequent rise in later pregnancy may give the appearance of the onset of PE. In addition, those with chronic hypertension may have previously unrecognized proteinuria: If seen only after midterm, the diagnosis of PE looks even more certain.

The distinction between chronic hypertension and PE is of more than academic interest: In the former,

hypertension is the major problem, whereas “preeclampsia is more than hypertension; it is a systemic syndrome and several of its ‘nonhypertensive’ complications can be life threatening even when blood pressure elevations are quite mild” (National HBPEP Working Group, 2000). The management of the hypertension and the pregnancy, as well as the prognosis for future pregnancies, varies with the diagnosis. The bottom line, however, is clear: When in doubt, diagnose PE and institute its treatment, because even mild PE may rapidly progress. If PE is correctly diagnosed and managed, the risks to both mother and baby can be largely overcome (Lindheimer et al., 2009).

Obviously, women should be evaluated before conception. If hypertensive, therapy should be revised to exclude ACEIs, ARBs, or direct renin inhibitors. If renal disease is present, more careful observation is needed since there is an increased risk of adverse outcomes (Vikse, 2013). Foreknowledge of BP and renal function is essential.

Epidemiology

The causes of PE must explain the following features, as delineated by Chesley (1985):

- It occurs almost exclusively during the first pregnancy; nulliparas are six to eight times more susceptible than are multiparas. Older primigravidas are more susceptible than are younger.
- It occurs more frequently in those with multiple fetuses, hydatidiform mole, or diabetes.

- The incidence increases as term approaches; it is unusual before the end of the second trimester.
- The features of the syndrome are hypertension, edema, proteinuria, and, when advanced, convulsions and coma.
- There is characteristic hepatic and renal pathology.
- The syndrome has a hereditary tendency; in the families of women who had PE, the syndrome developed in 25% of their daughters and granddaughters but in only 6% of their daughters-in-law.
- It rapidly disappears when the pregnancy is terminated.

As listed in Table 15-1, multiple risk factors for PE have been identified (Dekker & Sibai, 2001). What remains elusive is the initiating mechanism, the trigger

TABLE 15-1

Risk Factors for PE

Preconceptional or Chronic Risk Factors

Partner-related risk factors

- Nulliparity, primipaternity
- Limited sperm exposure, teenage pregnancy, donor insemination
- Partner who fathered a preeclamptic pregnancy in another woman
- Either parent the product of a pregnancy complicated by PE

Maternal-specific risk factors

- History of previous PE
- Increasing maternal age
- Longer interval between pregnancies
- Family history
- Black or Hispanic race
- Patient requiring oocyte donation
- Physical inactivity
- Presence of specific underlying disorders
- Chronic hypertension and renal disease
- Obesity, insulin resistance, low maternal birth weight

Exogenous factors

- Smoking (decreases risk)
- Stress, work-related psychosocial strain
- Inadequate diet

Pregnancy-Associated Risk Factors

- Multiple pregnancy
- Urinary tract infection
- Structural congenital anomalies
- Hydrops fetalis
- Chromosomal anomalies (trisomy 13, triploidy)
- Hydatidiform moles

Modified from Dekker G, Sibai B. Primary, secondary, and tertiary prevention of pre-eclampsia. *Lancet* 2001;357:209-215.

that sets off the oftentimes explosive course of this strange malady that disturbs up to 1 in 10 first pregnancies and is rarely seen again. The difficulty in identifying a specific cause is related to the likely presence of multiple mechanisms and, until recently, the lack of an experimental model for PE. Another difficulty is the inability to identify the early pathogenetic mechanisms, which remain invisible to current technology. Most of what is recognized are relatively late manifestations of a process that is initiated much earlier. As will be noted, no clinically useful screening test to predict the development of PE has been available until now, despite the recognition of circulating angiogenic (Levine et al., 2004) and antiangiogenic factors (Levine et al., 2006).

Pathophysiology

As stated by Delles and Freel (2013):

The pathogenesis of preeclampsia is thought to be triggered by excessive maternal immune response to the developing trophoblast leading to placental oxidative stress, hypoperfusion, and hypoxia, and the subsequent release of placental factors causing widespread endothelial dysfunction in the maternal circulation. In turn, the resulting placental hypoperfusion is probably further aggravated by reduced activity of growth factors, including vascular endothelial growth factor (VEGF), placental growth factor, and transforming growth factor β 1. Antiangiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1), a soluble form of the VEGF-1 receptor, and soluble endoglin, a part of the transforming growth factor β receptor, are released from apoptotic trophoblast cells and interact with and reduce the systemic and local levels of VEGF, placental growth factor, and transforming growth factor β 1.

Dechend and Staff (2012) have used the three-stage model proposed by Redman and Sargent (2010) thusly:

Dysregulated immunologic factors (stage 1) underlying defective placentation with reduced invasion of fetal extravillous trophoblast cells and reduced remodeling of maternal uteroplacental spiral arteries (stage 2) are initial pathophysiological events (Fig. 15-5). An unfavorable uteroplacental circulation ensues, with enhanced oxidative and endoplasmic reticulum stress and increased release of trophoblast-derived factors to the maternal circulation, which are thought to contribute to an excessive maternal inflammatory response and endothelial dysfunction (Buurma et al., 2013; Rajakumar et al., 2012).

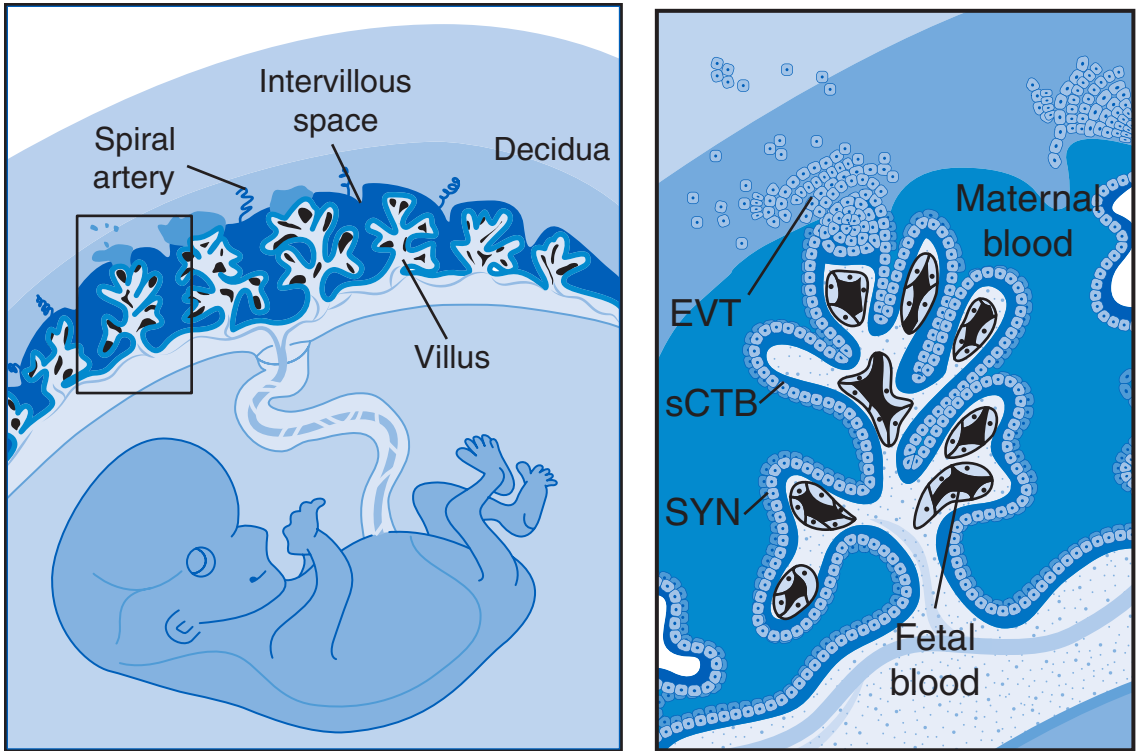


FIGURE 15-5 • The intervillous space of the placenta. Maternal blood bathes the villous trees, which are covered by syncytiotrophoblast (SYN), that are underlaid by a population of progenitor cells called cytotrophoblast (sCTB). The syncytial knots are formed on these villi, and trophoblast-derived material is transferred into the maternal circulation. EVT, extravillous trophoblasts. (Adapted from Dechend R, Staff AC. Placenta messages to the mother: Not just debris. *Hypertension* 2012;59:191–193.)

This induces the maternal clinical signs of preeclampsia with hypertension and proteinuria (stage 3).

Subsequently, Staff et al. (2013) recommended a redefinition of preeclampsia using placenta trophoblast-derived biomarkers (Fig. 15-6). Moreover, they emphasize that the current definition based on “thresholds of blood pressure and proteinuria does not correlate well with more severe maternal and perinatal outcome.” The rationale for a redefinition has become more logical since the findings of Rajakumar et al. (2012) and Buurma et al. (2013). As Dechend and Staff (2012) note:

“The interface between the fetally derived placenta and maternal blood is formed by syncytium of multinucleated syncytiotrophoblasts, which is a result from the fusion of an underlying mononucleate cytotrophoblast. The syncytiotrophoblasts come into direct contact with maternal blood in the placental intervillous space (see Fig. 15-5)... these deported trophoblast-derived structures are one part of a spectrum of traffic of material derived from the syncytiotrophoblast. This material

includes trophoblast-derived, anucleate microvesicles and the much smaller trophoblast-derived nanovesicles, which together have been called placental debris. Apoptosis may be a mechanism regulating the shedding of subcellular debris. The words “debris” and “garbage” are, however, misleading, because all subcellular vesicles may not be waste from a tired placenta but instead be important bioactive messengers from the fetally derived placenta to the mother.... In the maternal circulation, they are believed to contribute to a generalized systemic inflammation, endothelial dysfunction, followed by hypertension and proteinuria in the pregnant woman. Although the precise mechanisms are unknown, there is evidence that the vesicles can modify the sequence of several cellular responses that contribute to the proinflammatory phenotype and impair maternal vascular dilation. ... Rajakumar et al. (2012) report novel mechanistic data on one route by which the “antiangiogenic” protein soluble fms-like tyrosine kinase 1 (sFlt1), which is generated in the placenta, enters the systemic maternal circulation.” The authors show that some placental structures easily detach from

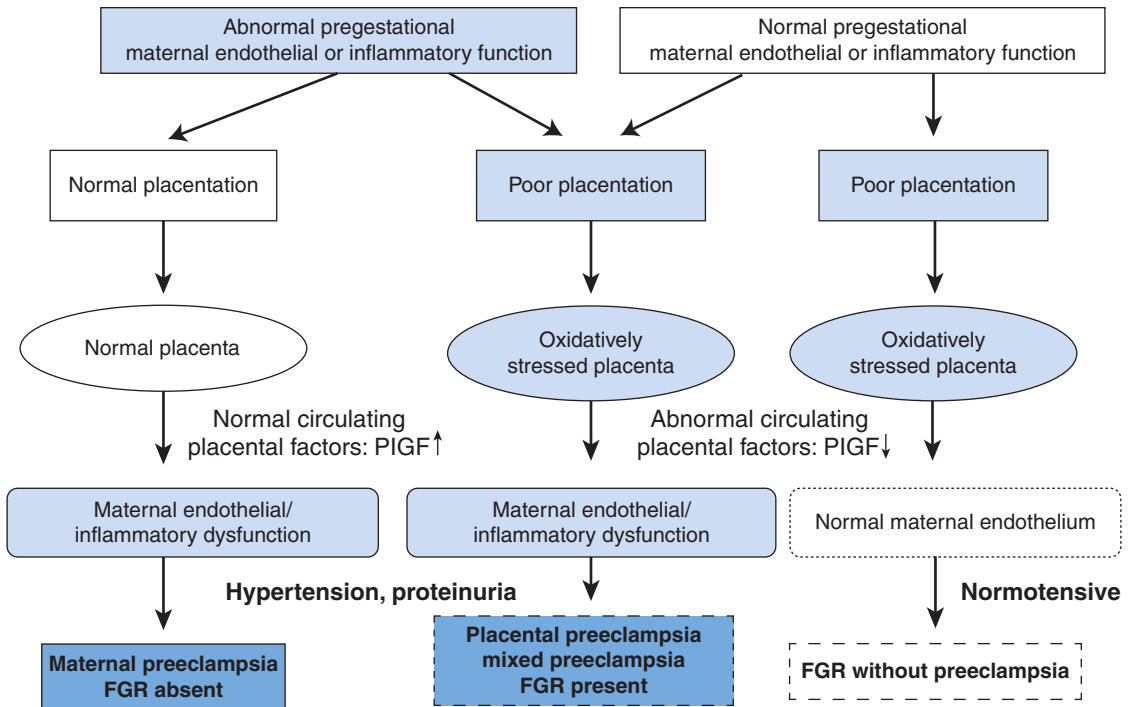


FIGURE 15-6 • A model of extended definition of PE on the basis of placenta-derived biomarkers. The figure illustrates the main alternative pathways during pregnancy leading to same diagnosis of PE, with or without fetal growth restriction (FGR), or to development of FGR without PE. The pathways are differentiated by maternal circulating PlGF as a biomarker of placental dysfunction. At present, it is not clear whether the addition of other placenta-derived biomarkers (such as soluble fms-like tyrosine kinase-1 and soluble endoglin), or even maternally derived biomarkers (such as inflammatory cytokines), should be added to this flow chart to improve the definition and subclassification of PE types. (From Staff AC, Benton SJ, von Dadelszen P, et al. Redefining preeclampsia using placenta-derived biomarkers. *Hypertension* 2013;61:932–942.)

the placenta and result in free, multinucleated fragments of 50 to 150 μm diameter that are loaded with sFlt1 protein and mRNA.

Buurma et al. (2013) extend their findings with the proof of the particular entrapment of these particles in the maternal lung, concluding

that detachment of syncytial knots from the placenta results in free transcriptionally active syncytial aggregates that represent an autonomous source of the anti-angiogenic sFlt1 delivery into the maternal circulation. The process of syncytial knot formation, shedding of syncytial aggregates, and appearance of placental microparticles in the maternal circulation appears to be greatly accelerated in preeclampsia and may contribute to the maternal vascular injury that characterizes this disorder. More recently, studies by Lyall et al (2014) have been interpreted by Burke and Karamanchi (2014) that “the lack of intramural trophoblasts in the myometrial vessels rather than defective interstitial troph -oblast invasion may be the primary abnormality in PE.

In a clinically oriented text as this, a great deal of the pathophysiology of preeclampsia cannot be provided. Publications by Staff et al. (2013), Wang et al. (2014), and Warrington et al. (2013) provide additional details. Warrington et al. (2013) focus primarily on the development of hypertension (Fig. 15-7).

Diagnosis

Early Diagnosis

Despite the impressive number of published series on the use of various angiogenic and antiangiogenic markers, uncertainty remains as to the most specific and sensitive to correctly identify those who are destined to develop PE early enough that mitigating therapies such as low-dose aspirin can be used.

Recently published data suggest that prediction may have improved to the level of clinical usefulness. Myatt et al. (2013) assayed biomarkers in low-risk nulliparous women, 153 who would develop PE and 468 who remained normotensive. They concluded

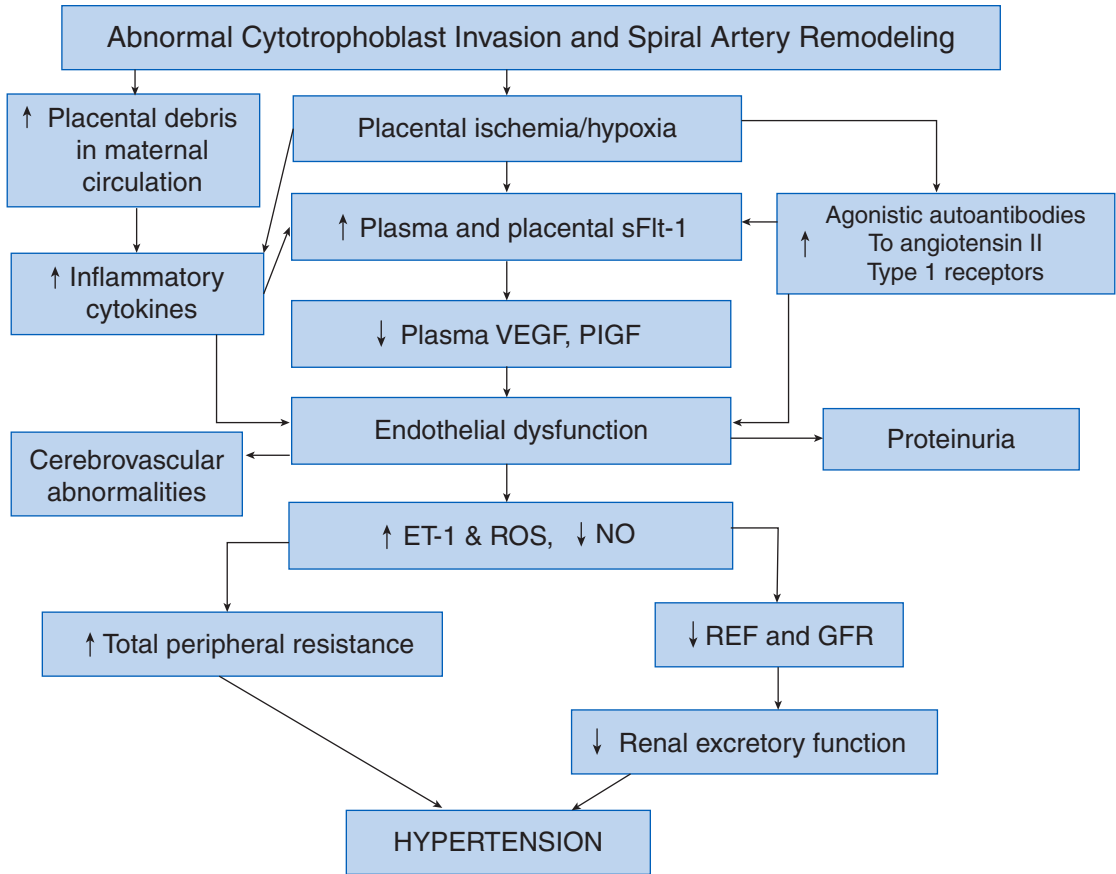


FIGURE 15-7 • Schematic representation of the proposed initiating events and factors in the pathophysiology of preeclampsia. ET-1, endothelin-1; GFR, glomerular filtration rate; PlGF, placental growth factor; RBF, renal blood flow; ROS, reactive oxygen species; sFlt-1, soluble fms-like tyrosine kinase-1; VEGF, vascular endothelial growth factor. (From Warrington JP, George EM, Palei AC, et al. Recent advances in the understanding of the pathophysiology of preeclampsia. *Hypertension* 2013;62:666–673.)

that “changes in angiogenic biomarkers between first and early second trimester combined with clinical characteristics have strong utility for predicting early-onset preeclampsia.”

Similar evidence has been presented by Ohkuchi et al. (2013) and Verlohren et al. (2014). Both groups used different cutoffs at two gestational phases to improve the diagnostic accuracy of levels of antiangiogenic factor soluble fms-like tyrosine kinase-1 (sFlt-1) and the pro-angiogenic placental growth factor (PlGF) and vascular endothelial growth factor (VEGF). Therefore, the question of whether the cost-effectiveness of early diagnostic testing for early PE is worthwhile that was posed by Hyde and Thornton (2013) may soon be answered “Yes” according to Schnettler et al. (2013).

Until these or other markers of early PE become clinically useful, the diagnosis of PE still depends on maternal characteristics.

Current Diagnosis

Hypertension developing after the 20th week of gestation with proteinuria in a young nullipara is probably PE, particularly if she has a positive family history for the syndrome. Because patients usually have no symptoms, prenatal care is crucial to detect the signs early and thereby prevent the dangerous sequelae of the fully developed syndrome.

In keeping with the list of known risk factors (Table 15-1), women with the following features should be more closely evaluated and monitored (Ananth and Cleary, 2013)

- First pregnancy
- Previous PE
- ≥ 10 years since last baby
- Body mass index ≥ 35
- Family history of PE (mother or sister)

- ▶ Patient had low birth weight
- ▶ Diastolic BP \geq 80 mm Hg
- ▶ Proteinuria (\geq + on more than one occasion and \geq 300 mg per 24 hours)
- ▶ Multiple pregnancy
- ▶ Underlying medical condition
 - ▶ Preexisting hypertension
 - ▶ Preexisting renal disease
 - ▶ Preexisting diabetes
 - ▶ Presence of antihypertensive phospholipid antibodies

Hypertension

The BP criterion is based on readings of 140/90 mm Hg or higher recorded on at least two occasions, 6 hours or more apart. Obviously, it is not possible to reconfirm the pressure levels over many weeks, as is recommended in nonpregnant patients.

Overdiagnosis

Despite the greater overall perinatal mortality with even transient elevations in pressure, for the individual patient, there is a significant chance of overdiagnosing PE on the basis of these values, which have been found to have only a 23% to 33% positive predictive value and an 81% to 85% negative predictive value (Dekker & Sibai, 2001). Higher ambulatory BP and heart rate are present at 18 weeks' gestation in those who later developed PE; but those signs, too, have low predictive value (Hermida et al., 2004). Therefore, multiple readings and careful follow-up over at least a few days or weeks are needed for women who display such findings in the absence of any other suggestive features before the clinician should make the diagnosis or institute therapy.

Consequences

On the other hand, the level of pressure may not be inordinately high for it to have serious consequences: Women may convulse because of hypertensive encephalopathy with pressures of only 160/110 mm Hg. As noted in the report of the National HBPEP Working Group (2000):

The clinical spectrum of preeclampsia ranges from mild-to-severe forms. In most women, progression through this spectrum is slow, and the disorder may never proceed beyond mild preeclampsia. In others, the disease progresses more rapidly, changing from mild to severe in days or weeks. In the most serious cases,

progression may be fulminant, with mild preeclampsia evolving to severe preeclampsia or eclampsia within days or even hours. Thus, for clinical management, preeclampsia should be overdiagnosed, because a major goal in managing preeclampsia is the prevention of maternal or perinatal morbidity and mortality, primarily through timing of delivery.

Proteinuria

Proteinuria is defined as more than 300 mg of protein in a 24-hour urine collection or 300 mg/L in two random, cleanly voided specimens collected at least 4 hours apart. The protein-creatinine ratio in a random urine sample has been found to be a poor predictor if levels are below 2,000 mg/d (Kayatas et al., 2013).

Hyperuricemia

Roberts et al. (2005) found that hyperuricemia was as important as proteinuria in identifying the fetal risk in women with GH. Bellomo et al. (2011) found that in a group of 206 primigravidas with a recent onset of hypertension, a serum uric acid above 5.2 mg/dL (309 μ mol/L) predicted the development of PE with 88% sensitivity and 93% specificity.

Differential Diagnosis

Most women with typical features of de novo hypertension in pregnancy with no other obvious disorders turn out to have PE (Maynard et al., 2008). The recognition of PE superimposed on chronic hypertension may be more difficult. As described in the report of the National HBPEP Working Group (2000):

Preeclampsia may occur in [15–25% of] women already hypertensive (i.e., who have chronic hypertension)... [T]he diagnosis of superimposed preeclampsia is highly likely with the following findings:

- ▶ New onset or sudden increase of proteinuria
- ▶ In women with hypertension and no proteinuria early in pregnancy (<20 weeks)
- ▶ In women with hypertension and proteinuria before 20 weeks' gestation
- ▶ A sudden increase in BP in a woman whose hypertension has previously been well controlled
- ▶ Thrombocytopenia (platelet count <100,000 cells per mm^3)
- ▶ An increase in ALT [alanine aminotransferase] or AST [aspartate aminotransferase] to abnormal levels

The presence of hypertensive retinopathy, described in Chapter 4, or left ventricular hypertrophy would favor chronic hypertension.

Treatment

Nonpharmacologic Management

Smoking Cessation: Through 2007, 26% of mothers smoked during pregnancy and their children had more hypertension, but this was mainly ascribed to their obesity (de Jonge et al., 2013).

Bed Rest: In women who were hospitalized for various preterm indications, strict bed rest was said to reduce the incidence of PE and IUGR (Abenhaim et al., 2008). But, on the basis of a complete Cochrane review, McCall et al. (2013) call it “unsupported by data and unethical.”

Exercise: Most studies find a protection against PE by moderate exercise (Genest et al., 2012).

Sodium: Maintenance of usual sodium intake has been recommended to avoid further reducing placental perfusion (Knuist et al., 1998).

Calcium Supplements: Although once claimed to be effective for prevention of PE in high-risk populations, they are not useful for therapy (Hofmeyr et al., 2008). However, in an in vitro study, calcium protected endothelial activation by trophoblastic debris (Chen et al., 2013).

Caffeine: Caffeine may increase the risk of miscarriage, so it seems prudent to restrict its intake even more in women with PE (Weng et al., 2008).

Alcohol: Most observational data report no adverse effects on the children of mothers who have consumed small amounts of alcohol during pregnancy

(Kelly et al., 2013; McCarthy et al., 2013), but Lewis et al. (2012) performed a genetic study of 4,117 eight-year-old children of mothers who consumed various amounts of alcohol during pregnancy and found that four genetic variants in alcohol-metabolizing genes in these children were strongly related to lower IQ. These data prompted Gray (2013) to recommend avoidance of alcohol during pregnancy.

Pharmacologic Therapy

The indications for drug therapy for hypertension during pregnancy remain uncertain since there is no evidence that such therapy improves neonatal outcomes. As stated by the 2013 ESH/ESC guidelines (Mancia et al., 2013) (Table 15-2):

In the absence of RCTs, recommendations can only be guided by expert opinion. While there is consensus that drug treatment of severe hypertension in pregnancy (>160 for SBP or >110 mm Hg for DBP) is required and beneficial, the benefits of antihypertensive therapy are uncertain for mildly or moderately elevated BP in pregnancy (<160/110 mm Hg), either preexisting or pregnancy-induced, except for a lower risk of developing severe hypertension. International and national guidelines vary with respect to thresholds for starting treatment and BP targets in pregnancy.

... Despite lack of evidence, the 2013 Task Force recommends that “physicians should consider early initiation of antihypertensive treatment at values >140/90 in women with (i) gestational hypertension (with or without proteinuria), (ii) preexisting hypertension with the superimposition of gestational hypertension, or (iii) hypertension

TABLE 15-2

Oral Drugs for Treatment of Chronic Hypertension in Pregnancy

Agent	Comments
Methyldopa	Preferred on the basis of long-term follow-up studies supporting safety
β-Blockers	Reports on intrauterine growth retardation (atenolol)
Labetalol	Increasingly preferred to methyldopa because of reduced side effects
Calcium antagonists (nifedipine)	Limited data
	No increase in major teratogenicity with exposure
Diuretics	Not first-line agents
	Probably safe to reduce fluid retention from other agents
ACEIs, A-II receptor blockers, direct renin inhibitors	Contraindicated: Reported fetal toxicity and death

with asymptomatic organ damage or symptoms at any time during pregnancy....

No additional information has been provided on the antihypertensive drugs to be used in hypertensive women: therefore the recommendations to use methyldopa, labetalol, or nifedipine (as the only calcium antagonist) really tested in pregnancy can be confirmed. Beta-blockers (possibly causing foetal growth retardation if given early in pregnancy) and diuretics (in preexisting reduction of plasma volume) should be used with caution. As mentioned, all agents interfering with the renin-angiotensin system (ACE inhibitors, ARBs, renin inhibitors) should absolutely be avoided. In emergency (preeclampsia), intravenous labetalol is the drug of choice with sodium nitroprusside or nitroglycerin in intravenous infusion being the other option.

These generally accepted preferences (Al Khaja et al., 2014) may reflect the hypertension per se and not the medications. In a population-based retrospective cohort study of over 100,000 deliveries including 1,964 with chronic hypertension, Orbach et al. (2013) found a similar rate of adverse perinatal outcomes in those women given no antihypertensive drugs as seen among those given either methyldopa or atenolol.

The previous preference given to hydralazine is not warranted. As noted in a meta-analysis of all 21 randomized controlled trials published between 1966 and 2002 involving 893 women given short-acting antihypertensives for severe hypertension in pregnancy, hydralazine was associated with more maternal and fetal side effects than nifedipine, isradipine, or labetalol (Magee et al., 2003).

Magnesium sulfate has been conclusively documented to be needed to prevent eclamptic convulsions, both when compared to placebo (Magpie Trial Collaborative Group, 2002) or a calcium channel blocker (Belfort et al., 2003). In addition, its use provides neuroprotection to infants delivered before 30 weeks' gestation, as may be needed in women with severe PE (Crowther et al., 2003).

Long-Term Consequences

Maternal

Postpartum, women who have suffered PE, particularly if early onset, continue to be at greater risk for hypertension, diabetes, and obesity (Ahmed et al., 2014; Collen et al., 2013). Part of this continued risk reflects their prepregnancy state, in particular obesity

(Gademan et al., 2013). As a consequence, these women suffer more cardiovascular (Hermes et al., 2013) and renal (Vikse, 2013) diseases later in life. Their immediate risk is low for serious complications, and, if given proper advice and follow-up, they may alter lifestyles better than most because of their prior experience during pregnancy (Hertig et al., 2008). As the consequences of maternal obesity have been recognized, prenatal weight reduction and little if any weight gain during pregnancy have been emphasized (Kominiarek et al., 2013).

Even without overt PE, women who have small for gestational age babies have more long-term cardiovascular (Melchiorre et al., 2012) and renal (Vikse, 2013) diseases. Similarly, preterm birth is a risk for subsequent maternal hypertension (Catov et al., 2013).

About 15% to 20% of women who have had PE will suffer it again during subsequent pregnancies. They should be more closely monitored during subsequent pregnancies as early as in the 12th week (Spaan et al., 2012).

Fetal

Children of women who are obese before their pregnancy have a significantly greater risk of being hypertensive (Gademan et al., 2013) and having early cardiovascular mortality (Reynolds et al., 2013) even more so if their mother had hypertension during the pregnancy.

Infants born small for gestational age, often from maternal undernutrition, suffer more hypertension and cardiovascular-renal diseases (Ingelfinger and Nuyt, 2012). Similar risks are seen with infants born preterm (de Jong et al., 2012). The consequences of maternal hypertension on their children extend to greater cognitive impairment 70 years later (Tuovinen et al., 2013).

Prevention

Dekker and Sibai (2001) have divided prevention into three stages:

1. *Primary* prevention will obviously be difficult without knowledge of the cause. However, avoidance of the known risk factors (Table 15-1) should help. In particular, avoiding teenage pregnancy, reducing obesity and insulin resistance, providing adequate nutrition, and avoiding multiple births during assisted pregnancies (Thomopoulos et al., 2013) should be protective.

2. *Secondary* prevention involves identifying the syndrome as early as possible and using strategies that are thought to influence pathogenic mechanisms. These include low-dose aspirin if given by the 16th week of gestation (Roberge et al., 2012) but not calcium supplementation (Levine et al., 1997). In addition, reduction of oxidative stress by antioxidants may work in animal models (Hoffmann et al., 2008), but neither vitamin C nor vitamin E have been preventative (Rossi & Mullin, 2011).
3. *Tertiary* prevention involves the various lifestyle changes and therapies described under management.

As noted in the ESH/ESC guidelines (Mancia et al., 2013):

There is considerable controversy regarding the efficacy of low-dose aspirin Two recent analyses came to opposing conclusions. Rossi and Mullin (2011) used pooled data from approximately 5,000 women at high risk and 5,000 at low risk for preeclampsia and reported no effect of low-dose aspirin in the prevention of the disease. Bujold et al. (2010), however, pooled data from over 11,000 women enrolled in RCTs of low-dose aspirin in pregnant women and concluded that women who initiated therapy at <16 weeks of gestation had a significant and marked reduction of the relative risk for developing preeclampsia (relative risk: 0.47) and severe preeclampsia (relative risk: 0.09) compared with control. [In yet another meta-analysis published before those used in the ESH/ECH guidelines, Roberge et al. (2012) concluded that "low-dose aspirin initiated at or before 16 weeks significantly reduces the risk of severe preeclampsia (relative risk: 0.22) but not mild preeclampsia (relative risk: 0.81)"].... Faced with these discrepant data, only prudent advice can be offered: women at high risk of preeclampsia.... may be advised to take 75 mg of aspirin

daily from 12 weeks until the birth of the baby, provided that they are at low risk of gastrointestinal haemorrhage.

ECLAMPSIA

Eclampsia is defined by the occurrence of seizures due to hypertensive encephalopathy on the background of PE (Fong et al., 2013). This serious complication is becoming less common as better prenatal care is given, but is still seen in about 1% of all pregnancies in developing societies (Miguil & Chekairi, 2008).

Manifestations of More Severe Disease

Intravascular Coagulation

As seen in Figure 15-8, activation of intravascular coagulation and subsequent fibrin deposition may be responsible for much of the eventual organ damage seen in severe PE. Increased plasma levels of indicators of platelet activation (β -thromboglobulin), coagulation (thrombin–antithrombin III complexes), and endothelial cell damage (fibronectin and laminin) have been measured up to 4 weeks before the onset of clinical features of PE (Powers et al., 2008). Various inflammatory markers are found after the process has begun (Catov et al., 2013) (Table 15-3).

HELLP Syndrome

A few women develop a more serious complication of eclampsia: The HELLP syndrome, which involves hemolysis, elevated liver enzymes, and low platelet counts (Walker, 2000). The syndrome shares many features with the hemolytic uremic syndrome and thrombotic thrombocytopenic purpura (TTP).

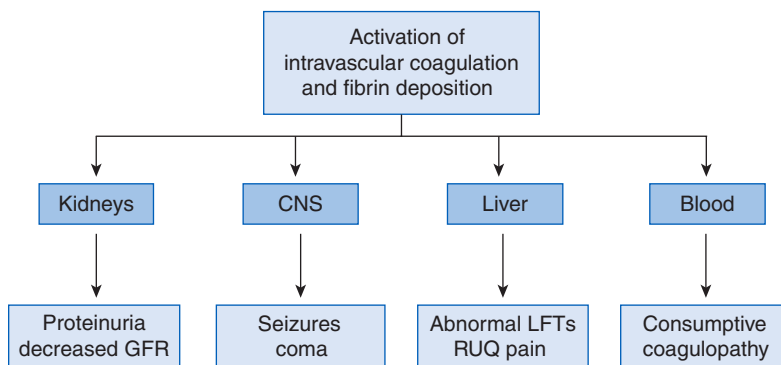


FIGURE 15-8 • Proposed model to explain the consequences of activation of intravascular coagulation and fibrin deposition in the pathophysiology of PE. CNS, central nervous system; GFR, glomerular filtration rate; LFT, liver function test; RUQ, right upper quadrant. (Modified from Friedman SA. Preeclampsia: A review of the role of prostaglandins. *Obstet Gynecol* 1988;71:122–137.)

TABLE 15-3

Criteria for the Diagnosis of Severe PE

Symptoms

Central nervous systems dysfunction such as blurred vision or severe headache
Liver capsule distension with right upper quadrant pain

Signs

BP above 160 mm Hg systolic or 110 mm Hg diastolic before and after 6-h rest
Pulmonary edema
Stroke
Cortical blindness
Intrauterine growth retardation

Laboratory findings

Proteinuria >5 g/d
Oliguria <500 mL/d and/or serum creatinine above 1.2 mg/dL
HELLP syndrome
Liver injury with serum transaminase above two times normal
Thrombocytopenia below 100,000 platelets/mm³
Coagulopathy with prolonged prothrombin time or low fibrinogen

Modified from Norwitz ER, Funai EF. Expectant management of severe preeclampsia remote from term: Hope for the best, but expect the worst. *Am J Obstet Gynecol* 2008;199:209–212.

If initial TTP is accompanied by the other manifestations of the HELLP syndrome, maternal mortality has occurred in almost half (Martin et al., 2008). Corticosteroids may be helpful (Wallace et al., 2013), but induction of labor is usually needed (Alanis et al., 2008).

Cerebral Blood Flow

As will be noted, convulsions may occur (i.e., eclampsia) with or without prior manifestations of PE. Most women with eclampsia develop headaches; a few develop cortical blindness (Apollon et al., 2000) and other neurologic features of hypertensive encephalopathy. As described in Chapter 8, hypertensive encephalopathy reflects breakthrough hyperperfusion on the background of vasospasm. Similar findings have been described in PE: Both vasospasm (Brackley et al., 2000) and brain edema (Schwartz et al., 2000) that reflects an increase in cerebral blood flow with a failure of autoregulation (Belfort et al., 2008).

Prophylactic magnesium sulfate is now recognized to be essential for prevention of eclampsia.

Treatment of Severe Preeclampsia/Eclampsia

The management of severe PE and eclampsia may require the use of parenteral agents (Table 15-4). In addition to antihypertensive drugs, women with high levels of endogenous digitalis-like factors may respond to an anti-digoxin antibody (Lam et al., 2013). Expectant management of severe PE before 24 weeks' gestation is almost always futile, and termination of the pregnancy should be offered (Bombrys et al., 2008). Norwitz and Funai (2008) conclude that (Table 15-4)

There is absolutely no medical benefit to the mother remaining pregnant once she has been diagnosed with severe preeclampsia. By agreeing to continued expectant treatment, she is taking on a small, but significant, risk to

TABLE 15-4

Treatment of Acute Severe Hypertension in PE

Hydralazine	5 mg IV bolus, then 10 mg every 20–30 min to a maximum of 25 mg, repeat in several hours as necessary
Labetalol	20 mg IV bolus, then 40 mg 10 min later, 80 mg every 10 min for two additional doses to a maximum of 220 mg
Nifedipine	10 mg PO, repeat every 20 min to a maximum of 30 mg. Caution when using nifedipine with magnesium sulfate, can see precipitous BP drop. Short-acting nifedipine is not approved by U.S. Food and Drug Administration for managing hypertension
Sodium nitroprusside (rarely when others fail)	0.25 µg/kg/min to a maximum of 5 µg/kg/min. Fetal cyanide poisoning may occur if used for >4 h

her own health in an attempt to delay delivery until a more favorable gestational age is reached. In our view, expectant management of severe preeclampsia remote from term should be undertaken only under specific circumstances: if the woman has a viable pregnancy (≥ 24 weeks of gestation) without evidence of IUGR, if she is hospitalized in a tertiary care center, and if she agrees to take on the potential risks to her health of continuing the pregnancy after extensive counseling by subspecialists in both maternal-fetal medicine and neonatology.

Management

The report of the National HBPEP Working Group (2000) provides these three tenets for management:

1. Delivery is always appropriate therapy for the mother but may not be so for the fetus. The cornerstone of obstetric management of PE is based on whether the fetus is more likely to survive without significant neonatal complications in utero or in the nursery.
2. The pathophysiologic changes of severe PE indicate that poor perfusion is the major factor leading to maternal physiologic derangement and increased perinatal morbidity and mortality. Attempts to treat PE by natriuresis or by lowering BP may exacerbate the important pathophysiologic changes.
3. The pathogenic changes of PE are present long before clinical diagnostic criteria are manifested. These findings suggest that irreversible changes affecting fetal well-being may be present before the clinical diagnosis. If there is a rationale for management other than delivery, it would be to palliate the maternal condition to allow fetal maturation and cervical ripening.

CHRONIC HYPERTENSION AND PREGNANCY

As more women in developed countries delay pregnancies until they are in their 30s and 40s and are often obese, the prevalence of preexisting hypertension will continue to increase (Bateman et al., 2012).

Pregnant women may have any of the other types of hypertension listed in Chapter 1. Because the BP usually falls during the first half of pregnancy, preexisting hypertension may not be recognized if the woman is first seen during that time. If the pressure is high during the first 20 weeks, however, chronic hypertension

rather than PE is almost always the cause (American College of Obstetrics and Gynecology, 2012).

Pregnancy seems to bring out latent primary hypertension in certain women whose pressures return to normal between pregnancies but eventually remain elevated. In most patients, such "transient hypertension" appears late in gestation, is not accompanied by significant proteinuria or edema, and recedes within 10 days after delivery. Transient hypertension usually recurs during subsequent pregnancies and is often the basis for the misdiagnosis of PE in multiparous women (National HBPEP Working Group, 2000).

To elucidate the true nature of hypertension seen during a pregnancy, it is often necessary to follow up with the patient postpartum (see Fig. 15-1). By 3 months, complete resolution of the various changes seen in pregnancy will have resolved so that, if indicated, further studies to elucidate the cause of the hypertension can be obtained. If seen before week 20, the diagnosis is usually evident. Chronic hypertension is more likely if left ventricular hypertrophy or hypertensive retinopathy is present.

Risks to Mother and Fetus

Women with chronic hypertension have a 30% increased risk for superimposed PE and placental abruption, and at least their male babies have a three-fold greater risk for perinatal mortality (Zetterstrom et al., 2008). Even without superimposed PE, women with chronic hypertension have more complicated pregnancies with more intrauterine growth retardation and perinatal mortality (Chappell et al., 2008). These risks are even greater for black women in the U.S., for those with a diastolic BP above 110 mm Hg during the first trimester and for those with proteinuria early in pregnancy (Sibai et al., 1998a). For those with serum creatinine exceeding 2.0 mg/dL, a one in three chance of entering end-stage renal failure after pregnancy has been reported (Epstein, 1996), so that these women should be strongly advised against pregnancy. Nonetheless, successful pregnancies have been reported in most women who conceive during chronic dialysis (Bagon et al., 1998).

Management

Women with mild to moderate hypertension should be watched closely, warned about signs of early PE, and delivered at 38 to 39 weeks' gestation (Cruz et al.,

2012). They should be cautioned not to exercise intensively, told not to drink alcohol or smoke, and advised to restrict dietary sodium to 100 mmol per day (National HBPEP Working Group, 2000).

As with preeclampsia, uncertainty remains both about the decision to use antihypertensive drugs and about which drugs to choose among them (Bramham et al., 2014).

As noted in Table 15-2, drugs that block the renin–angiotensin system are contraindicated during pregnancy, even during the first trimester (Cooper et al., 2006). Hypertension whether untreated or treated during pregnancy increases the risk of fetal malformations slightly (Caton et al., 2009).

Other Causes of Hypertension During Pregnancy

Identifiable secondary forms of hypertension occur only rarely during pregnancy (American College of Obstetrics and Gynecology, 2012). Their diagnosis may be confounded by the multiple changes in the renin–aldosterone and other hormonal systems that occur during pregnancy, and their therapy may be made difficult by adverse effects on the fetus. Coverage of these various identifiable forms of hypertension during pregnancy is provided in the respective chapters. Those of adrenal origin have been well reviewed (Monticone et al., 2012).

POSTPARTUM SYNDROMES

In women who were preeclamptic, continued close monitoring is needed after delivery (Hertig et al., 2008). As noted earlier, PE and eclampsia may appear after delivery. If BP remains elevated at 6 weeks' postpartum, a variety of other causes may be responsible (Bramham et al., 2013).

Peripartum cardiomyopathy is rare, reported in about 1 in 3,000 live births (Mielniczuk et al., 2006), but serious form of left ventricular systolic dysfunction that appears in the last month of pregnancy or within 5 months after delivery in the absence of identifiable causes or prior recognizable heart disease (Bello et al., 2013).

Hypertension and Lactation

Breast-feeding for at least 6 months is associated with a lower incidence of hypertension in both mother (Lupton et al., 2013) and child (van Rossem et al., 2012). All

antihypertensive drugs taken by mothers enter their breast milk; most are present in very low concentrations, except propranolol and nifedipine according to the 2011 ESC guidelines, which cover many drugs that may be used during pregnancy (Regitz-Zagrosek et al., 2011).

HYPERTENSION WITH ORAL CONTRACEPTIVES

OCs have been used by millions of women since the early 1960s. OCs are safe for most women, but their use carries some very small risk.

Incidence of Hypertension

The BP rises a little in most women who take estrogen-containing OCs (Hickson et al., 2011). In a prospective cohort study of almost 70,000 nurses covering the 4 years between 1989 and 1993, when the dose of estrogen was twofold to threefold greater than in current OCs, the overall *relative risk* for hypertension was 50% higher for current OC users as compared to never users and 10% higher as compared to former users (Chasan-Taber et al., 1996). The 50% increase in relative risk translated to 41 cases per 10,000 person-years of OC use.

Predisposing Factors

In the prospective U.S. Nurses Study, the risk for hypertension was not significantly modified by age, family history of hypertension, ethnicity, or body mass index (Chasan-Taber et al., 1996).

Mechanism

Whether OCs cause hypertension *de novo* or simply uncover the propensity toward primary hypertension that would eventually appear spontaneously is unknown. The mechanism for OC-induced hypertension is also unknown, particularly because estrogen appears to be vasodilative (Lee et al., 2000). In a comparison of 225 young women who were on an OC versus 660 who were not, the OC users had a 2 mm Hg higher systolic BP and a statistically significant increase in measures of large artery stiffness (Hickson et al., 2011).

Risks in Perspective

In a cohort study with data from all Danish women 15 to 49 years of age over the interval of 1995 to 2009, Lidegaard et al. (2012) found a 1.5- to 2-fold *relative*

increase in thrombotic stroke and myocardial infarction in those who took either a 30 to 40 µg or a 20 µg ethinyl estradiol-containing OC with no differences between the various progestins. Progestin-only OCs cause no detectable increase in vascular risks.

As noted by Petitti (2012), “the number of ‘extra’ arterial thrombotic events attributable to hormonal contraceptives is about 1 to 2 per 10,000 women per year.... These are small numbers. For an individual woman, the probability of an event is quite small.” Petitti also notes that “that the small risk could be minimized and perhaps eliminated by abstinence from smoking.... and by avoidance of hormonal contraceptive use if the blood pressure is raised.”

Venous thromboembolism was not associated with OCs containing levonorgesterl (Lidegaard et al., 2011) or norgestimate (Martinez et al., 2012). An OC with only 10 µg of ethinyl estradiol is now available (Archer et al., 2013) as are newer non-OCs containing only progestogen (Bateson et al., 2013).

HYPERTENSION AND ESTROGEN REPLACEMENT THERAPY

In 2013, the U.S. Preventive Services Task Force reinforced its recommendation against the use of postmenopausal estrogen use for the primary prevention of chronic conditions (Moyer and Force USPST, 2013). However, estrogen will continue to be used since nothing else will effectively prevent hot flushes (North American Menopause Society, 2012).

In view of the known prohypertensive effect of estrogens given in superphysiologic doses for contraception, there are concerns that the smaller doses for replacement might also raise the BP, adding to the frequent rise in BP after menopause related to increased body weight and aging (Coylewright et al., 2008). In a prospective study of 1,000 postmenopausal and premenopausal untreated women followed for a median of 5.3 years, 15% developed hypertension, more so if they had at least one pregnancy (Giubertoni et al., 2013). In an RCT, the half of 1,006 women in early menopause who took estrogen had a significantly *reduced* risk of cardiovascular events over a 10-year follow-up (Schierbeck et al., 2012). Most controlled trials find either no difference or a *decrease* in ambulatory BP and a greater dipping of nocturnal BP in estrogen users (Coylewright et al., 2008), particularly in the initial period of use (Barton & Meyer, 2009). Women who are already hypertensive may have a fall

in BP with transdermal estradiol (Ahmed et al., 2008; Chu et al., 2008; Vongpatanasin et al., 2003).

We will turn next to hypertension in children and adolescents, a rapidly growing problem.

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Hypertension in Childhood and Adolescence

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Hypertension, especially obesity-related primary hypertension, should no longer be considered uncommon in children and adolescents. This chapter will describe the features of hypertension in children and adolescents and will also examine the increasingly strong evidence that the genesis of adult cardiovascular disease has its origins in childhood (Expert Panel, 2011).

PREVALENCE OF HYPERTENSION IN THE YOUNG

Childhood hypertension was first recognized in the mid-1960s (Londe et al., 1971). Initially, the thresholds used for defining hypertension in the young were the same as those used in adults. Unsurprisingly, hypertension was found to be exceedingly rare in young children but could affect up to 2% of adolescents (Table 16-1). Later screening studies applied population-based percentiles of blood pressure (BP) as the threshold for diagnosis and confirmed that fewer than 2% of children were hypertensive (Fixler et al., 1979). These screening programs also demonstrated the importance of performing repeated measures of BP before labeling a child as hypertensive: studies that used just one BP determination found significantly higher “prevalences” of hypertension than studies in which repeated measurements were obtained (Table 16-1).

The impact of the childhood obesity epidemic on the prevalence of hypertension in the young can be seen in several recent studies from the Houston Screening Project (McNiece et al., 2007a; Sorof et al., 2002, 2004a). In multiple publications, these investigators have demonstrated an increased prevalence of hypertension among obese children—as high as 4.5%—compared to nonobese children. Indeed, a

recent examination of BP data in 8- to 17-year-old children from the NHANES and other related population-based studies conducted in the United States (U.S.) from 1963 to 2002 clearly demonstrates an increase in the prevalence of elevated BP in children (Fig. 16-1), with much of the increase attributable to the increase in childhood obesity (Din-Dzietham et al., 2007). According to this analysis, the prevalence of prehypertension has now reached 10% and the prevalence of hypertension nearly 4%. Of significant concern is that this increase has been much greater in non-Hispanic black and Mexican American children than in white children (Fig. 16-1).

Similar findings have been seen in screening studies performed in other countries, including China (Cao et al., 2012) and Iceland (Steinthorsdottir et al., 2011) (Table 16-1). Thus, it is apparent that the increased prevalence of high BP in children is a global phenomenon, likely related to the increasing prevalence of childhood obesity worldwide (Flynn, 2013).

CHILDHOOD PRECURSORS OF ADULT HYPERTENSION AND CARDIOVASCULAR DISEASE

It is increasingly clear that adult hypertension and other cardiovascular diseases have their origins in childhood. Not only BP levels but also other known cardiovascular risk factors can be measured in the young and then related to the subsequent development of hypertension and its cardiovascular manifestations in adult life (Expert Panel, 2011). The significance of hypertension in the young is further underscored by the many studies documenting the occurrence of hypertensive target organ damage in children and adolescents.

TABLE 16-1

Prevalence of Hypertension in Children and Adolescents from Screening Studies

Study Location	Number Screened	Age (Years)	No. of Screenings	Normative Criteria	Prevalence	Reference
Edmonton, Canada	15,594	15–20	1	150/95	2.2%	Silverberg et al. (1975)
New York, U.S.	3,537	14–19	2	140/90	1.2% SHTN 2.4% DHTN	Kilcoyne et al. (1974)
Dallas, TX, U.S.	10,641	14	3	95th percentile	1.2% SHTN 0.4% DHTN	Fixler et al. (1979)
Minneapolis, MN, U.S.	14,686	10–15	1	1987 TF	4.2%	Sinaiko et al. (1989)
Tulsa, OK, U.S.	5,537	14–19	1	1987 TF	6.0%	O'Quin et al. (1992)
Minneapolis, MN, U.S.	14,686	10–15	2	1996 WG	0.8% SHTN 0.4% DHTN	Adrogue and Sinaiko (2001)
Houston, TX, U.S.	5,102	12–16	3	1996 WG	4.5%	Sorof et al. (2004a)
Houston, TX, U.S.	6,790	11–17	3	2004 Fourth Report	3.2% HTN 15.7% PHTN	McNiece et al. (2007a)
Reykjavík, Iceland	1,071	9–10	3	2004 Fourth Report	3.1%	Steinthorsdottir et al. (2011)
Changsha, China	88,974	12–17	3	2004 Fourth Report	3.1% HTN 7.2% PHTN	Cao et al. (2012)

DHTN, diastolic hypertension; PHTN, prehypertension; SHTN, systolic hypertension; TF, Second Task Force Report (Task Force on Blood Pressure Control in Children, 1987); WG, Working Group Report (National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents, 1996).

Blood Pressure Tracking

The pattern of BP over time, referred to as tracking, has been supported by data from a number of longitudinal cohort studies, most notably those conducted in Muscatine, Iowa (Lauer et al., 1993), and Bogalusa, Louisiana (Berenson, 2002). In all studies, the best predictive indicator of subsequently sustained elevated

BP is an antecedent elevated BP level (Bao et al., 1995). Although an initially elevated BP level may not evolve into later sustained elevation, Lauer et al. (1993) found that 24% of young adults whose BP ever exceeded the 90th percentile as children had adult BP greater than the 90th percentile, a percentage that is 2.4 times higher than expected. In the Bogalusa cohort, 40% of those with systolic BP and 37% of

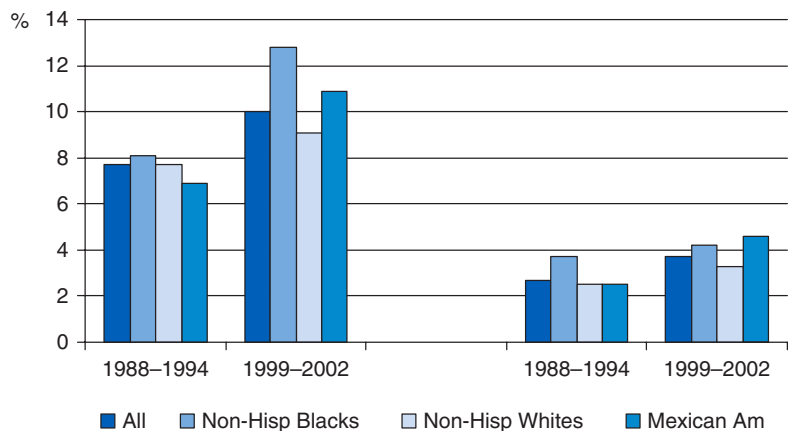


FIGURE 16-1 • Prevalence of prehypertension (left-hand bars) and hypertension (right-hand bars) among American children in 1999 to 2002 compared to 1988 to 1994. (Data from Din-Dzietham R, Liu Y, Bielo MV, et al. High blood pressure trends in children and adolescents in national surveys, 1963 to 2002. *Circulation* 2007;116:1488–1496.)

those with diastolic BP above the 80th percentile at baseline continued to have BP above the 80th percentile 15 years later (Bao et al., 1995). More recently, data from the Fels Longitudinal study have added further weight to the concept that an elevated childhood BP reading predicts an increased chance of adult hypertension (Carrico et al., 2013).

Tracking is more consistent if the elevated childhood BP levels are combined with obesity, a parental history of hypertension, or increased left ventricular mass by echocardiography (Lauer et al., 1993; Shear et al., 1986). However, the strength of tracking appears to decrease with longer periods of follow-up (Chen & Wang 2008; Toschke et al., 2010).

In view of the higher prevalence of hypertension in black adults than in white adults, comparisons of the tracking phenomenon in black and white children have been made (Lane & Gill, 2004). Black children have significantly higher mean BP than white children even after adjustments for potential confounders such as weight gain (Bao et al., 1995), growth, or socioeconomic status (Dekkers et al., 2002). Dekkers et al. (2002) found that ethnic differences in systolic BP become manifest earlier in girls than in boys, and both systolic and diastolic differences tended to increase with age.

The importance of BP tracking was highlighted in a meta-analysis of 50 cohort studies conducted between 1970 and 2006 (Chen & Wang, 2008). The average tracking coefficient was 0.38 for systolic BP and 0.28 for diastolic BP, and the strength of BP tracking increased with baseline age for both systolic and diastolic BP. Similar modest tracking coefficients were found in another meta-analysis that was performed to examine the impact of BP tracking on longitudinal intervention trials (Toschke et al., 2010). Taken together, these data indicate that BP does track over time at a population level and support interventions designed to prevent future development of hypertension.

Hypertensive Target Organ Damage in the Young

Left ventricular hypertrophy (LVH), increased carotid intima media thickness (cIMT), and even impaired cognitive function stand as concrete evidence of the consequences of elevated BP in childhood and the potential for lifelong morbidity. LVH was first demonstrated to occur in hypertensive youth by Laird and Fixler (1981) and has subsequently been shown to occur in a significant proportion of hypertensive children and

adolescents, with reported prevalences ranging between 20% and 41% depending upon the diagnostic criteria utilized (Brady et al., 2008; Flynn & Alderman, 2005; Hanevold et al., 2004; McNiece et al., 2007b; Sorof et al., 2003). The prevalence of LVH may be affected by ethnicity (Brady et al., 2010; Hanevold et al., 2004), concurrent obesity (Falkner et al., 2013; Hanevold et al., 2004), and the degree of BP elevation (Falkner et al., 2013; McNiece et al., 2007b). Only one study performed in hypertensive children has failed to demonstrate any relationship between LVH and specific parameters of BP elevation (Brady et al., 2008).

Increased cIMT, well documented as a cardiovascular consequence of elevated BP in large population studies (Vos et al., 2003), has also been found in children and adolescents with primary hypertension in single-center reports (Lande et al., 2006; Litwin et al., 2006; Sorof et al., 2003). While early studies of cIMT in hypertensive youth were confounded by the effects of obesity (Litwin et al., 2006; Sorof et al., 2003), one carefully conducted study that controlled for body mass index (BMI) demonstrated a definitive relationship between elevated BP itself and increased cIMT in young patients (Lande et al., 2006).

An additional target organ effect of elevated BP that has been described in the young is impaired cognitive function (Lande et al., 2003). While longstanding hypertension has long been recognized as a risk factor for the development of cognitive impairment and even dementia in the elderly (Paglieri et al., 2004), this study demonstrated that children and adolescents with BP greater than 90th percentile had poorer performance on selected tests of cognition compared to normotensive children. In a recent follow-up study, hypertensive children were found to have decreased executive function that was associated with decreased cerebrovascular reactivity in response to hypercapnia (Ostrovskaya et al., 2013). These provocative findings, while requiring confirmation, add impetus to consensus recommendations for instituting antihypertensive drug therapy in children and adolescents with persistently elevated BP.

Fewer pediatric data are available on the other major target organ effect of hypertension, namely renal damage. Although hypertension commonly accompanies chronic kidney disease (CKD) in children, it is rarely its cause (Shatat & Flynn, 2005). Even microalbuminuria, which is commonly seen in hypertensive adults, is infrequently seen in children with isolated hypertension, even when LVH is present (Sorof et al., 2004b). However, a more recent study

demonstrated that approximately 58% of hypertensive adolescents had microalbuminuria, with an increased prevalence in stage 2 hypertension compared to stage 1 (Assadi, 2007). Reduction of BP in the latter study was accompanied by a reduction in both microalbuminuria and LVH. And another study showed that children with prehypertension on ambulatory BP monitoring (ABPM) had higher urinary protein excretion and lower glomerular filtration rate than normotensive children, albeit within the normal range (Lubrano et al., 2009). Thus, there may be increasing evidence that high BP even in childhood has detrimental renal effects.

Childhood BP and Subsequent CV Disease

As has been recently pointed out by the U.S. Preventive Services Task Force (Thompson et al., 2013), there are no data at present that clearly document a relationship between childhood BP and cardiovascular morbidity and mortality in adulthood. However, a number of studies have shown that BP and other traditional cardiovascular risk factors in childhood predict the subsequent presence of increased cIMT (Davis et al., 2001; Li et al., 2003; Raitakari et al., 2003; Vos et al., 2003) and increased arterial stiffness (Juonala et al., 2006; Li et al., 2004), two well-accepted surrogate markers for atherosclerosis.

Additionally, longitudinal studies have demonstrated that children with elevated BP are at increased risk of development of the metabolic syndrome as adults (Sun et al., 2007) and that components of the metabolic syndrome, an important risk factor for cardiovascular morbidity, track over time from childhood to adulthood (Chen et al., 2007). Taken together, these data indicate that over time, adult morbidity and mortality will be more tightly connected with childhood precursors and emphasize the need for early intervention (Expert Panel, 2011).

POTENTIAL CAUSATIVE FACTORS OF CHILDHOOD HYPERTENSION

Multiple factors have been reported to correlate with BP levels in children (Table 16-2) and have been examined as potential causative factors for childhood hypertension. Some factors are either genetic or environmental, but most have contributions of both. Height, body

TABLE 16-2

Factors Related to Blood Pressure Levels in Children and Adolescents

Genetic/Familial

- Autonomic abnormalities (Lopes et al., 2000)
- Deletion of the ACE gene (Taittonen et al., 1999)
- Ethnicity (Hohn et al., 1994; Sorof et al., 2004a)
- Increased salt sensitivity in African Americans (Wilson et al., 1996)
- Obesity (Sorof et al., 2004a)
- Parental and sibling BP levels (Schieken, 1993)
- Parental smoking (Giussani et al., 2013)

Environmental

- Birth weight (Huxley et al., 2002)
- Breast-feeding (Martin et al., 2004)
- Early childhood growth (Belfort et al., 2007)
- Neonatal weight gain (Singhal et al., 2004)
- Socioeconomic status (Dekkers et al., 2002)
- Exercise/physical activity (Alpert, 2000; Giussani et al., 2013; Knowles et al., 2013)

Mixed Genetic and Environmental

- Height (Daniels et al., 1996)
- Weight (Sorof et al., 2004a)
- Body mass (Kvaavik et al., 2003)
- Pulse rate (Zhou et al., 2000)
- Somatic growth and sexual maturation (Daniels et al., 1996)
- Sodium and other nutrient intakes (Falkner et al., 2000)
- Sympathetic nervous system reactivity (Urbina et al., 1998)
- Stress (Saab et al., 2001)
- Uric Acid (Feig & Johnson, 2007)

mass, and somatic development depend not only on genetic influences but also on nutrition and exercise.

The Critical Role of Obesity

Obesity is growing at an alarming pace among children and adolescents in all developed societies, with—as in many other aberrant behaviors—the U.S. leading the way (Wang & Lobstein, 2006). Recent data indicate that this trend shows no signs of abating (Ogden et al., 2010); indeed, among younger children, the prevalence of obesity continues to increase worldwide (de Onis et al., 2010). Unfortunately, adolescent obesity tracks closely with adult obesity (Kvaavik et al., 2003), setting the foundation for all of the consequences. Interestingly, a recent meta-analysis indicates that childhood obesity alone is not an

independent factor for adult cardiovascular disease, except among those whose BMI increases from childhood to adulthood, supporting the concept that intervention in childhood is crucial for prevention of adult cardiovascular disease (Lloyd et al., 2010).

Mainly as a consequence of increasing obesity, the mean BP of US children and adolescents has risen by 1.4/3.3 mm Hg from 1990 to 2000 (Muntner et al., 2004), and the prevalence of hypertension and prehypertension has increased (Din-Dzietham et al., 2007). The pathophysiologic links between childhood obesity and the development of hypertension, including the crucial role of sympathetic nervous system activation, have recently been reviewed (Flynn, 2013).

Low Birth Weight and Early Childhood Growth

Population studies conducted by Barker and others have demonstrated an inverse correlation between birth weight and adult BP (Gamborg et al., 2007; Law et al., 2002; Zureik et al., 1996). A relationship between birth weight and coronary heart disease and type 2 diabetes has also been noted (Barker et al., 2002). Proposed explanations for these findings include deficient maternal nutrition (Barker et al., 1993; Law et al., 1991), possibly leading to acquisition of a reduced number of nephrons (Mackenzie et al., 1996). Autopsy studies demonstrating a reduced number of nephrons in patients with primary hypertension (Keller et al., 2003) have added intriguing evidence to the latter hypothesis.

Other data indicate that early childhood growth may be more important than birth weight as an influence on future BP. Those children who were small at birth but who have accelerated weight gain either very early after birth (Singhal et al., 2003) or between ages 1 and 5 (Law et al., 2002) have more insulin resistance, obesity, and hypertension later in life. This association between rapid postnatal weight gain and higher BP has been prospectively documented in 3-year-olds (Belfort et al., 2007), 8-year-olds (Burke et al., 2004), and 11- to 14-year-olds (Falkner et al., 2004).

Those infants who are breast-fed and thereby have a lower rate of weight gain during infancy have lower BPs in later life than those who are fed enriched formula (Singhal et al., 2001). Although this protection against higher BP by breast-feeding may have been exaggerated by selective publication (Owen et al., 2003), the weight of evidence supports an association

(Martin et al., 2004). Whether there is more to breast-feeding than a reduced rate of excess weight gain (Grummer-Strawn & Mei, 2004) is uncertain, but slower early growth appears to be beneficial for long-term cardiovascular health (Singhal et al., 2004).

Genetic Factors

The heritability of BP was established decades ago by the findings of a correlation of BP levels between parents and their natural offspring but no correlation between parents and their adopted children (Biron et al., 1976). Recently published studies have demonstrated that a large percentage of children and adolescents with primary hypertension have positive family histories of hypertension in a parent or grandparent (Flynn & Alderman, 2005; Robinson et al., 2005). Genetic influences on BP have been shown in comparisons of siblings (Wang et al., 1999) and twins (Kupper et al., 2006).

Table 16-3 lists some of the differences reported among normotensive children with a positive family history versus those with a negative family history of hypertension. It is likely that yet-undiscovered genetic polymorphisms may account for the development of

TABLE 16-3

Characteristics of FH+ Normotensive Compared with FH- Normotensives

- ↑ Carotid artery stiffness (Meaney et al., 1999)
- ↑ Blood pressure reactivity (Lemne, 1998)
- ↑ Leptin and insulin levels (Makris et al., 1999)
- ↑ Pulse and DBP with dynamic exercise; ↑ pulse with isometric exercises (Mehta et al., 1996)
- ↑ SBP in African American male adolescents homozygous for the deletion polymorphism of the ACE gene (Taittonen et al., 1999)
- ↑ Rate of sodium-lithium countertransport (McDonald et al., 1987)
- ↑ Sleep BP in African American adolescents as measured with ABPM (Harshfield et al., 1994)
- ↑ Activity of components of the autonomic nervous system (Lopes et al., 2000)
- Cardiac indices:
 - ↑ Intravascular septum:posterior wall mass index ratio (de Leonardis et al., 1988)
 - ↑ Thickness of the interventricular septum during systole (Hansen et al., 1992)
 - ↑ LVMI (van Hoof et al., 1993)

SBP, systolic blood pressure.

“primary” hypertension in families and that these in combination with environmental factors may explain the early appearance of hypertension in some non-obese children and adolescents.

Environmental Factors

Of environmental factors that can affect BP, increased body mass has already been discussed as a major determinant of higher BP levels throughout childhood and adolescence. The relationship between sodium and BP is comprehensively reviewed in Chapter 6. A recent analysis of childhood sodium intake and BP conducted in Great Britain showed that an increase of 1 g/day in salt intake was related to an increase of 0.4 mm Hg in systolic BP (He et al., 2008). Sodium intake may exert its effect on BP in those who are genetically predisposed to higher BP levels and are sodium sensitive, especially African Americans (Wilson et al., 1996). Obese adolescents also have heightened responsiveness to sodium intake (Rocchini et al., 1989).

Other dietary constituents, including calcium, potassium, protein and fiber, have been shown in an intervention study to have inverse associations with BP in children and adolescents (Simons-Morton et al., 1997). Increased intake of dairy products in 8-year-old children leads to higher intake of calcium, potassium, and magnesium, which was accompanied by lower systolic and diastolic BP (Rangan et al., 2012). In another study, Falkner et al. (2000), using folate as a surrogate for adequacy of micronutrient intake, concluded that African American adolescents with higher folate and micronutrient intakes had lower mean diastolic BP. Caffeine intake has also been associated with an elevated BP in adolescents, with the effect greater in African Americans than in Caucasians (Savoca et al., 2004).

PREVENTION OF HYPERTENSION

The need for early recognition and appropriate management of elevated BP in children is being increasingly emphasized (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). Practitioners working with children and their families are in an ideal position to introduce preventive measures that will ensure future cardiovascular health (Expert Panel, 2011; Kavey et al., 2003).

Children and their families need detailed information about optimal dietary intakes, with appropriate cultural orientation. Once the dietary needs for cholesterol and myelination of the central nervous system have been met (typically by the age of 2 years), recommendations for a prudent intake of fat such as in the DASH diet (Appel et al., 1997; Couch et al., 2008) should be provided. Family meals are an ideal setting to create lifetime healthful food habits.

Similarly, family activities that include age-appropriate exercise are helpful, not only to prevent hypertension but also to control obesity (Torrance et al., 2007). Families must be informed of the deleterious effects of pressor agents—including tobacco, street drugs, and nonsteroidal anti-inflammatory drugs—and their potential to increase BP with chronic use. With these proactive steps, the health of children will be improved. Whether adult hypertension will be prevented remains unknown.

CLASSIFICATION AND DIAGNOSIS OF HYPERTENSION IN CHILDREN AND ADOLESCENTS

Diagnostic criteria for elevated BP in childhood are based on the concept that BP in children increases with age and with body size, which makes it impossible to utilize a single BP level to define hypertension as is done in adults. This was recognized by early investigators of juvenile hypertension, who initially adopted the adult threshold of 140/90 but later realized that this represented a severe level of BP elevation in pediatrics, particularly in young children, and that population data were needed in order to better define the normal BP distribution and what constitutes an elevated BP in the young (Loggie, 1977).

Under the auspices of the National Heart, Lung and Blood Institute, consensus guidelines with recommendations for identification and management of elevated BP in childhood have been issued on four occasions since 1977. These guidelines have also included normative data on childhood BP derived from large-scale, cross-sectional studies of BP in healthy children. The most recent of these guidelines “The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents” (National High Blood Pressure Education Program Working Group on

High Blood Pressure in Children and Adolescents, 2004) adapted terminology and staging criteria utilized in the JNC-7 consensus guidelines for adult hypertension (Chobanian et al., 2003) to the problem of childhood hypertension and emphasized the prevention of adult cardiovascular disease by early intervention in children and adolescents with elevated BP.

Since the publication of the Fourth Report, two additional sets of guidelines for childhood hypertension have been issued (Expert Panel, 2011; Lurbe et al., 2009), but with one notable exception (see discussion of treatment), neither of these documents differ substantially from the Fourth Report. Given the increase in knowledge about high BP in the young in the decade since publication of the Fourth Report, a revised pediatric guideline is clearly needed.

Definitions and Classification of Elevated Blood Pressure

As noted above, the definitions of normal and elevated BP in children aged 1 to 17 years are statistical constructs based upon the distribution of childhood BP:

- Normal BP: systolic and diastolic BP less than 90th percentile for age, gender and height (Tables 16-4 and 16-5)
- Prehypertension: systolic or diastolic BP between the 90th and 95th percentiles, or BP $\geq 120/80$ in an adolescent
- Hypertension: systolic and/or diastolic BP persistently ≥ 95 th percentile

While it would be preferable to have a risk-based definition of hypertension in the young (Chioloro, 2014),

TABLE 16-4

Blood Pressure Levels for Boys by Age and Height Percentile^a

Age (Year)	BP Percentile ↓	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		← Percentile of Height →							← Percentile of Height →						
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
1	50	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99	117	118	120	122	124	125	126	82	82	83	84	85	86	86

TABLE 16-4

Blood Pressure Levels for Boys by Age and Height Percentile^a (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		← Percentile of Height →													
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
8	50	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99	139	140	141	143	145	146	147	92	93	93	94	95	96	97

^aTo use the table, first plot the child's height on a standard growth curve (www.cdc.gov/growthcharts). The child's measured SBP and DBP are compared with the numbers provided in the table according to the child's age and height percentile.

BP, blood pressure.

Reproduced from National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. National Heart, Lung, and Blood Institute, Bethesda, Maryland. *Pediatrics* 2004;114:555–576.

TABLE 16-5

Blood Pressure Levels for Girls by Age and Height Percentile^a

Age (Year)	BP Percentile	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		← Percentile of Height →													
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
1	50	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99	127	127	128	130	131	132	133	86	86	87	88	88	89	90

TABLE 16-5

Blood Pressure Levels for Girls by Age and Height Percentile^a (Continued)

Age (Year)	BP Percentile ↓	Systolic BP (mm Hg)							Diastolic BP (mm Hg)						
		← Percentile of Height →													
		5	10	25	50	75	90	95	5	10	25	50	75	90	95
13	50	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	50	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	50	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	50	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95	125	126	127	128	130	131	132	82	82	83	84	85	85	86
17	50	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95	125	126	127	129	130	131	132	82	83	83	84	85	85	86
17	99	133	133	134	136	137	138	139	90	90	91	91	92	93	93

^aTo use the table, first plot the child's height on a standard growth curve (www.cdc.gov/growthcharts). The child's measured SBP and DBP are compared with the numbers provided in the table according to the child's age and height percentile.

BP, blood pressure.

Reproduced from National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. National Heart, Lung, and Blood Institute, Bethesda, Maryland. *Pediatrics* 2004;114:555–576.

the above statistical definitions remain the only ones available at present.

The Fourth Report additionally provides guidelines for staging the severity of hypertension in children and adolescents, which can then be used clinically to guide evaluation and management (Table 16-6). Children or adolescents with stage 2 hypertension should be evaluated and treated more quickly and/or aggressively than those with lower degrees of BP elevation. The overall approach to the classification of elevated BP in children and adolescents is summarized in Figure 16-2.

Assessment

Confirmation of BP Elevation

The first step in evaluating the hypertensive child or adolescent is to confirm that the BP is truly elevated.

Since the BP distributions published in the Fourth Report are based upon auscultated BPs, and given the inherent inaccuracies of oscillometric BPs and their variation from auscultated BPs in the young (Butani & Morgenstern, 2003; Eliasdotir et al., 2013; Park et al., 2001), it is recommended that if a child's BP is found to be elevated using an automated device, it should be confirmed by auscultation. Exceptions to this would include infants and young children who are unable to cooperate with manual BP determination. Furthermore, unless there are symptoms of hypertension present, the child's or adolescent's BP should be shown to be elevated on at least three occasions before making the diagnosis of hypertension (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004).

TABLE 16-6

Classification of Hypertension in Children and Adolescents, with Measurement Frequency and Therapy Recommendations

	SBP or DBP Percentile^a	Frequency of BP Measurement	Therapeutic Lifestyle Changes	Pharmacologic Therapy
Normal	<90th	Recheck at next scheduled physical examination	Encourage healthy diet, sleep, and physical activity	—
Prehypertension	90th to <95th or if BP exceeds 120/80 even if below 90th percentile up to <95th percentile ^b	Recheck in 6 mo	Weight management counseling if overweight; introduce physical activity and diet management	None unless compelling indications such as CKD, diabetes mellitus, heart failure, and LVH
Stage 1 hypertension	95th percentile to the 99th percentile plus 5 mm Hg	Recheck in 1–2 wk or sooner if the patient is symptomatic; if persistently elevated on two additional occasions, evaluate or refer to the source of care within 1 mo	Weight management counseling if overweight; introduce physical activity and diet management	Initiate therapy based on indications in Table 16-6 or if compelling indications as above
Stage 2 hypertension	>99th percentile plus 5 mm Hg	Evaluate or refer to the source of care within 1 wk (or immediately) if the patient is symptomatic	Weight management counseling if overweight; introduce exercise and diet management	Initiate therapy

^aFor sex, age, and height measured on at least three separate occasions; if systolic and diastolic categories are different, categorize by the higher value.

^bThis occurs typically at 12 years old for SBP and at 16 years old for DBP.

BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; SBP, systolic blood pressure.

Adapted from National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. National Heart, Lung, and Blood Institute, Bethesda, Maryland. *Pediatrics* 2004;114:555–576.

Techniques for manual BP measurement recommended by the American Heart Association (Pickering et al., 2005) with respect to cuff size, patient position, etc. should be followed in children and adolescents whenever feasible. As in adults, the fifth Korotkoff sound should be reported as the diastolic BP, except in those children and adolescents in whom Korotkoff sounds can be heard down to “zero”; in such children, the fourth Korotkoff sound should be reported as the diastolic BP (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004).

Ambulatory BP Monitoring, White-Coat and Masked Hypertension

ABPM has been endorsed as an appropriate technique for the evaluation of elevated BP in children and adolescents (Flynn et al., 2014; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004; Urbina et al., 2008). Recommended indications for performance of ABPM in children include identification of white-coat and masked hypertension, assessment of BP control in those treated with antihypertensive medications, and investigation of hypotensive episodes

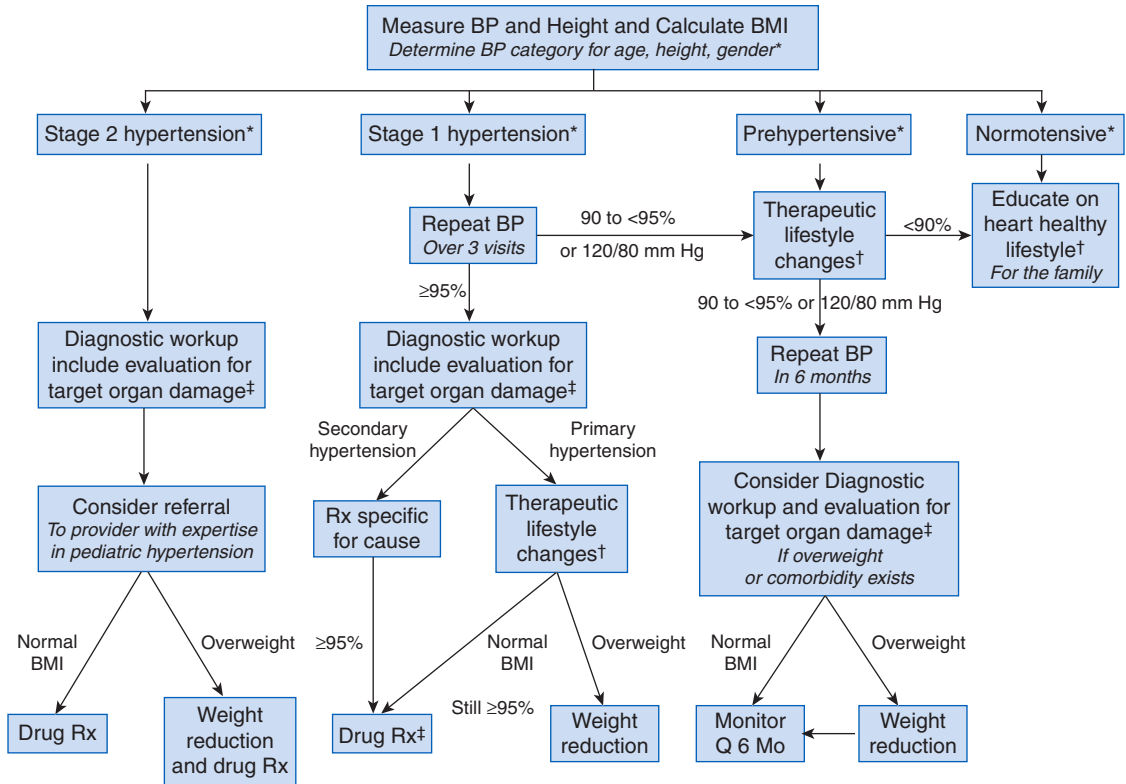


FIGURE 16-2 • Suggested management algorithm for children and adolescents with elevated blood pressure. BMI, body mass index; Q, every. *See Tables 16-4–16-6. †Diet modification and physical activity. ‡Especially if younger, very high BP, little or no family history, diabetic, or other risk factors. (Reproduced from National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. National Heart, Lung, and Blood Institute, Bethesda, Maryland. *Pediatrics* 2004;114:555–576.)

(Flynn & Urbina, 2012; Flynn et al., 2014; Lurbe et al., 2004; Urbina et al., 2008). The use of ABPM in a referred pediatric population has been shown to reduce the cost of evaluation of elevated BP by identifying those with white-coat hypertension, who then could receive a less-extensive workup (Swartz et al., 2008).

Children and adolescents with secondary hypertension have been found to have more significant nocturnal hypertension and greater daytime diastolic hypertension than those with primary hypertension (Flynn, 2002) as well as blunted nocturnal dipping (Seeman et al., 2005), suggesting that ambulatory monitoring can be used to identify children who need a more exhaustive evaluation for underlying causes of secondary hypertension.

White-coat hypertension appears to be at least as common in children as it is in adults (Flynn & Urbina, 2012), although it should be noted that white-coat hypertension is less likely at higher levels of office BP (Sorof et al., 2001). Several studies have indicated that

children found to have white-coat hypertension actually have early signs of target organ damage, such as increased left ventricular mass (Kavey et al., 2007; Lande et al., 2008; Stabouli et al., 2005). These data, in combination with the data from tracking studies that suggest that these children are likely at increased risk of development of hypertension in the future, imply that children found to have white-coat hypertension should receive lifestyle modification and should be followed prospectively for the development of definite hypertension.

Masked hypertension has also been recently described in pediatric populations (Lurbe et al., 2005; Matsuoka & Awazu, 2004; Stabouli et al., 2005) and is associated with hypertensive target organ damage, specifically LVH (Lurbe et al., 2005; McNiece et al., 2007b; Stabouli et al., 2005; Urbina, 2008). Such children probably merit further evaluation for underlying causes of hypertension and institution of pharmacologic treatment. However, since ABPM remains a specialized

technique in pediatrics, further studies are needed to identify groups of children at increased risk of masked hypertension who could benefit from ABPM.

Differential Diagnosis

Traditionally, most hypertension in children has been felt to be secondary to an underlying disorder. As can be seen in Table 16-7, this is certainly the case for infants and young children. In hypertensive children in these age groups, renal disease, renovascular disease, and cardiac disease will often be found after an appropriate diagnostic evaluation. This was illustrated quite clearly in a recently published analysis of subjects enrolled in two antihypertensive drug studies: 80% of enrolled children less than 6 years of age had secondary causes of hypertension (Flynn et al., 2012). Primary hypertension in young children is therefore usually considered a diagnosis of exclusion.

In adolescents, however, hypertension is most likely to be primary in origin. This was demonstrated two decades ago in a study of over 1,000 hypertensive children evaluated at a Polish children's hospital (Wyszynska et al., 1992). In this series, the vast majority of adolescents with persistent BP elevation had no identifiable underlying cause found. Other features that support the diagnosis of primary hypertension include normal growth (and/or obesity), lack of symptoms of hypertension, unremarkable past medical history, and a family history of hypertension (Flynn & Alderman, 2005). Hypertensive adolescents that fit this profile may not need as extensive an evaluation as those who do not.

Diagnostic Evaluation

Hypertension in childhood and adolescence is typically asymptomatic, although up to half of patients may report one or more symptoms, most frequently headache (Croix & Feig, 2006). In adolescent athletes, headaches may occur after strenuous exercise. Symptoms such as seizures, nosebleeds, dizziness, and syncope are rare and, if present, suggest that the BP elevation has been exacerbated by ingested substances or by emotional upset. On the other hand, if these symptoms occur in conjunction with elevated BP in a younger child, they may be a clue to the presence of secondary hypertension. For this reason, it is important to include a systems review designed to elicit signs and symptoms of underlying conditions such as renal disease that may be causing the elevated BP.

The family history should include not only hypertension but also associated conditions and complications such as dyslipidemia, stroke, myocardial infarction, and diabetes. Many substances commonly used or abused in children and adolescents can elevate BP, including prescribed and over-the-counter medications (e.g., corticosteroids or decongestants) and street drugs such as amphetamines and cocaine.

The physical examination should begin with plotting of growth parameters, especially height and BMI, and measurement of BP in both arms and at least one leg. From there, the examination should be focused on detecting the signs of secondary causes of hypertension, such as decreased femoral pulses, abdominal bruits, and cushingoid stigmata (Table 16-8).

TABLE 16-7

Causes of Childhood Hypertension by Age Group

Table with 4 columns: Cause, Infants* (%), School-Age (%), and Adolescents (%). Rows include Primary/Essential, Secondary (Renal parenchymal disease, Renovascular, Endocrine, Aortic coarctation, Reflux nephropathy, Neoplastic, Miscellaneous).

*Less than 1 y of age.

^bBreakdown of causes is generally similar to that for school-age children.

TABLE 16-8

Physical Examination Findings and Etiology of Hypertension in Children and Adolescents

	Finding	Possible Etiology
Vital signs	Tachycardia	Hyperthyroidism, pheochromocytoma, neuroblastoma, primary hypertension
	Diminished femoral pulses; BP lower in the legs than arms	Aortic coarctation
Height/weight	Growth retardation	Chronic renal failure
	Obesity	Primary hypertension, metabolic syndrome
Head and neck	Truncal/central obesity	Cushing syndrome
	Moon facies	Cushing syndrome
	Elfin fades	Williams syndrome (renovascular)
	Webbed neck	Turner syndrome (coarctation of the aorta)
Skin	Thyromegaly, proptosis	Hyperthyroidism
	Pallor, flushing, diaphoresis	Pheochromocytoma
	Acne, hirsutism, striae	Cushing syndrome, anabolic steroid abuse
	Café-au-lait spots	Neurofibromatosis (renovascular), von Hippel-Lindau disease (pheochromocytoma)
Chest	Adenoma sebaceum	Tuberous sclerosis (renal cystic disease)
	Malar rash	Systemic lupus erythematosus
	Widely spaced nipples/shield chest	Turner syndrome (coarctation of the aorta)
	Heart murmur	Aortic coarctation
Abdomen	Friction rub	Systemic lupus erythematosus (pericarditis)
	Apical heave	LVH/chronic hypertension
	Mass	Wilms tumor, neuroblastoma, pheochromocytoma
	Epigastric/flank bruit	Renal artery stenosis
Genitalia Extremities	Palpable kidneys	Polycystic kidney disease, hydronephrosis, multicystic dysplastic kidney
	Ambiguous/virilization	Adrenal hyperplasia
	Edema	Renal parenchymal disease
	Joint swelling	Systemic lupus erythematosus
	Muscle weakness	Hyperaldosteronism, Liddle syndrome

Except in young children, the likelihood that an asymptomatic child with persistently elevated BP will have an underlying cause for the elevation is remote low. In children with an identifiable cause for their hypertension, the history and physical examination usually reveal suggestive evidence of the cause, so detailed diagnostic evaluation of children without suggestive evidence is not warranted. Basic screening tests, including serum chemistries and lipids as well as a urinalysis, should be obtained in all patients. Specific specialized studies may be required in some children, particularly those with symptomatic hypertension or stage 2 hypertension (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004; Varda & Gregoric, 2005).

As discussed above, consideration should be given to including ABPM in evaluation of all children and adolescents with persistent office BP elevation

(Flynn & Urbina, 2012), in order to identify children with white-coat hypertension and also to identify those with possible secondary hypertension. Given the high frequency of LVH in hypertensive children and adolescents (Flynn & Alderman, 2005; Hanevold et al., 2004; Sorof et al., 2004b), echocardiography should be considered part of the baseline evaluation, especially if pharmacologic intervention is required, so that reversal of abnormalities can be monitored and correlated with the adequacy of BP control.

MANAGEMENT OF HYPERTENSION IN CHILDREN AND ADOLESCENTS

Treatment of hypertension in children and adolescents is still largely empiric because there are no long-term

studies of either dietary intervention or drug therapy. Even though more data are now available on safety and effectiveness of drug therapy than in the past (Ferguson & Flynn, 2013), the decision as to whether a specific child should receive medication must be individualized.

Nonpharmacologic Management

Guideline-issuing organizations emphasize that treatment of hypertension in children and adolescents should begin with nonpharmacologic measures (Fig. 16-2) (Expert Panel, 2011; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). Although the magnitude of change in BP may be modest, weight loss, aerobic exercise, and dietary modifications have been shown to reduce BP in children and adolescents (Bianchini et al., 2013; Maggio et al, 2011; Torrance et al., 2007). For example, for exercise, sustained training over 3 to 6 months has been shown to result in a reduction of 6 to 12 mm Hg for systolic BP and 3 to 5 mm Hg for diastolic BP (Alpert, 2000). Exercise has been shown to improve body composition and reduce other cardiovascular risk factors associated with obesity (Zorba et al., 2011). However, cessation of training is generally promptly followed by a rise in BP to preexercise levels. It is important to emphasize that aerobic exercise activities such as running, walking, and cycling are preferred to static forms of exercise in the management of hypertension.

Many children may already be participating in one or more appropriate activities and may only need to increase the frequency and intensity of these activities to see a benefit in terms of lower BP. Along the same lines, it is important to note that baseline physical activity has been shown to be inversely related to BP in children as young as 5 to 7 years (Knowles et al., 2013). Hypertension is *not* considered a contraindication to participation in competitive sports, so long as the child's BP is "controlled" (McCambridge et al., 2010).

Several studies have demonstrated that weight loss in obese children and adolescents lowers BP (Hobkirk et al., 2012; Torrance et al., 2007). Weight loss not only decreases BP but also improves other cardiovascular risk factors such as dyslipidemia and insulin resistance (Bianchini et al., 2013; Reinehr et al., 2006). In studies where a reduction in BMI of about 10% was achieved, short-term reductions in BP were in the range of 8 to 12 mm Hg. Unfortunately, weight loss is notoriously difficult and usually

unsuccessful, especially in the primary care setting. Comprehensive programs have better success rates. However, identifying a complication of obesity such as hypertension can perhaps provide the necessary motivation for patients and families to make the appropriate lifestyle changes.

The role of diet in the treatment of hypertension has received a great deal of attention, most of which has focused on sodium. Once hypertension has been established, "salt sensitivity" becomes more common, and reduction in sodium intake may be of benefit (Cutler, 1999; Hanevold, 2013). Other dietary constituents that have been examined in patients with hypertension include potassium and calcium, both of which have been shown to have antihypertensive effects (Cutler, 1999; Mu et al., 2005). Therefore, a diet that is low in sodium and enriched in potassium and calcium may be even more effective than a diet that restricts sodium only.

An example of such a diet is the so-called "DASH" diet, which has been shown to have a clear BP-lowering effect in adults with hypertension, even in those receiving antihypertensive medication (Appel et al., 1997). A study of a DASH-type eating plan confirmed its efficacy in lowering the BP in hypertensive children (Couch et al., 2008). The DASH diet also incorporates measures designed to reduce dietary fat intake, an important strategy given the frequent presence of both hypertension and elevated lipids in children and adolescents and the imperative to begin prevention of adult cardiovascular disease at as early an age as possible (Expert Panel, 2011; Kavey et al., 2003).

Pharmacologic Management

As discussed earlier, ample data exist documenting the development of hypertensive target organ damage in hypertensive children and adolescents, and a growing body of data suggests that elevated BP in the young may have adverse cardiovascular effects in adulthood. However, it has also been argued that the long-term consequences of untreated hypertension in an asymptomatic, hypertensive child or adolescent without underlying secondary hypertension or hypertensive target organ damage are completely unknown (Thompson et al., 2013). There is also a significant lack of data on the long-term effects of antihypertensive medications on the growth and development of children. Therefore, a definite indication for initiating pharmacologic therapy should be ascertained before medication is prescribed.

Accepted indications for use of antihypertensive medications in children and adolescents include the following (Lurbe et al., 2009; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004):

- Symptomatic hypertension
- Secondary hypertension
- Hypertensive target organ damage
- Diabetes (types 1 and 2)
- Persistent hypertension despite nonpharmacologic measures (Fig. 16-2)
- Stage 2 hypertension

Pharmacologic reduction of BP for hypertensive children who fall into one of these categories is felt to result in health benefit.

The number of antihypertensive medications that have been systematically studied in children has increased markedly over the past decade due to incentives provided to the pharmaceutical industry under the auspices of the 1997 Food and Drug Administration Modernization Act (FDAMA) and subsequent legislation (Ferguson & Flynn, 2013; Flynn, 2003; Welch et al., 2012). Published results of the industry-sponsored clinical trials (which have been summarized elsewhere [Ferguson & Flynn, 2013]) can be used to guide the prescribing of antihypertensive agents in children and adolescents who require pharmacologic treatment, thereby increasing the confidence of the practitioner who treats such children. The dosing recommendations contained in Table 16-9 incorporate data from many of these studies.

No studies demonstrating a specific benefit of one class of antihypertensive agent over another are available for the pediatric age group; therefore, the choice of initial antihypertensive agent for use in children remains up to the preference of the individual practitioner. Diuretics and β -adrenergic blockers, which were recommended as initial therapy in the First and Second Task Force Reports (Blumenthal et al., 1977; Task Force on Blood Pressure Control in Children, 1987), have a long track record of safety and efficacy in hypertensive children and are still widely used in the young despite a lack of FDA-approved pediatric labeling (Welch et al., 2012). Newer classes of agents, including angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and angiotensin receptor blockers (ARBs), have been shown to be safe and well tolerated in hypertensive children in recent industry-sponsored trials (Ferguson & Flynn, 2013), now have pediatric labeling, and may be prescribed if indicated.

Consideration should be given to using specific classes of antihypertensive medications in hypertensive children with specific underlying or concurrent medical conditions (Ferguson & Flynn, 2013). The best example of this would be the use of ACE inhibitors or ARBs in children with diabetes or proteinuric renal diseases (Lurbe et al., 2009). This parallels the approach outlined in the JNC-7 report, which recommends that specific classes of antihypertensive agents be used in adults in certain high-risk categories (Chobanian et al., 2003).

Antihypertensive drugs in children are generally prescribed in a stepped-care manner (Fig. 16-3): The child is initially started on the lowest recommended dose, and then the dose is increased until the highest recommended dose is reached, or until the child experiences adverse effects from the medication, at which point a second drug from a different class should be added, and so on, until the desired goal BP is reached. Treatment goals recommended by the Fourth Report are less than 95th percentile for children with primary hypertension and less than 90th percentile for hypertensive children with secondary hypertension or hypertensive target organ damage (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004). The European Society of Hypertension has recommended lower goals, less than 90th percentile for children with primary hypertension and less than 75th percentile for children with secondary hypertension, particularly those with CKD (Lurbe et al., 2009). A recent study conducted in the Czech Republic demonstrated that it can be difficult to reach these lower BP goals in the pediatric age group, especially without using multiple drugs (Seeman & Gilik, 2013).

Although not an antihypertensive medication, allopurinol has been reported effective in lowering BP in a small study of hypertensive adolescents (Feig et al., 2008), supporting a pathophysiologic role for uric acid in the development of hypertension (Feig & Johnson, 2007). However, further confirmatory studies are required before uric acid reduction can be advocated as a treatment of hypertension, especially given the known adverse risk profile of allopurinol (Yanik & Feig, 2013).

Treatment of childhood hypertension should include ongoing monitoring of BP, surveillance for medication side effects, periodic monitoring of renal function and electrolytes (in children treated with ACE inhibitors, ARBs, or diuretics), counseling

TABLE 16-9

Recommended Doses for Selected Antihypertensive Agents for Use in Hypertensive Children and Adolescents

Class	Drug	Starting Dose	Interval	Maximum Dose ^a
Aldosterone receptor antagonists	Eplerenone	25 mg/d	QD–BID	100 mg/d
	Spirolactone ^b	1 mg/kg/d	QD–BID	3.3 mg/kg/d up to 100 mg/d
ACE inhibitors	Benazepril ^b	0.2 mg/kg/d up to 10 mg/d	QD	0.6 mg/kg/d up to 40 mg/d
	Captopril ^b	0.3–0.5 mg/kg/dose	BID–TID	6 mg/kg/d up to 450 mg/d
	Enalapril ^b	0.08 mg/kg/d	QD	0.6 mg/kg/d up to 40 mg/d
	Fosinopril	0.1 mg/kg/d up to 10 mg/d	QD	0.6 mg/kg/d up to 40 mg/d
	Lisinopril ^b	0.07 mg/kg/d up to 5 mg/d	QD	0.6 mg/kg/d up to 40 mg/d
	Quinapril	5–10 mg/d	QD	80 mg/d
Angiotensin receptor blockers	Candesartan	4 mg/d	QD	32 mg/d
	Losartan ^b	0.75 mg/kg/d up to 50 mg/d	QD	1.4 mg/kg/d up to 100 mg/d
	Olmesartan	20–35 kg: 10 mg/d ≥35 kg: 20 mg/d	QD	20–35 kg: 20 mg/d ≥35 kg: 40 mg/d
	Valsartan ^b	1.3 mg/kg/d up to 40 mg/d <6 y: 5–10 mg/d	QD	2.7 mg/kg/d up to 160 mg/d <6 y: 80 mg/d
α- and β-adrenergic antagonists	Labetalol ^b	2–3 mg/kg/d	BID	10–12 mg/kg/d up to 1.2 g/d
	Carvedilol	0.1 mg/kg/dose up to 6.25 mg BID	BID	0.5 mg/kg/dose up to 25 mg BID
β-adrenergic antagonists	Atenolol ^b	0.5–1 mg/kg/d	QD–BID	2 mg/kg/d up to 100 mg/d
	Bisoprolol/HCTZ	0.04 mg/kg/d up to 2.5/6.25 mg/d	QD	10/6.25 mg/d
	Metoprolol	1–2 mg/kg/d	BID	6 mg/kg/d up to 200 mg/d
	Propranolol	1 mg/kg/d	BID–TID	8 mg/kg/d up to 640 mg/d
Calcium channel blockers	Amlodipine ^b	0.1 mg/kg/d	QD	0.6 mg/kg/d up to 10 mg/d
	Felodipine	2.5 mg/d	QD	10 mg/d
	Isradipine ^b	0.05–0.15 mg/kg/dose	TID–QID	0.8 mg/kg/d up to 20 mg/d
	Extended-release nifedipine	0.25–0.5 mg/kg/d	QD–BID	3 mg/kg/d up to 120 mg/d
	Central α agonist	Clonidine ^b	5–10 mcg/kg/d	BID–TID
Diuretics	Amiloride	5–10 mg/d	QD	20 mg/d
	Chlorthalidone	0.3 mg/kg/d	QD	2 mg/kg/d up to 50 mg/d
	Furosemide	0.5–2.0 mg/kg/dose	QD–BID	6 mg/kg/d
	HCTZ	0.5–1 mg/kg/d	QD	3 mg/kg/d up to 50 mg/d
	Vasodilators	Hydralazine	0.25 mg/kg/dose	TID–QID
Minoxidil		0.1–0.2 mg/kg/d	BID–TID	1 mg/kg/d up to 50 mg/d

^aThe maximum recommended adult dose should never be exceeded.

^bInformation on preparation of a stable extemporaneous suspension is available for these agents.

BID, twice daily; HCTZ, hydrochlorothiazide; QD, once daily; QID, four times daily; TID, three times daily; ACE, angiotensin-converting enzyme.

regarding other cardiovascular risk factors, and continued emphasis on therapeutic lifestyle changes. Hypertensive target organ damage such as LVH, if present, should be reassessed periodically.

It may also be appropriate to consider “step-down” therapy in selected children and adolescents.

This involves an attempt at gradual reduction in medication dose after an extended course of good BP control, with the eventual goal of completely discontinuing the drug therapy. Children with uncomplicated primary hypertension, especially obese adolescents who successfully lose weight and maintain their weight

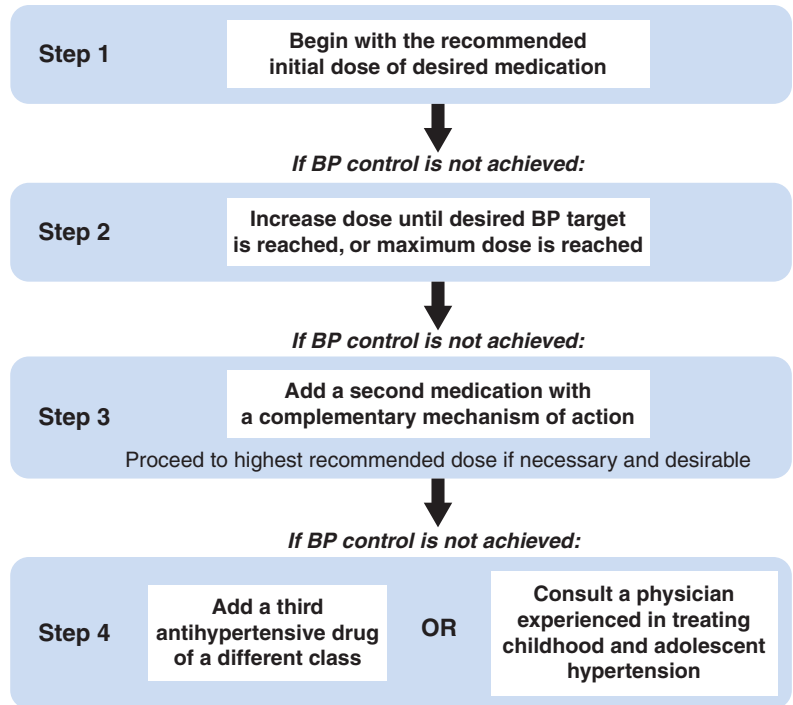


FIGURE 16-3 • Stepped-care approach to pharmacologic management of childhood hypertension.

loss, are the best candidates for withdrawal of medication. These children should receive continued BP monitoring after drug therapy is withdrawn as well as continued nonpharmacologic treatment.

SPECIAL TOPICS

Hypertension in Infancy

Few robust normative data on BP levels in newborn and premature infants are available. Additionally, BP in infancy varies according to body size, gestational age, and postconceptual age, among other factors (Dionne et al., 2012). Thus, it can be difficult to ascertain whether an infant's BP value is sufficiently high to warrant evaluation and treatment.

Although one study found that 28% of infants with BWs less than 1,500 g had at least one elevated BP documented during their NICU stay (Al-Aweel et al., 2001), the actual incidence of hypertension in neonates is very low, ranging from 0.2% in healthy newborns to between 0.7% and 2.5% in high-risk newborns (Dionne et al., 2012). Certain categories of infants are at significantly higher risk, however. For example, the odds of hypertension are increased in neonates with a history of umbilical artery catheterization, those who suffered acute kidney injury in the NICU, or those with chronic lung disease compared to neonates without

these risk factors (Blowey et al., 2011; Sahu et al., 2013; Saliem et al., 2007). On the other hand, hypertension is so uncommon in otherwise healthy term infants that routine BP determination is not even recommended (AAP Committee on Fetus and Newborn, 1993).

The differential diagnosis of hypertension in neonates and older infants is wide ranging (Tables 16-7 and 16-10). The most important categories of causes of neonatal hypertension include renovascular disease (most commonly umbilical artery catheterization–related aortic or renal thromboembolism) (Bauer et al., 1975), renal parenchymal disease, and bronchopulmonary dysplasia (Alagappan & Malloy, 1998; Sahu et al., 2013; Saliem et al., 2007). The most common cardiac cause is coarctation of the thoracic aorta, in which hypertension may persist or recur after surgical repair (O'Sullivan et al., 2002). For a more comprehensive discussion, the reader is encouraged to consult other references (Dionne et al., 2012).

Investigation of hypertensive infants should proceed in a similar fashion to the evaluation of older children with hypertension. As in older children, cuffs of proper size should be used in infants to avoid measurement error. Additionally, it is important to be consistent in the choice of extremity for BP measurement, particularly in hospitalized infants (Nwankwo et al., 1997). A thorough review of the infant's history and a

focused physical examination should point to the underlying cause in most cases. Selected laboratory studies should be obtained as indicated. Renal ultrasonography is particularly useful given the preponderance of renal causes (Table 16-10).

Therapy of neonatal hypertension should be tailored to the severity of the hypertension and the infant's overall clinical status. For example, critically ill infants with severe hypertension should be treated with an intravenous agent administered by continuous infusion, as this will allow the greatest control over the magnitude and rapidity of the BP reduction.

On the other hand, relatively well infants with mild hypertension may be treated with oral antihypertensive agents. Recommended doses for antihypertensive drugs in infants can be found in Table 16-11. A recent study demonstrated that antihypertensive agents of numerous classes have been employed in neonates (Blowey et al., 2011). Unfortunately, the legislative initiatives that have increased data on pediatric drug efficacy and safety have not extended to infants (Flynn, 2003). Thus, the choice of antihypertensive medications for use in neonates relies heavily on the experience of the individual practitioner.

TABLE 16-10
Causes of Neonatal Hypertension
Renovascular

- Thromboembolism
- Renal artery stenosis
- Midaortic coarctation
- Renal venous thrombosis
- Renal artery compression
- Abdominal aortic aneurysm
- Idiopathic arterial calcification
- Congenital rubella syndrome

Renal Parenchymal Disease

- Congenital
 - Polycystic kidney disease
 - Multicystic–dysplastic kidney disease
 - Tuberous sclerosis
 - Ureteropelvic junction obstruction
 - Unilateral renal hypoplasia
 - Primary megaureter
 - Congenital nephritic syndrome
- Acquired
 - Acute tubular necrosis
 - Cortical necrosis
 - Interstitial nephritis
 - Hemolytic uremic syndrome
 - Obstruction (stones, tumors)

Pulmonary

- Bronchopulmonary dysplasia
- Pneumothorax

Cardiac

- Aortic coarctation

Endocrine

- Congenital adrenal hyperplasia
- Hyperaldosteronism
- Hyperthyroidism
- Pseudohypoaldosteronism type II (Gordon syndrome)

Medications/Intoxications

- Infant
 - Dexamethasone
 - Adrenergic agents
 - Vitamin D intoxication
 - Theophylline
 - Caffeine
 - Pancuronium
 - Phenylephrine
- Maternal
 - Cocaine
 - Heroin

Neoplasia

- Wilms tumor
- Mesoblastic nephroma
- Neuroblastoma
- Pheochromocytoma

Neurologic

- Pain
- Intracranial hypertension
- Seizures
- Familial dysautonomia
- Subdural hematoma

Miscellaneous

- Total parenteral nutrition
- Closure of abdominal wall defect
- Adrenal hemorrhage
- Hypercalcemia
- Traction
- ECMO
- Birth asphyxia

TABLE 16-11

Recommended Doses for Selected Antihypertensive Agents for Treatment of Hypertensive Infants

Class	Drug	Route	Dose	Interval
ACE inhibitors ^a	Captopril	Oral	<3 m: 0.01–0.5 mg/kg/dose Max 2 mg/kg/d >3 m: 0.15–0.3 mg/kg/dose Max 6 mg/kg/d	TID
	Enalapril	Oral	0.08–0.6 mg/kg/d	QD–BID
	Lisinopril	Oral	0.07–0.6 mg/kg/d	QD
α- and β-antagonist	Labetalol	Oral	0.5–1.0 mg/kg/dose Max 10 mg/kg/d	BID–TID
		IV	0.20–1.0 mg/kg/dose 0.25–3.0 mg/kg/h	Q4–6h infusion
	Carvedilol	Oral	0.1 mg/kg/dose up to 0.5 mg/kg/dose	BID
β-antagonists	Esmolol	IV	100–500 mcg/kg/min	Infusion
	Propranolol	Oral	0.5–1.0 mg/kg/dose Max 8–10 mg/kg/d	TID
Calcium channel blockers	Amlodipine	Oral	0.05–0.3 mg/kg/dose Max 0.6 mg/kg/d	QD–BID
	Isradipine	Oral	0.05–0.15 mg/kg/dose Max 0.8 mg/kg/d	QID
	Nicardipine	IV	1–4 mcg/kg/min	Infusion
Diuretics	Chlorothiazide	Oral	5–15 mg/kg/dose	BID
	Hydrochlorothiazide	Oral	1–3 mg/kg/dose	QD
	Spirolactone	Oral	0.5–1.5 mg/kg/dose	BID
Vasodilators	Hydralazine	Oral	0.25–1.0 mg/kg/dose Max 7.5 mg/kg/d	TID–QID
		IV	0.15–0.6 mg/kg/dose	Q4h
	Minoxidil	Oral	0.1–0.2 mg/kg/dose	BID–TID
	Sodium nitroprusside	IV	0.5–10 mcg/kg/min	Infusion

^aNot recommended for infants with corrected gestational age of <44 wk.

BID, twice daily; IV, intravenous; Q, every; QD, once daily; QID, four times daily; TID, three times daily.

Acute Severe Hypertension

The pathophysiology, management, and outcome of severe hypertension in children and adolescents have been reviewed in detail elsewhere (Flynn & Tullus, 2009; Singh et al., 2012). Many aspects are similar to hypertensive emergencies and urgencies in adults as reviewed in Chapter 8. However, a few unique aspects warrant consideration.

Underlying conditions that may produce acute severe hypertension in a child or adolescent commonly include acute or chronic renal disease, solid organ transplantation, renal artery stenosis, and congenital renal diseases such as autosomal recessive polycystic kidney disease. Medication nonadherence in patients with established hypertension, the most common cause of acute severe hypertension in adults (Bender

et al., 2006), occurs rarely in pediatric patients, except perhaps in those with established renal disease.

Hypertensive encephalopathy is the most frequent life-threatening symptom in children and adolescents with severe hypertension, emphasizing the need for slow, controlled reduction in BP to prevent complications arising through loss of normal autoregulatory processes (Singh et al., 2012). Less severe symptoms may include nausea, vomiting, or unusual irritability; since these may be somewhat nonspecific, especially in younger children, a high degree of clinical suspicion must be maintained.

Although evidence-based recommendations are lacking, the usual goal in the treatment of a hypertensive emergency is to reduce the BP by no more than 25% over the first 8 hours, with a gradual return to normal/good BP over 24 to 48 hours (Flynn & Tullus, 2009).

Treatment of hypertensive emergencies in children should be initiated with a continuous infusion of an intravenous antihypertensive, with nicardipine and labetalol being the agents most commonly used. Other intravenous agents that have found use in children with severe hypertension include sodium nitroprusside, esmolol, hydralazine, and fenoldopam (Singh et al., 2012). It should be noted that there is little clinical trial evidence available for these drugs in pediatric patients, so their use is largely based on expert opinion.

Oral antihypertensive agents can be used in pediatric patients with acute severe hypertension who do not have life-threatening symptoms. The choice of oral antihypertensives for use in management of severe hypertension in pediatric patients is fairly limited. As in adults, short-acting nifedipine is no longer recommended (Flynn & Tullus, 2009). For recommended doses of both oral and intravenous drugs useful in the treatment of acute severe hypertension in children and adolescents, see Table 16-12.

TABLE 16-12

Antihypertensive Drugs for Management of Severe Hypertension in Children and Adolescents

Drug	Class	Dose	Route	Comments
Useful for Severely Hypertensive Patients with Life-Threatening Symptoms				
Esmolol	β-adrenergic blocker	100–500 mcg/kg/min	IV infusion	Very short acting—constant infusion preferred. May cause profound bradycardia
Hydralazine	Direct vasodilator	0.2–0.6 mg/kg/dose	IV, IM	Should be given q4h when given IV bolus
Labetalol	α- and β-adrenergic blockers	Bolus: 0.20–1.0 mg/kg/dose, up to 40 mg/dose Infusion: 0.25–3.0 mg/kg/h	IV bolus or infusion	Asthma and overt heart failure are relative contraindications
Nicardipine	Calcium channel blocker	Bolus: 30 mcg/kg up to 2 mg/dose Infusion: 0.5–4 μg/kg/min	IV bolus or infusion	May cause reflex tachycardia
Sodium nitroprusside	Direct vasodilator	0.5–10 mcg/kg/min	IV infusion	Monitor cyanide levels with prolonged (>72 h) use or in renal failure: or coadminister with sodium thiosulfate
Useful for Severely Hypertensive Patients with Less Significant Symptoms				
Clonidine	Central α-agonist	0.05–0.1 mg/dose, may be repeated up to 0.8 mg total dose	PO	Side effects include dry mouth and drowsiness
Enalaprilat	ACE inhibitor	0.05–0.10 mcg/kg/dose up to 1.25 mg/dose	IV bolus	May cause prolonged hypotension and acute renal failure, especially in neonates
Fenoldopam	Dopamine receptor agonist	0.2–0.8 mcg/kg/min	IV infusion	Produced modest reductions in BP in a pediatric clinical trial in patients up to 12 y
Hydralazine	Direct vasodilator	0.25 mg/kg/dose up to 25 mg/dose	PO	Extemporaneous suspension stable for only 1 wk
Isradipine	Calcium channel blocker	0.05–0.1 mg/kg/dose up to 5 mg/dose	PO	Stable suspension can be compounded
Minoxidil	Direct vasodilator	0.1–0.2 mg/kg/dose up to 10 mg/dose	PO	Most potent oral vasodilator: long acting

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Patient Information

WHAT IS HYPERTENSION?

The term *hypertension* is synonymous with high blood pressure. For most people, a blood pressure above 140/90 is considered as hypertension. The upper number, the *systolic* pressure, is the highest pressure in the arteries when the heart beats and fills the arteries. The lower number, the *diastolic* pressure, is the lowest pressure in the arteries when the heart relaxes between beats.

As part of aging, blood vessels usually become stiff or rigid, so that they are less able to dilate when blood enters from the heart. Therefore, the systolic pressure usually increases with age.

WHAT CAUSES HYPERTENSION?

In most patients, no specific cause for hypertension can be found. In about 10%, a specific cause can be found and often relieved by either medical or surgical treatment.

The term used for the usual type of hypertension has been “essential,” but “primary” is preferable. These factors are involved:

- ▶ Hereditary
- ▶ Obesity
- ▶ High sodium (salt) intake
- ▶ Psychological stress

In addition, a number of other factors sometimes play a role, including

- ▶ Excessive alcohol (drinking more than two to three portions a day)
- ▶ Smoking
- ▶ Sleep apnea
- ▶ Herbal remedies
- ▶ Diet pills and other stimulants, such as ephedra
- ▶ Physical inactivity

CAN HYPERTENSION BE CURED?

Not usually. Some people who lose considerable excess weight, reduce a high intake of sodium (or alcohol),

and relieve stress may have a return of elevated blood pressure to a normal level.

WHAT ARE THE CONSEQUENCES OF HYPERTENSION?

By placing a burden on the heart and blood vessels, hypertension in concert with other risk factors induces heart attacks, heart failure, strokes, and kidney damage. The other important cardiovascular risk factors are

- ▶ Smoking
- ▶ Abnormal (“bad”) blood lipids (an elevated low-density lipoprotein cholesterol or a low high-density lipoprotein (“good”) cholesterol)
- ▶ Diabetes

HOW IS HYPERTENSION TREATED?

Treatment should always include an improvement in all the unhealthy lifestyle habits, including

- ▶ Stopping smoking
- ▶ Losing excess weight
- ▶ Increasing physical activity. The American Heart Association and American College of Cardiology recommend engaging in three to four 40-minute sessions of moderate-to-intense aerobic physical activity per week
- ▶ Reducing sodium intake, easiest accomplished by eating a diet rich in fresh fruits and vegetables, and cooking at home. Most salt comes from processed food, especially those high in starch or carbohydrates (for example, a plate of pasta at a restaurant). Reading labels on processed foods and avoiding any with more than 300 mg of sodium per portion is also important
- ▶ Adopting the DASH diet (which stands for Dietary Approach to Stop Hypertension). This diet is high in: vegetables, nuts, fruits, grains, low-fat dairy products, fish, poultry; and low in: sweets, sugar-sweetened

beverages, and red meats. Each individual will need to adapt this dietary pattern to calorie requirements, personal/cultural food preferences, and medical conditions such as diabetes. (For more information and recipes, visit <http://dashdiet.org/>).

- ▶ Drinking no more than a healthy quantity of alcohol

Antihypertensive drugs are usually needed. These include three major types:

- ▶ **Calcium Channel Blockers** which open blood vessels.
- ▶ **Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARBs)** which counteract the hypertensive action of the hormone angiotensin
- ▶ **Diuretics** which remove some of the excess sodium and water from the circulation

Additional drugs are sometime needed:

- ▶ **Beta-blockers** which decrease the rate and strength of heart contraction
- ▶ **Alpha-blockers** which both lower blood pressure and, for older men, can improve symptoms of an enlarged prostate
- ▶ **Centrally-acting drugs** which reduce adrenaline
- ▶ **Other Vasodilators** which, like calcium channel blockers, also open blood vessels

All of these may cause side effects, and your physician should be contacted if you feel unwell after starting one or more drugs. The action of most drugs can be reduced by weight gain, excessive sodium or alcohol, and certain drugs such as nonsteroidal anti-inflammatories (ibuprofen, Naprosyn, Celebrex, etc.). Inform your physician about all over-the-counter or prescription drugs you take. Take your pills every day at the same time, usually soon after awakening or at bedtime.

HOW TO ENSURE GOOD CONTROL OF HYPERTENSION

In the past, only occasional readings in the physician's office were used to determine the degree of hypertension. Increasingly, home measurements with a battery-operated, semiautomatic device are being used to ensure adequate but not excessive treatment. With such a device, costing \$40 to \$100, you can monitor your blood pressure, particularly when changes in the type or doses of medications are made.

GUIDELINES FOR HOME BLOOD PRESSURE MONITORING

Equipment

The device should be checked against the conventional manual measurement in the physician's office to ensure its accuracy. The cuff should be large enough to encircle the upper arm. For most adults, a "large adult cuff" should be used. If the device comes with a smaller cuff, a larger one can be substituted.

Procedure

Do not smoke or drink coffee for 30 minutes before taking the reading. Sit with the back and arm supported, the arm at the level of the heart (middle of the chest). After 3 to 5 minutes of quiet sitting, take two readings, a minute apart. If the two readings differ by more than 10 mm (points), take additional readings each minute until they are within 10 mm Hg.

Record the readings in this manner:

Date	Time	First Reading	Second Reading	Circumstances
May 3	7 a.m.	150/95	145/90	Before breakfast
May 5	6 p.m.	135/85	130/80	After exercise
May 7	8 a.m.	110/70	105/60	Dizzy after standing

The American Heart Association recommends that you monitor your blood pressure every day for one week at a time. On each of these days, take two readings every morning before breakfast (and before taking your pills) and take two more readings every evening (after dinner). During this week, take extra readings if you feel unwell, such as being dizzy or light headed or having a bad headache. You usually cannot tell when your pressure is rising, but the pressure can rise if you are anxious.

If the readings are being taken to diagnose hypertension, this procedure may be extended for a second week.

If the readings are being taken to monitor treatment, the procedure may be repeated every month until your blood pressure is at goal: typically an overall average value of below 135/85.

The readings may vary as much as 40 mm Hg from one time to another. They rarely remain the same. Take your diary with you on your next appointment. Once your blood pressure is well controlled on a well-tolerated medication regimen, you will not need to monitor your pressure at home again for several months.

More information can be obtained from the American Heart Association at www.heart.org/

Note: Page numbers followed by “f” indicate figures; those followed by “t” indicate tables.

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