Chapter 69. Pathophysiology of Hypertension - *John E. Hall / Joey P. Granger / Michael E. Hall / Daniel W. Jones*

INTRODUCTION

More than 1 *billion* individuals worldwide, including 50 million Americans, have high blood pressures warranting some form of treatment.[1-4] Higher-than-optimal blood pressure is the number one attributable risk for death throughout the world and approximately 7.1 million deaths per year are attributed to uncontrolled hypertension.[3] As life expectancy increases, hypertension is becoming an even more important medical and public health issue as blood pressure rises with aging in industrialized countries. In the United States, 50 percent of people 60 to 69 years old, and approximately 75 percent of people 70 years and older, have hypertension.[1]
In some isolated, nonindustrialized populations, however, blood pressure does not increase with increasing age and only a small fraction of the population develops hypertension. This suggests that predisposing environmental factors play a major role in causing hypertension and that a rise in blood pressure with aging is not inevitable when these factors are absent.

A direct positive relationship between blood pressure and cardiovascular disease (CVD) risk has been observed in men and women of all ages, races, ethnic groups, and countries, regardless of other risk factors for CVD.[4] Observational studies indicate that death from CVD increases progressively and linearly as blood pressure rises above 115 mmHg systolic and 75 mmHg diastolic pressure.[3] For every 20 mmHg systolic or 10 mmHg diastolic increase in blood pressure there is a doubling of mortality from both ischemic heart disease and stroke in all age groups from 40 to 89 years old.[5] Despite major advances in our understanding of its pathophysiology and the availability of many drugs that can effectively reduce blood pressure in most hypertensive subjects, hypertension continues to be the most important modifiable risk factor for CVD.

CLASSIFICATION OF HYPERTENSION

Blood pressure is a variable quantitative trait with a normal distribution that is slightly skewed to the right. Although there is no clear level of blood pressure where cardiovascular disease begins to occur, a definition of hypertension, although somewhat arbitrary, is useful for making decisions about treatment. A commonly used blood pressure classification was proposed in 2003 by the Seventh Report of the United States Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (Table 69-1).[6] This classification is based on the average of two or more blood pressure readings after an initial screening visit, and is for individuals who are not on antihypertensive medication and who are not acutely ill. When systolic and diastolic blood pressures fall into different categories, the JNC 7 recommends that the higher category be selected to classify the person's blood pressure.

According to JNC 7 criteria, normal blood pressure is defined as a systolic blood pressure <120 mmHg and a diastolic blood pressure <80 mmHg. Persons with a systolic blood pressure between 120 and 139 mmHg or diastolic blood pressure between 80 and 89 mmHg are designated as having *prehypertension*. The diagnosis of hypertension is made by a confirmed systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg. Hypertension is further characterized into two stages according to the patient's level of systolic and diastolic blood pressure. Stage 1, the milder (systolic 140 to 159 mmHg and/or diastolic 90 to 99 mmHg) and most common form of hypertension, accounts for approximately 80 percent of hypertension. Stage 2 hypertension includes those with systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg. Isolated systolic hypertension is defined as systolic blood pressure of ≥140 mmHg and diastolic blood pressure <90 mmHg and staged appropriately.

Using these definitions and including those who are taking antihypertensive medication, approximately 24 percent of the adult population in the United States has hypertension.[6]
This percentage varies with (1) race, being higher in blacks (32 percent) and lower in whites (23 percent) and Mexican Americans (23 percent); (2) age, because systolic blood pressure rises throughout life in the United States, as well as in most industrialized countries, whereas diastolic blood pressure rises until age 55 to 60 years; (3) gender, with hypertension being more prevalent in men than in premenopausal women; (4) geographic patterns, with hypertension being more prevalent in the southeastern United States; and (5) socioeconomic status, which is inversely related to the prevalence, morbidity, and mortality rates of hypertension.

DEFINITION OF PRIMARY (ESSENTIAL) HYPERTENSION

Primary (essential) hypertension, which accounts for 95 percent of all cases of hypertension, has been traditionally defined as high blood pressure for which an obvious secondary cause (e.g., renovascular disease, aldosteronism, pheochromocytoma, or gene mutations) cannot be determined.

Although primary hypertension is a heterogeneous disorder, some of the main causes of high blood pressure in primary hypertension are known. For example, overweight and obesity may account for a much as 65 to 75 percent of the risk for primary hypertension, as discussed later in this chapter. Other factors, such as sedentary lifestyle, excess intake of alcohol or salt, and low potassium intake, are also known to increase blood pressure in many patients who are classified as having primary hypertension. Therefore, it is probably inappropriate to define primary hypertension as a rise in blood pressure without cause because identified causes can be found in many patients.[7,8]

This chapter discusses basic concepts of circulatory regulation, the physiologic mechanisms involved in short-term and long-term control of blood pressure, and the pathophysiologic changes in the major blood pressure control systems that can lead to a few types of secondary hypertension, as well as primary hypertension. We also review interactions between genetic and environmental factors that influence intermediate phenotypes such as sympathetic nerve system (SNS) activity, the renin-angiotensin system (RAS), endothelial factors, oxidative stress, and natriuretic hormones, which, in turn, influence vascular resistance, cardiac output, renal excretion of salt and water, and, therefore, blood pressure.

BASIC CONCEPTS OF CIRCULATORY CONTROL

Cardiac Output and Tissue Blood Flow Regulation

A discussion of cardiac output regulation often begins with the well-known formula: *cardiac output = stroke volume × heart rate.*

[**TABLE 69-1. Classification of Blood Pressure for Adults Age 18 Years and Older According to JNC 7[a]**]

This equation provides a conceptual framework that is adequate to describe the general determinants of cardiac pumping but it does not elucidate another major determinant of cardiac output—the venous return, or total tissue blood flow. To illustrate this point, consider the following question: *Which of the following changes in cardiac output would you expect to find 7 days after surgical reduction of kidney mass by 50 percent (removal of one kidney): an increase, a decrease, or no change?* The correct answer is a *decrease* in cardiac output. Why is cardiac output reduced by removal of a kidney when there has been no obvious effect on cardiac pumping ability or heart rate? This is not easy to comprehend if we think in a "cardiocentric" manner. However, the answer becomes obvious if we consider that cardiac output is, in the steady state, equal to the sum of the blood flows of all of the tissues.

Figure 69-1
illustrates the important relationship between cardiac output and tissue blood flow, and shows why removing a kidney, or any of other organ, reduces cardiac output. Removing one kidney decreases venous return to the heart by approximately 10 percent (assuming that total flow to both kidneys is approximately 20 percent of the cardiac output). There is very little change in blood volume because the remaining kidney is able to rapidly increase its excretion to match intake of water and electrolytes. A reduction in cardiac output would also be observed with amputation of an arm or a leg, or removal of any other tissue from the body. This example illustrates that cardiac output is determined not only by the function of the heart, but also by the peripheral circulation. Except when the heart is severely weakened and unable to adequately pump the venous return, cardiac output (total tissue blood flow) is determined mainly by the metabolic needs of the tissues and organs of the body, although intrinsic and neurohumoral mechanisms allow the heart to effectively accommodate changes in venous return.

This conceptual framework is very helpful in explaining changes in cardiac output during exercise (where metabolic activity and blood flow to skeletal muscles are increased), after eating a large meal (which increases metabolic activity and blood flow in the gastrointestinal system) and in pathophysiologic conditions such as hypertension
where cardiac output is also determined largely by the metabolic demands of the tissues. In most circumstances, cardiac pumping ability plays a permissive role in determining the cardiac output.

Tissue Blood Flow Autoregulation and Cardiac Output

The importance of integrating the principles of tissue blood flow regulation in discussing cardiac output can be illustrated by consideration of the effects of vasodilators and vasoconstrictors. In most cases, cardiac output changes very little even when there are high levels of circulating vasoconstrictors (e.g., angiotensin II [ANG II]) or vasodilators (e.g., calcium channel blockers). If cardiac output regulation is the sum of all local blood flow regulations, why is cardiac output not

significantly altered in these conditions?

To answer this question we must consider one of the most fundamental principles of circulatory function—the ability of each tissue to *autoregulate* its own blood flow according to the metabolic needs and other functions of the tissue.[9-11] Administration of a powerful vasoconstrictor, such as ANG II, may cause a transient decrease in cardiac output, but usually has little long-term effect if it does not alter metabolic rate of the tissues. Likewise, most vasodilators cause only short-term changes in tissue blood flow and cardiac output if they do not alter tissue metabolism.

[**Figure 69-1.** Relationship between cardiac output, peripheral blood flow regulation, and venous return.]

Therefore, to effectively explain cardiac output regulation, it is necessary to discuss the mechanisms that control blood flow in the different tissues. Local blood flow regulation, as is true for most physiologic control systems, involves short-term and long-term mechanisms. Acute control occurs within seconds or minutes as a result of constriction or dilation of the vasculature. After administration of a vasoconstrictor that does not alter metabolic rate of the tissues, there is a transient decrease in the supply of nutrients and oxygen to the tissues and an accumulation of metabolic waste products. This, in turn, causes vasodilation and a return of tissue blood flow toward normal. In some tissues where blood flow regulation is not determined mainly by metabolic needs, such as the kidney, some vasoconstrictors, such as ANG II, may cause a small, sustained decrease in blood flow that barely alters cardiac output. Other short-term controls, such as the *myogenic response*, also alter vascular resistance in response to changes in blood pressure and help to autoregulate blood flow in the different tissues.

Long-term blood flow regulation takes place over several days or weeks and involves structural changes in the blood vessels, such as thickening of vessel walls and decreased numbers of capillaries (rarefaction) in some tissues when blood pressure is chronically elevated. Together, the short-term and long-term mechanisms maintain the required levels of blood flow in each tissue to insure normal tissue function. Thus, in most physiologic conditions, excluding those associated with impaired cardiac pumping ability, the cardiac output reflects mainly the combined actions of the multiple control mechanisms for blood flows in the different tissues of the body.

In conditions such as heart failure or when large increases in cardiac output are needed to meet the metabolic demands of the body's tissues, such as exercise, the various factors that alter cardiac pumping also play a major role in regulating cardiac output regulation.

Blood Flow Regulation in Normotensive and Hypertensive Subjects

The main function of the circulation is to provide adequate blood flow to each tissue to meet its requirements. This is achieved by a combination of local tissue controls that regulate vascular tone as well as overall adjustments of the circulation that influence cardiac pumping and vascular tone.[11,12] For example, during intense exercise, local conditions (e.g., accumulation of metabolites or decreased levels of oxygen and nutrients) in the skeletal muscles cause intense vasodilation that permits adequate blood flow to match the increased metabolic requirements of the muscles. However, this also reduces peripheral vascular resistance that tends to decrease blood pressure. Normally, this is offset by multiple neurohumoral changes that tend to elevate the blood pressure.

If for some reason peripheral vasodilation continues for several days, such as occurs with anemia or with opening a large arteriovenous fistula, additional adjustments take place that cause salt and water retention by the kidneys and increased blood volume, or even hypertrophy of the heart if the stimulus lasts for several weeks. Thus, the multiple factors that control the circulation, including those that influence cardiac output, blood pressure, blood volume, and others, normally work in concert to provide adequate blood flow to the tissues of the body.

In hypertension, the same control mechanisms are also operative. However, one of the important characteristics of many, but not all, hypertensive patients is that they have increased total peripheral vascular resistance. Does this also mean that blood flow to the tissues is impaired? Excluding those hypertensive persons with heart failure or severe target-organ injury, the answer to this question is generally no. In most instances, blood flows in most tissues are approximately the same in normotensive and hypertensive subjects and are regulated at a level that is adequate to supply the needs of the tissues.[13] Thus, the hemodynamic pattern that is often (but not always) observed in nonobese subjects with essential hypertension is normal blood flow, normal oxygen consumption, and elevated vascular resistance.[13]

Cerebral blood flow, for example, shows a normal value of about 50 mL/min per 100 g/tissue weight in essential hypertension. Coronary blood flow is elevated in essential hypertension in proportion to the increase in myocardial hypertrophy. Blood flow per unit weight of heart muscle is usually normal, however, with a value of about 80 mL/min per 100 g/tissue weight. Splanchnic blood flow is slightly reduced in essential hypertension, having a typical value of about 750 mL/min/m^2 of surface area compared with about 800 mL/min/m^2 in normotensive subjects. Skin blood flow is also normal in essential hypertension.

Although resting skeletal muscle blood flow is, for the most part, normal in essential hypertension, several differences in blood flow regulation have been noted. For example, the ability of skeletal muscle blood vessels to dilate in some patients with essential hypertension is impaired and the minimal attainable vascular resistance is reduced.[14] This reduced blood flow "reserve" in hypertension is probably a result of structural limitations imposed by blood vessel hypertrophy and of endothelial dysfunction and impaired release of nitric oxide.

In general, the maximal level of exercise as quantified by oxygen uptake is depressed in proportion to the severity of hypertension. Arterial pressure is high before exercising and increases even further during exercise. In the presence of impaired vasodilation, elevated blood pressure boosts blood flow through the skeletal muscle but it also increases cardiac afterload, which limits both cardiac output and exercise performance. At each level of exercise below maximum, however, cardiac output and skeletal muscle blood flow are generally identical to flows seen in normotensive subjects.[13] These flows, however, are achieved at higher vascular resistances and higher blood pressures; the resistance and blood pressure effects cancel each other to yield a normal blood flow in most tissues.

In obese hypertensive patients, resting skeletal muscle blood flow per gram of tissue weight may be somewhat elevated compared to lean individuals; however, the increase in skeletal muscle blood flow that occurs in exercise is attenuated and the forearm reactive hyperemia after temporary occlusion of the brachial artery patients is less in obese than in lean normotensive subjects.[15] Thus, although obesity-associated hypertension may be associated with increased resting blood flow, flow reserve is often reduced.

In older hypertensive individuals, total tissue blood flow (i.e., cardiac output) is often reduced, compared to the flow in younger individuals. This is perhaps not surprising if one considers that lean muscle mass usually decreases with aging. Because cardiac output is a sum of all tissue blood flows, decreased muscle mass and decreased physical activity characteristic of older hypertensive patients also are associated with reduced cardiac output and decreased total body oxygen consumption.

Renal blood flow has been observed to be increased, normal, or decreased in essential hypertension.[16] These seemingly disparate observations, however, should be interpreted with regard to the special functional needs of the kidney and the conditions under which renal blood flow is studied. For example, increased dietary protein, high sodium intake, and excess weight gain all are associated with increased renal blood flow. Nephron loss, which can occur with prolonged, uncontrolled hypertension and diabetes, leads to reduction in renal blood flow. Impaired renal blood flow is also related to the etiology of hypertension in some individuals.

Importance of Arterial Pressure in Regional Blood-Flow Regulation

Adequate tissue blood flow in response to normal daily activities requires an adequate blood pressure. This is illustrated by the response to physical exercise in patients with autonomic dysfunction. As a person with normal autonomic reflexes begins to exercise, skeletal muscle vascular resistance is reduced whereas skeletal muscle blood flow and cardiac output increase markedly and blood pressure remains relatively constant. In persons with autonomic dysfunction, exercise also decreases skeletal muscle vascular resistance but blood pressure falls and muscle blood flow and cardiac output increase only modestly because of impaired autonomic reflexes. Therefore, exercise is not well tolerated and syncope often occurs.

When cardiac output is inadequate to meet normal tissue needs, as occurs in heart failure or severe hypovolemia, activation of the SNS, the RAS, and other hormonal factors produce vasoconstriction that may override normal flow regulation in some organs, such as skeletal muscle and skin. This keeps blood pressure from falling too low and provides adequate blood flow to the vital organs, especially the brain and the heart.

Figure 69-1. Relationship between cardiac output, peripheral blood flow regulation, and venous return.

Basic Principles of Blood Pressure Regulation

The most important function of blood pressure is to provide the driving force that moves blood through the vascular system in order to supply the needs of the tissues. Consequently, the regulation of blood pressure is a complex physiologic function that depends on the integrated actions of multiple cardiovascular, renal, neural, endocrine, and local tissue control systems.

Blood pressure varies considerably throughout the day depending on the activity of the body, environmental influences, and the responses of these multiple blood pressure control systems. Hypertension is usually considered to be a disorder of the average level at which blood pressure is regulated, although there is increasing interest in other measures of blood pressure, including peak arterial pressure, lability of blood pressure, nighttime and daytime blood pressure, blood pressure responses to stress, and so forth. Many of the cardiovascular derangements associated with hypertension, such as cardiac and vascular hypertrophy, arise as compensatory mechanisms for the hypertension, and reducing blood pressure can largely reverse these changes if they have not progressed too far.

The multiple local control, hormonal, neural, and renal systems that regulate blood pressure are often discussed in terms of how they influence cardiac pumping or vascular resistance because of the well-known formula: *mean arterial pressure = cardiac output × total peripheral resistance*. This conceptual framework (with the addition of factors that influence vascular capacity and transcapillary exchange) is adequate to explain short-term blood pressure regulation, but is inadequate when discussing abnormalities of long-term blood pressure regulation, such as hypertension.

To illustrate this point let us consider the following question: *What changes in blood pressure, cardiac output, and extracellular fluid volume would you expect to find several days after a 50 percent increase in total peripheral vascular resistance (TPR) caused by closure of a large arteriovenous (A-V) fistula?* In this case, cardiac pumping ability is not directly altered and TPR is chronically increased by 50 percent. One might assume that blood pressure would also rise chronically if increased TPR is sustained. However, several days after closure of an A-V fistula there are no detectable changes in mean arterial pressure despite a sustained increase of TPR. Likewise, increasing TPR by amputation of a limb or hypothyroidism (which reduces metabolic rate of the tissues and increases vascular resistance), or decreasing TPR by creating an A-V fistula, anemia, or hyperthyroidism, fail to have a significant long-term effect on mean arterial pressure (Fig. 69-2). Why do these large chronic changes in TPR have no significant long-term effect on mean arterial pressure? To explain blood pressure regulation in these circumstances, we must introduce two other concepts: (1) time-dependency of blood pressure control mechanisms, and (2) the necessity of maintaining balance between intake and output of water and electrolytes, and the role of blood pressure in maintaining this balance.

Feedback Control Systems for Blood Pressure Are Time Dependent Blood pressure control systems are often considered as if they were static, and time dependency is usually not discussed. Short-term control mechanisms are often emphasized to a greater degree than long-term controls, probably because they have been studied much more extensively and are easier to explain, even though most cardiovascular disorders, including hypertension, involve abnormalities of long-term regulation.

If we examine the maximal feedback gain of several blood pressure controllers, it is obvious that their quantitative importance is highly time dependent. Figure 69-3 shows the response of some of the major control systems following a sudden change in blood pressure, as might occur with rapid blood loss. The degree of response of the different control systems can be expressed in terms of *feedback gain* of the system; the higher the gain, the greater the response. Three important neural control systems begin to function within seconds: (1) the arterial baroreceptors, which detect changes in blood pressure and send appropriate autonomic reflex signals back to the heart and blood vessels to return the blood pressure toward normal; (2) the chemoreceptors, which detect changes in oxygen or carbon dioxide in the blood and initiate autonomic feedback responses that influence blood pressure; and (3) the central nervous system, which responds within a few seconds to ischemia of the vasomotor centers in the medulla, especially

[**Figure 69-2.**
Failure of changes in total peripheral vascular resistance (TPR) to cause chronic changes in arterial pressure in several clinical conditions in which the kidneys are functioning normally. In each case there is a reciprocal relationship between TPR and cardiac output, but no long-term effect on arterial pressure.]

when blood pressure falls below about 50 mmHg. Each of these nervous control mechanisms works rapidly and can have potent effects on blood pressure.

Within a few minutes or hours after a blood pressure disturbance, several additional control systems react, including (1) a shift of fluid from the interstitial spaces into the blood stream in response to decreased blood pressure (or a shift of fluid out of the blood into the interstitial spaces in response to increased blood pressure); (2) the RAS which is activated when blood pressure falls too low and suppressed when blood pressure increases above normal; (3) multiple vasodilators systems (not shown in the figure) that are suppressed when blood pressure decreases and stimulated when blood pressure rises above normal.

Most of the blood pressure regulators are *proportional* control systems. This means that they will correct a blood pressure abnormality only part of the way back toward the normal level, but never all the way back. The arterial baroreceptor reflex system, for example, has a proportional feedback gain of approximately 2.0 during acute changes in blood pressure and therefore buffers about two-thirds of a sudden change in the blood pressure.[11]

There is one blood pressure control system, the renal-body fluid feedback system, with *infinite feedback gain* if it is given enough time to operate.[16,17] Thus, the renal-body fluid feedback control mechanism does not stop functioning until the arterial pressure returns all the way back to its original control level, as discussed

below.

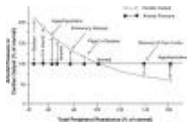

Figure 69-2. Failure of changes in total peripheral vascular resistance (TPR) to cause chronic changes in arterial pressure in several clinical conditions in which the kidneys are functioning normally. In each case there is a reciprocal relationship between TPR and cardiac output, but no long-term effect on arterial pressure. *Source: Redrawn from Guyton AC, Hall JE. Textbook of Medical Physiology, 11th ed. Philadelphia: Elsevier, 2006.*

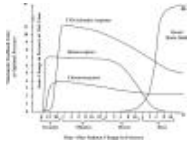

Figure 69-3. Time dependency of blood pressure control mechanisms. Approximate maximum feedback gains of various blood pressure control mechanisms at different time intervals after the onset of a disturbance to arterial pressure. *Source: Redrawn from Guyton AC, Hall JE. Textbook of Medical Physiology, 11th ed. Philadelphia: Elsevier, 2006, p. 230.*

The Renal-Body Fluid Feedback is a Dominant Mechanism for Long-Term Blood Pressure Regulation

Figure 69-4
shows the conceptual framework for understanding long-term control of blood pressure by the renal-body fluid feedback mechanism. Extracellular fluid volume is determined by the balance between intake and excretion of salt and water by the kidneys. Even a temporary imbalance between intake and output can lead to a change in extracellular volume and potentially a change in blood pressure. Under steady-state conditions there must always be a precise balance between intake and output of salt and water; otherwise, there would be continued accumulation or loss of fluid leading to complete circulatory collapse within a few days. In fact, it is more critical to maintain salt and water balance than to maintain a normal level of blood pressure and, as discussed below, increased blood pressure is a means of regulating these balances in the face of impaired kidney function.

[**Figure 69-3.**
Time dependency of blood pressure control mechanisms. Approximate maximum feedback gains of various blood pressure control mechanisms at different time intervals after the onset of a disturbance to arterial pressure.]

A key mechanism for regulating salt and water balance is pressure natriuresis and diuresis, the effect of increased blood pressure to raise sodium and water excretion.[18,19]
Under most conditions this mechanism acts to stabilize blood pressure and body fluid volumes. For example, when blood pressure is increased above the renal setpoint, because of increased TPR or increased cardiac pumping ability, this also increases sodium and water excretion via pressure natriuresis if kidney function is not impaired. As long as fluid excretion exceeds fluid intake, extracellular fluid volume will continue to decrease, reducing venous return and cardiac output, until blood pressure returns to normal and fluid balance is reestablished.

An important feature of pressure natriuresis is that various hormonal and neural control systems can greatly amplify or blunt the basic effects of blood pressure on sodium and water excretion.[19] For example, during chronic increases in sodium intake only small changes in blood pressure are needed to maintain sodium balance in most people. One reason for this insensitivity of blood pressure to changes in salt intake is decreased formation of antinatriuretic hormones such as ANG II and aldosterone, which enhance the effectiveness of pressure natriuresis and allow sodium balance to be maintained with minimal increases in blood pressure. On the other hand, excessive activation of these antinatriuretic systems can reduce the effectiveness of pressure natriuresis, thereby necessitating greater increases in blood pressure to maintain sodium balance.

Another important feature of pressure natriuresis is that it continues to operate until blood pressure returns to the original setpoint. In other words, it acts as part of an *infinite gain* feedback

[**Figure 69-4.** Block diagram showing the basic elements of the renal-body fluid feedback mechanism for long-term regulation of arterial pressure.]

control system.[17]

As far as we know, it is the only infinite gain feedback system for blood pressure regulation in the body, and it is this property which makes it a dominant long-term controller of blood pressure.

Figure 69-5
illustrates the infinite gain characteristic of the renal-body fluid feedback system. In this case, blood pressure is increased without a change in pressure natriuresis, as would occur with increased TPR because of closure of an A-V fistula, coarctation of the aorta *below* the kidneys (aortic coarctation *above* the kidneys causes marked hypertension), or other changes that increase peripheral vascular resistance without influencing renal vascular resistance. The peripheral constriction initially increases blood pressure from point A to point B, but the rise in blood pressure cannot be sustained; as long as pressure natriuresis is unaltered, sodium excretion will increase above intake, thereby reducing extracellular fluid volume until blood pressure eventually returns all the way back to normal. In fact, the normal blood pressure is the only point at which sodium and water balance can be maintained. Likewise, disturbances that decrease peripheral vascular resistance or alter cardiac function without influencing renal pressure natriuresis have no long-term effect on arterial pressure.[16,17]

Therefore, in all forms of human or experimental hypertension studied thus far, there is a shift of pressure natriuresis that appears to initiate and sustain the hypertension. In some cases, abnormal kidney function is caused by intrarenal disturbances that alter renal hemodynamics or increased tubular reabsorption. In other cases, the altered kidney function is caused by extrarenal disturbances, such as increased SNS activity or excessive formation of antinatriuretic hormones that reduce the kidney's ability to excrete sodium and water and eventually raise arterial pressure. Consequently, effective treatment of hypertension requires interventions that reset pressure natriuresis toward normal levels of blood pressure either by directly increasing renal excretory capability (e.g., with diuretics), or by reducing extrarenal antinatriuretic influences (e.g., with RAS blockers) on the kidneys.

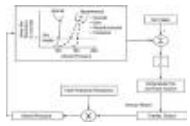

Figure 69-4. Block diagram showing the basic elements of the renal-body fluid feedback mechanism for long-term regulation of arterial pressure.

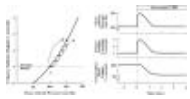

Figure 69-5. Long-term effects of increased total peripheral resistance (TPR), such as that caused by closure of a large arteriovenous fistula, with no change in the renal pressure natriuresis relationship. Blood pressure is initially increased from point A to point B, but elevated blood pressure cannot be sustained because sodium excretion exceeds intake, reducing extracellular fluid volume until blood pressure returns to normal and sodium balance is reestablished. *Source: Redrawn from Hall JE. The kidney, hypertension, and obesity. Hypertension 2003;41:625-633.*

RENAL MECHANISMS OF HYPERTENSION

Introduction

For more than 100 years severe kidney disease has been recognized as closely associated with hypertension. However, the importance of more subtle renal dysfunction in the pathogenesis of essential hypertension has not been as well appreciated, partly because there are no obvious renal defects in most patients with primary hypertension. Many of the measurements commonly used to evaluate kidney function, such as glomerular filtration rate (GFR), renal blood flow, serum creatinine, and sodium excretion are often within the normal range, at least in the early stages of hypertension. On the other hand, increased TPR is an obvious abnormality found in most patients with hypertension, leading many researchers to emphasize peripheral vasoconstriction as a cause of increased blood pressure. However, as discussed previously, increased peripheral vascular resistance in the absence of altered kidney function does not cause sustained hypertension.

An observation that points toward abnormal kidney function as a key factor in hypertension is that almost all forms of experimental hypertension, as well as all monogenic forms of human hypertension thus far discovered, are caused by obvious insults to the kidneys that alter renal hemodynamics or tubular reabsorption. For example, constriction of the renal arteries (e.g., Goldblatt hypertension), compression of the kidneys (e.g., perinephritic hypertension), or administration of sodium-retaining hormones (e.g., mineralocorticoids or ANG II) are all associated with either initial reductions in renal blood flow and GFR or increases in tubular reabsorption prior to development of hypertension. Likewise, in all known monogenic forms of human hypertension, the common pathway to hypertension appears to be increased renal tubular sodium reabsorption caused by mutations that directly increase renal electrolyte transport or the synthesis and/or activity of antinatriuretic hormones. As blood pressure rises, the initial renal changes are often obscured by compensations that restore kidney function toward normal. The rise in blood

pressure then initiates a cascade of cardiovascular changes, including increased peripheral vascular resistance that may be more striking than the initial disturbance of kidney function. For this reason, the importance of renal dysfunction in causing hypertension has often been underestimated.

Although specific abnormalities of kidney function are difficult to identify in most patients with primary hypertension, the one aspect of kidney function that is abnormal in all types of experimental and clinical hypertension is renal pressure natriuresis.[16,18] The fact that a normal rate of sodium excretion (equal to sodium intake) is maintained in chronic hypertension despite elevated blood pressure, which would normally cause natriuresis and diuresis, indicates that pressure natriuresis is reset in hypertensive subjects.

Because tubular reabsorption and GFR are both approximately 100-fold greater than urinary excretion, relatively small changes in either of these variables can have large effects on urinary excretion. Any long-term reduction in GFR must be perfectly compensated for by mechanisms that either restore GFR or decrease tubular reabsorption if renal excretion is to be returned toward normal and sodium and fluid balance are maintained. Likewise, any chronic increase in tubular reabsorption must be compensated for by increased GFR or by a restoration of tubular reabsorption to normal. Otherwise, fluid retention would continue eventually causing circulatory collapse.

If intrinsic renal mechanisms or neurohumoral adjustments are capable of returning renal excretion to normal in the face of insults to the kidneys, hypertension may not develop. However, the fact that hypertension occurs so frequently indicates that intrinsic renal mechanisms and neurohumoral controls may not be powerful enough to completely prevent alterations in renal excretion when there are major abnormalities of GFR or tubular reabsorption. In these instances, increased arterial pressure helps to maintain glomerulotubular balance and normal rates of sodium and water excretion, equal to intake, despite abnormal kidney function. The general types of renal abnormalities that can cause chronic hypertension include (1) increased preglomerular resistance, (2) decreased glomerular capillary filtration coefficient, (3) reduced numbers of functional nephrons, and (4) increased tubular reabsorption (see Table 69-1 and Fig. 69-6).

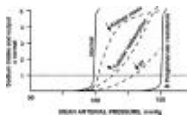

Figure 69-6. Steady-state relationships between arterial pressure and urinary sodium excretion and sodium intake for subjects with normal kidneys and four general types of renal dysfunction that cause hypertension: decreased kidney mass, increased reabsorption in distal and collecting tubules, reductions in glomerular capillary filtration coefficient (K_f), and increased preglomerular resistance. Note that increased preglomerular resistance causes *salt-insensitive* hypertension, whereas the other renal abnormalities cause *salt-sensitive* hypertension.

Hypertension Caused by Generalized Increases in Preglomerular Resistance

Examples of a generalized increase in preglomerular resistance are those caused by suprarenal aortic coarctation or constriction of one of the renal arteries and removal of the contralateral kidney (e.g., one-kidney, one-clip Goldblatt hypertension). Immediately after constriction of the renal artery or aortic coarctation, renal blood flow is reduced and there is a rapid rise in renin secretion and transient sodium retention. Within a few days, sodium excretion returns to normal and sodium balance is reestablished. If sodium intake is normal and adequate volume is available, renin secretion also returns to normal in the established phase of hypertension. At this point, most indices of renal function are nearly normal, including pressure distal to the stenosis if the constriction is not too severe. The rate at which renal function returns to normal and time course for development of hypertension depend the severity of the stenosis, the sodium intake, and the rate of ANG II formation.[17]

[**Figure 69-5.**
Long-term effects of increased total peripheral resistance (TPR), such as that caused by closure of a large arteriovenous fistula, with no change in the renal pressure natriuresis relationship. Blood pressure is initially increased from point A to point B, but elevated blood pressure cannot be sustained because sodium excretion exceeds intake, reducing extracellular fluid volume until blood pressure returns to normal and sodium balance is reestablished.]

How do these experimental models of increased preglomerular resistance relate to human hypertension, other than the obvious conditions of aortic coarctation or renal artery stenosis? When Harry Goldblatt first introduced hypertension in dogs by constricting the main renal artery, his goal was to produce an experimental model that mimicked the pathologic changes found in human essential hypertension.[20] Goldblatt has previously noted that many hypertensive patients at autopsy had nephrosclerosis and hypothesized that essential hypertension might be caused by diffuse renal arteriolar sclerosis, particularly in preglomerular vessels. Presumably, functional or pathologic increases in preglomerular resistance at other sites besides the main renal arteries, such as the interlobular arteries or afferent arterioles, could increase blood pressure through the same mechanisms as activated by clipping the renal artery. For example, widespread structural increases in

afferent arteriolar resistance (e.g., nephrosclerosis) or functional increases in resistance caused by excessive activation of the SNS or high levels of catecholamines (e.g., pheochromocytoma) would also cause hypertension through the same mechanisms as constriction of the main renal artery.

Some have questioned whether Goldblatt hypertension is relevant to human essential hypertension because of the observation that many hypertensive patients have no obvious indication of renal ischemia and have nearly normal renal blood flow and GFR. However, as previously discussed, there is little indication of renal ischemia even in experimental Goldblatt hypertension after compensatory increases in blood pressure have occurred.

[**Figure 69-6.**
Steady-state relationships between arterial pressure and urinary sodium excretion and sodium intake for subjects with normal kidneys and four general types of renal dysfunction that cause hypertension: decreased kidney mass, increased reabsorption in distal and collecting tubules, reductions in glomerular capillary filtration coefficient (K_f), and increased preglomerular resistance. Note that increased preglomerular resistance causes *salt-insensitive* hypertension, whereas the other renal abnormalities cause *salt-sensitive* hypertension.]

It is interesting to note that some patients with primary hypertension have the same characteristics seen in the one-kidney, one-clip Goldblatt model of hypertension, including nearly normal GFR and plasma renin activity, a parallel shift of pressure natriuresis to higher blood pressure, and a relatively salt-insensitive form of hypertension.[18,21]
Indeed, studies in hypertensive patients show that drug therapy that decreases preglomerular resistance, such as calcium channel blockers, causes a parallel shift of pressure natriuresis toward lower blood pressure.[22] Thus, primary hypertension in some patients may be caused by functional or pathologic increases in preglomerular resistance. This is almost certainly the case in patients who have severe artherosclerotic lesions in the renal blood vessels.

Hypertension Caused by Patchy Increases in Preglomerular Resistance

In the two-kidney, one-clip Goldblatt model of hypertension, or in patients with a stenosis in only one renal artery, there is a nonhomogeneous increase in preglomerular resistance with ischemia occurring in nephrons of the clipped/stenotic kidney, while nephrons in the contralateral nonclipped/nonstenotic kidney have increased single-nephron blood flow and GFR. The underperfused clipped kidney secretes large amounts of renin, whereas the untouched kidney secretes very little renin.[18,19]

An important distinction between a generalized increase in preglomerular resistance and patchy, nonhomogeneous increases in preglomerular resistance is the evolution of renal injury associated with hypertension. When there is a generalized, homogeneous increase in preglomerular resistance, the glomeruli are protected from the damaging effects of increased blood pressure. In the two-kidney, one-clip model, however, the glomeruli of the untouched kidney are subjected to the full effects of increased blood pressure. With prolonged hypertension, pathologic changes in the untouched kidney add to the impairment of overall renal excretory capability. At this stage, removal of the clipped kidney only partially restores arterial pressure to normal. However, removal of the contralateral untouched kidney and unclipping the stenotic kidney normalizes blood pressure. Thus, chronic exposure to high blood pressure in the untouched kidney apparently causes structural changes as well as functional changes that contribute to the progression of hypertension in this model.

The relevance of experimental models of nonhomogeneous increases in preglomerular resistance to human hypertension is obvious in those cases in which there is stenosis of only one renal artery, with the contralateral kidney being initially unaffected. If the contralateral nonstenotic kidney eventually becomes injured as a result of being exposed to high blood pressure, this kidney may also contribute to the hypertension.

Some patients with essential hypertension may have patchy nephrosclerosis within each kidney also providing a clinical counterpart to the two-kidney, one-clip Goldblatt model of hypertension. In these instances, the ischemic nephrons secrete large amounts of renin and the nonischemic nephrons vasodilate and initially have increased single nephron GFR. The combined effects of hypertension and hyperfiltration, however, may eventually damage the nephrons that were initially nonischemic, leading to progressive nephron loss.

Hypertension Caused by Decreased Glomerular Capillary Filtration Coefficient

Reducing the glomerular capillary filtration coefficient (K_f) initially lowers GFR and sodium excretion while stimulating renin release and causing vasodilation of afferent arterioles via a macula densa feedback.[18,19] The sodium retention and increased ANG II formation raise arterial pressure, which then helps to restore GFR and renin release to normal. After these compensations, the main persistent abnormalities of kidney function are reduced filtration fraction, increased glomerular hydrostatic pressure, and increased renal blood flow.

Unfortunately, compensatory increases in blood pressure and glomerular hydrostatic pressure, which are needed to offset a fall in K_f and to restore sodium excretion to normal, may also lead to additional renal dysfunction over a period of years by causing further glomerular injury; this further reduces K_f and requires additional increases in blood pressure to maintain normal water and electrolyte balances. Such a sequence may initiate progressive kidney damage.

The clinical counterparts of this sequence may be found in hypertension caused by glomerulonephritis or by other conditions that cause thickening and damage to the glomerular capillary membranes, such as chronic diabetes mellitus.[23]

Reduced Nephron Number Increases Salt-Sensitivity of Blood Pressure

A factor that contributes to salt sensitivity of blood pressure in some hypertensive patients is a loss of functional nephrons. Complete loss of nephrons (such as surgical reduction of kidney mass or unilateral nephrectomy) in the absence of other abnormalities usually does not lead to significant hypertension.[18,19] In contrast, loss of functional nephrons because of ischemia or infarction of renal tissue usually causes marked hypertension that is initially caused by increased renin secretion and then is eventually mediated by additional abnormalities, such as immunologic and renal injury, in the established phase of the hypertension.[24]

Considering the previous discussion, one might predict that reductions in nephron number should impair renal excretory capability and cause hypertension regardless of whether the loss was associated with renal ischemia. Yet, experimental studies show that surgical removal of large amounts of the kidney, to the point that uremia occurs, rarely causes severe hypertension as long as sodium intake is normal.[18,25] The reason hypertension does not develop is that overall glomerular filtration and tubular reabsorption capability are proportionally reduced so that balance between filtration and reabsorption can be maintained without major adaptive changes in blood pressure.

Reducing the number of functional nephrons, however, does make the kidneys very susceptible to additional insults that impair their function or to additional challenges of sodium homeostasis. Thus, hypertension associated with excess mineralocorticoids is much more severe after reducing kidney mass. Likewise, the kidney's ability to increase sodium excretion in response to the additional challenge of high sodium intake is accompanied by much larger increases in blood pressure when kidney mass is reduced.[18,19]

With the loss of entire nephrons, each surviving nephron must excrete greater amounts of sodium and water to maintain balance. This is achieved by increasing GFR and decreasing reabsorption in the remaining nephrons, resulting in increased sodium chloride delivery to the macula densa and suppression of renin release. This, in turn, impairs the kidney's ability to further decrease renin secretion during high sodium intake. Therefore, after loss of kidney mass blood pressure becomes very salt sensitive.

Nephron loss may also initiate compensatory changes that eventually damage the surviving nephrons.[23] For example, renal vasodilation and increased single nephron GFR can, over long periods of time, lead to glomerulosclerosis and reductions in K_f. These pathologic changes, in addition to the loss of functional nephrons, may eventually shift pressure natriuresis sufficiently to cause severe hypertension.

What is the relevance of experimental models produced by surgically removing kidney mass to human hypertension? With normal aging, especially after age 40 to 50 years, there is gradual nephron loss that is accelerated by renal diseases, such as glomerulonephritis, diabetes mellitus, or long-standing hypertension. Thus, even though hypertension may not begin with loss of nephrons, chronic elevations in glomerular pressure and other metabolic abnormalities that are often associated with hypertension may eventually cause glomerular injury and progressive nephron loss that amplifies the hypertension and makes blood pressure more salt-sensitive.

Nephron Loss by Partial Renal Infarction Causes Hypertension The experimental model of surgical reduction of kidney mass discussed above should not be confused with the model of partial renal infarction hypertension produced by tying off branches of the renal artery, the so-called *5/6 ablation* model. This model is usually produced by removing one kidney and obstructing two of the three branches of the renal artery of the remaining kidney. In the infarction model, hypertension develops even without a high sodium intake because of ischemia of the surviving nephrons, activation of the RAS, and immune-mediated injury of the kidney.[23,24] The 5/6 renal ablation hypertension is a model of severe patchy renal ischemia with characteristics similar to that described for the two-kidney, one-clip Goldblatt model or nonhomogeneous patchy glomerulosclerosis. The clinical counterpart of this model occurs with partial renal infarction caused by septic emboli, thrombus, trauma, or sometimes after corrective surgery for renal artery stenosis.

Hypertension Caused by Increased Renal Tubular Sodium Reabsorption

Hypertension can also be caused by factors that raise renal tubular sodium reabsorption, such as excessive levels of mineralocorticoids or ANG II. The severity of hypertension depends on the degree to which tubular reabsorption is stimulated and on other factors, such as the functional kidney mass and sodium intake.[18,19] With loss of functional nephrons or high sodium intake, the hypertensive potency of mineralocorticoids or ANG II is greatly enhanced.

Increased Distal and Collecting Tubule Reabsorption Causes *Salt-Sensitive* Hypertension One feature of hypertension caused by increased distal or collecting tubular reabsorption is that it is usually salt sensitive, with increased sodium intake exacerbating the hypertension. Increased reabsorption at sites beyond the macula densa, such as the distal tubules and collecting tubules, elicits chronic increases in sodium chloride delivery to the macula densa, which, in turn, suppress renin secretion.[16,18,19] The reduction of renin secretion to *very low* levels, characteristic of disorders associated with increased distal or collecting tubular reabsorption, prevents further suppression of ANG II formation during high sodium intake, making blood pressure salt sensitive.

Another feature of blood pressure caused by increased tubular reabsorption is that it is often associated with extracellular volume expansion. When increased tubular reabsorption is associated with marked peripheral vasoconstriction, such as occurs with very high levels of ANG II, the degree of volume expansion depends on the relative effects of the vasoconstrictor on the peripheral blood vessels and the renal blood vessels.[18,19] With severe peripheral vasoconstriction and decreased vascular capacitance, relatively small amounts of volume retention can lead to marked substantial hypertension.

Increased Proximal Reabsorption Causes *Salt-Insensitive* Hypertension An increase in tubular reabsorption occurring prior to the macula densa (e.g., in the proximal tubules or loop of Henle) usually results in a salt-insensitive form of hypertension. Increased tubular reabsorption prior to the macula densa tends to increase renin secretion and elicits a compensatory renal vasodilation that raises GFR and renal plasma flow. However, as hypertension develops, macula densa sodium chloride delivery and renin secretion return to nearly normal, and the RAS is fully capable of responding to additional challenges such as increased sodium intake. Therefore, high sodium intake is accompanied by appropriate suppression of renin release and ANG II formation, which permits sodium balance to be maintained with only small increases in blood pressure.[16,18] Nevertheless, the pressure natriuresis mechanism is shifted to higher blood pressure, parallel to the normal curve, and the severity of the hypertension depends on the degree to which reabsorption is increased in the proximal tubules and loops of Henle.

SALT-SENSITIVE AND SALT-INSENSITIVE HYPERTENSION

Salt sensitivity of blood pressure is a quantitative phenotype, rather than following a bimodal categorization of *salt-sensitive* or *salt-insensitive*, and there is considerable heterogeneity of blood pressure responses to changes in sodium intake in normotensive, as well as in hypertensive, individuals.[26]

Although various methods have been used to assess salt sensitivity, none are widely used in clinical practice. Most salt-sensitivity protocols involve relatively short-term changes in sodium intake, usually over a few days. Weinberger et al.[26] defined salt sensitivity as a 10 mmHg or greater change in mean blood pressure from the level measured after a 4-hour infusion of 2 L of normal saline compared to the level measured the morning after 1 day of a low-sodium (10 mmol) diet and administration of three doses of furosemide. With this definition, 51 percent of hypertensive and 26 percent of normotensive subjects were found to be salt sensitive.[26]
However, there has been little effort to determine the repeatability of salt sensitivity in the same persons over long periods of time (years), and it is not known whether short-term blood pressure responses reliably predict the long-term effects of changes in salt intake.

From clinical observations it is clear that there are many demographic and pathophysiologic conditions associated with salt sensitivity. Older individuals are usually more salt sensitive than young people and African Americans are often more salt sensitive than whites. However, there are many exceptions to these generalizations and considerable heterogeneity exists in the blood pressure responses to changes in salt intake even in these populations.

Genetic factors independent of race have also been linked to salt sensitivity of blood pressure. For example, monogenic disorders that increase distal and collecting tubule sodium reabsorption or that cause excess secretion of sodium-retaining hormones (e.g., mineralocorticoids) cause salt-sensitive hypertension.[27] Also, diabetes mellitus, renal diseases that cause nephron loss, and abnormalities of the RAS are all associated with increased salt sensitivity of blood pressure.[19,28] All of these examples appear to share two common pathways to salt sensitivity of blood pressure: loss of functional nephrons or reduced responsiveness of the RAS.

Loss of Functional Nephrons Causes Salt-Sensitive Blood Pressure As discussed previously, the effect of nephron loss to enhance salt-sensitivity is well established by experimental and clinical studies. Figure 69-7 shows the effect of surgically reducing kidney mass on salt sensitivity in dogs. As long as sodium intake was normal, surgical reduction of kidney mass by 25 percent, or even as much as 70 percent, did not markedly alter blood pressure.[25] However, after loss of kidney

mass, blood pressure became exquisitely sensitive to changes in sodium intake and with high sodium intake, blood pressure rose by approximately 40 mmHg.

How is this experimental study conducted in dogs relevant to human hypertension? Even in normal, healthy people, there is a years the average healthy individual typically has at least a 30 percent decrease in the number of nephrons, compared to a young adult, a factor that may contribute to the rise in blood pressure with age in industrialized societies. When there is underlying renal disease, hypertension, or diabetes, the loss of nephrons with aging is greatly exacerbated. Other, less-common causes of nephron loss include primary renal diseases such as glomerulonephritis, acquired renal disease caused by analgesic abuse, uncontrolled diabetes mellitus, and developmental causes because of poor maternal nutrition or placental ischemia.

[**Figure 69-7.**
The effect of reducing kidney mass on salt sensitivity in dogs. Note that as long as sodium chloride intake was normal, surgical reduction of kidney mass by 25 or even 70 percent did not markedly alter arterial pressure. However, after loss of kidney mass, blood pressure became exquisitely sensitive to high sodium chloride intake.]

Reduced Responsiveness of the RAS Causes Salt Sensitivity of Blood Pressure Because the RAS is the most powerful hormonal system in the body for controlling sodium excretion, it plays a major role in determining salt sensitivity of blood pressure.[30] With high sodium intake, suppression of the RAS permits normal excretion of sodium and water without substantial increases in blood pressure. Conversely, activation of the RAS is a primary mechanism for preventing a reduction in blood pressure during low sodium intake.

Figure 69-8
shows the importance of changes in ANG II formation in maintaining blood pressure relatively constant during variations in salt intake from a very low level of 5 mmol/d up to 80, 240, and 500 mmol/d for 8 days at each level. In normal dogs, with a functional RAS, there were only small increases in blood pressure associated with this 100-fold range of sodium intakes.[31] However, when ANG II was infused at a low level that had initially no effect on blood pressure, but which prevented ANG II from being suppressed as sodium intake was raised, blood pressure became very salt sensitive. After blockade of ANG II formation, blood pressure also became salt sensitive, although pressure was maintained at a much lower level, especially when sodium intake was low.[31] Thus, one of the major functions of the RAS is to permit wide variations in intake and excretion of sodium without large fluctuations in blood pressure that would otherwise be needed to maintain sodium balance.

[**Figure 69-8.**
Changes in mean arterial pressure during chronic changes in sodium intake in normal control dogs, after ACE inhibition, or after ANG II infusion (5 ng/kg/min) to prevent ANG II from being suppressed when sodium intake was raised.]

What clinical conditions can lead to reduced responsiveness of the RAS? As discussed previously, focal nephrosclerosis or patchy preglomerular vasoconstriction, as occurs with renal infarction, leads to increased renin secretion in ischemic nephrons and very low levels of renin release by overperfused nephrons.[18,19,32] Thus, in ischemic, as well as overperfused, nephrons the ability to adequately suppress renin secretion during high salt intake is impaired.

Another cause of reduced responsiveness of the RAS is increased distal and collecting tubular sodium reabsorption, as occurs with mineralocorticoid excess or mutations that increase distal and collecting tubule reabsorption (e.g., Liddle syndrome). In these conditions, excess sodium retention causes almost complete suppression of renin secretion, resulting in an inability to further decrease renin release during high sodium intake. Consequently, blood pressure becomes very salt sensitive.

Not all renal abnormalities cause salt-sensitive hypertension. Some, such as generalized diffuse increases in preglomerular resistance, cause a parallel shift of pressure natriuresis and hypertension, but do not cause blood pressure to be salt sensitive. Salt sensitivity is not increased in this form of hypertension because the RAS system is fully capable of appropriate suppression during high sodium intake and sodium balance is maintained with minimal rises in blood pressure.

Salt-Sensitive Subjects May Have Greater Target-Organ Injury What is the clinical significance of salt sensitivity besides the obvious fact that it provides insight into the pathogenesis of hypertension and it indicates which patients may benefit most from reduction of salt intake? Some studies suggest salt sensitivity also predicts which patients are at greatest risk for hypertensive target-organ injury. Salt-sensitive forms of hypertension caused by increased distal tubular reabsorption, nephron loss, or inability to suppress ANG II formation are usually associated with glomerular hyperfiltration and increased glomerular hydrostatic pressure that is further amplified by the hypertension (Table 69-2)[19]; together the hypertension and renal hyperfiltration promote glomerular injury and may eventually cause loss of nephron function. Clinical studies support this concept and demonstrate that salt-sensitive individuals typically have an increase in glomerular hydrostatic pressure and albumin excretion when given a salt load, whereas salt-resistant individuals have lower glomerular hydrostatic pressure and less

urinary albumin excretion.[33]

There is also evidence that salt-sensitive subjects may die earlier than individuals who are salt resistant. In a study by Weinberger et al. in which individuals were followed for more than 20 years, normotensive individuals with increased salt sensitivity died almost at the same rate as hypertensive individuals and much faster than salt-resistant individuals who were normotensive.[34] Whether this increased mortality was related to blood pressure effects of salt or to other effects is still unclear. It is also not known whether long-term high salt intake, lasting over many years, may cause a person who is initially "salt insensitive" to become "salt sensitive" as a consequence of gradual renal injury.

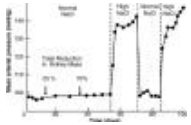

Figure 69-7. The effect of reducing kidney mass on salt sensitivity in dogs. Note that as long as sodium chloride intake was normal, surgical reduction of kidney mass by 25 or even 70 percent did not markedly alter arterial pressure. However, after loss of kidney mass, blood pressure became exquisitely sensitive to high sodium chloride intake. *Source: Redrawn from Langston JB, Guyton AC, Douglas BH, et al. Effect of changes in salt intake on arterial pressure and renal function in partially nephrectomized dogs. Circ Res 1963;12:508-512.*

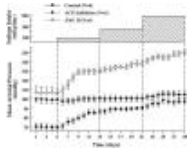

Figure 69-8. Changes in mean arterial pressure during chronic changes in sodium intake in normal control dogs, after ACE inhibition, or after ANG II infusion (5 ng/kg/min) to prevent ANG II from being suppressed when sodium intake was raised. *Source: Redrawn from Hall JE, Guyton AC, Smith MJ Jr, et al. Blood pressure and renal function during chronic changes in sodium intake: role of angiotensin. Am J Physiol 1980;239:F271-F280.*

NEUROHUMORAL MECHANISMS OF HYPERTENSION

Introduction

Although impaired renal pressure natriuresis plays a central role in all forms of experimental and human hypertension studied thus far, not all disorders of pressure natriuresis originate within the kidneys. Inappropriate activation of the multiple antinatriuretic hormone systems (e.g., ANG II, aldosterone) that normally regulate sodium excretion or a deficiency of natriuretic influences (e.g., atrial natriuretic peptide, nitric oxide) on the kidneys can impair renal pressure natriuresis and cause chronic hypertension. Likewise, excessive activation of the SNS plays a major role in elevating blood pressure in many hypertensive patients. The following sections discuss the multiple neural, hormonal, and autacoid mechanisms that contribute to long-term blood pressure regulation, their actions on the kidneys, and their potential roles in hypertension.

The Sympathetic Nervous System

The SNS is a major short-term and long-term controller of blood pressure. Sympathetic vasoconstrictor fibers are distributed to almost

[**TABLE 69-2. Renal Causes and Characteristics of Salt-Sensitive and Salt-Insensitive Hypertension**]

all of regions of the vasculature, as well as to the heart, and activation of the SNS can raise blood pressure within a few seconds by causing vasoconstriction, increased cardiac pumping capability, and increased heart rate. Conversely, sudden inhibition of SNS activity can decrease blood pressure to as low as half normal within less than a minute. Therefore, changes in SNS activity, caused by various reflex mechanisms, central nervous system ischemia, or by activation of higher centers in the brain, provide powerful and rapid, moment-to-moment regulation of blood pressure.

The SNS also plays an important role in long-term regulation of blood pressure and in the pathogenesis of hypertension, in large part by activation of the renal sympathetic nerves.[35] There is extensive innervation of the renal blood vessels, the juxtaglomerular apparatus, and the renal tubules and excessive activation of these nerves causes sodium retention, increased renin secretion, and impaired renal pressure natriuresis.[35] Except for extreme circumstances, such as severe hemorrhage or other conditions associated with marked circulatory depression, activation of the renal sympathetic nerves is usually not great enough to cause marked reductions in renal blood flow or GFR. However, even mild increases of the renal sympathetic activity stimulate renin secretion and sodium reabsorption in

multiple segments of the nephron, including the proximal tubule, the loop of Henle, and more distal segments.[35] Thus, the renal nerves provide a mechanism by which the various reflex mechanisms and higher central nervous system (CNS) centers can contribute to long-term regulation of blood pressure.

The preganglionic neurons that synapse with the renal sympathetic postganglionic fibers are located in the lower thoracic and upper lumbar segments of the spinal cord and receive multiple inputs from various regions of the brain, including the brainstem, the forebrain, and the cerebral cortex. These complex neural pathways provide multiple pathways by which neural reflexes and higher CNS centers can influence renal SNS activity and chronic regulation of blood pressure.[36,37]

Evidence for a role of the renal nerves in hypertension comes from multiple studies showing that renal denervation reduces blood pressure in several models of experimental hypertension.[35] For example, complete renal denervation attenuates the development of hypertension in spontaneously hypertensive rats[35] as well as in obese hypertensive dogs.[38] Renal denervation may also delay or attenuate increased blood pressure in several forms of experimental hypertension, although some studies have not found an important role for the renal nerves in various forms of secondary hypertension. In ANG II hypertension, for example, *decreased* renal sympathetic activity appears to attenuate the rise in blood pressure.[39]

Human primary hypertension, especially when associated with obesity, is often associated with increased renal sympathetic activity.[40] Although the mechanisms that cause activation of renal sympathetic nerves in primary hypertension or in most experimental models are still unclear, we will briefly discuss three that have attracted the interest of many researchers.

Resetting of Baroreceptor Reflexes in Hypertension

The importance of the arterial baroreceptors in buffering moment-to-moment changes in blood pressure is clearly evident in baroreceptor-denervated animals in which there is extreme variability of blood pressure associated with normal daily activities.[41] Although blood pressure increases to very high levels or falls to low levels throughout the day after baroreceptor denervation, the average 24-hour mean arterial pressure is not markedly altered.

The arterial baroreceptors clearly provide a powerful means for moment-to-moment regulation of arterial pressure, but their role in long-term blood pressure regulation is controversial. Some studies suggest that the baroreceptors are relatively unimportant in chronic regulation of blood pressure because they tend to reset within a few days to the level of blood pressure to which they are exposed.[41] In most forms of chronic hypertension, the arterial baroreflexes are reset to higher blood pressures. To the extent that resetting of baroreceptors occurs, this would attenuate their potency as a long-term controller of blood pressure.

Some experimental studies, however, suggest that the baroreceptors do not completely reset and therefore may contribute to long-term blood pressure regulation. With prolonged increases in arterial pressure, the baroreflexes may contribute to *reductions* in renal sympathetic activity and promote sodium and water excretion.[39] This, in turn, may attenuate the rise in arterial blood pressure. Thus, impairment of baroreflexes may contribute to increased lability of blood pressure in hypertension, but there is little evidence that baroreceptor dysfunction plays a major role in *causing* chronic hypertension. Instead, their primary role in hypertension, as in normotension, is to buffer changes in blood pressure from the set-point determined by renal pressure natriuresis.

Increased blood pressure lability associated with baroreflex dysfunction, however, is accompanied by periodic large increases in blood pressure that may cause gradual renal injury and eventually lead to chronic hypertension. Studies in experimental animals show, for example, that baroreceptor-denervated animals have significant structural changes in the kidneys, including glomerular injury.[42]

Does Chronic Stress Cause Hypertension by SNS Activation?

Acute physiologic stresses, including pain, exercise, exposure to cold, and mental stress, can all lead to increased SNS activity and transient hypertension. It is also widely believed, however, that chronic stress may lead to long-term increases in blood pressure. Support for this concept comes largely from a few epidemiologic studies showing that air traffic controllers, lower socioeconomic groups, and other groups who are believed to lead more stressful lives, also have increased prevalence of hypertension.[43] There is limited evidence, however, for a direct cause-and-effect relationship between psychosocial stress and chronic hypertension. Nevertheless, there is widespread belief by many researchers and by the general public that stress is an important cause of hypertension in humans.

Obesity

As discussed in more detail later, excess weight gain appears to be a major cause of human primary hypertension. The mechanisms responsible for obesity

hypertension appear to be closely linked to increased renal SNS activity.[16,44] Obese persons have elevated SNS activity in various tissues, including the kidneys and skeletal muscle, as assessed by microneurography, tissue catecholamine spillover, and other methods.[16,40] Studies in experimental animals and humans indicate that combined α- and β-adrenergic blockade markedly attenuates the hypertension associated with obesity.[16,44,45] Moreover, the renal sympathetic efferent nerves mediate much of the chronic effects of SNS activation on blood pressure in obesity as bilateral renal denervation greatly attenuates the sodium retention and hypertension in obese dogs.[38] Thus, obesity increases renal sodium reabsorption, impairs pressure natriuresis, and causes hypertension in part by increasing renal SNS activity.

The mechanisms that increase renal SNS activity in obesity have not been fully elucidated although several potential mediators have been suggested including hyperinsulinemia, increased ANG II, activation of chemoreceptor-mediated reflexes associated with sleep apnea, and hyperleptinemia.[16,44] One of the most promising of these is increased leptin, a peptide secreted by adipocytes in proportion to the degree of adiposity. However, further studies are needed to determine the role of leptin and other potential pathways that increase renal SNS activity and raise blood pressure in human primary hypertension.

The Renin-Angiotensin System

The RAS is perhaps the most powerful hormone system for regulating body fluid volumes and blood pressure as evidenced by the effectiveness of various RAS blockers in reducing blood pressure in normotensive and hypertensive subjects. Although the RAS has many components, its most important effects on blood pressure regulation are exerted by ANG II which participates in both short-term and long-term control of arterial pressure.

ANG II is a powerful vasoconstrictor and helps maintain blood pressure in conditions associated with acute volume depletion (e.g., hemorrhage), sodium depletion, or circulatory depression (e.g., heart failure). The long-term effects of ANG II on blood pressure, however, are closely intertwined with volume homeostasis through direct and indirect effects on the kidneys.

When the RAS is fully functional, the chronic renal pressure natriuresis curve is steep, and sodium balance can be maintained over a wide range of intakes with minimal changes in blood pressure (Fig. 69-9). One reason for the effectiveness of the normal pressure natriuresis mechanism is that ANG II levels are suppressed during high sodium intake and increased when sodium intake is restricted, thereby adjusting renal sodium excretion appropriately without the need to invoke large changes in blood pressure to maintain sodium balance.

Blockade of the RAS, with ANG II receptor blockers (ARBs) or angiotensin-converting enzyme (ACE) inhibitors, increases renal excretory capability so that sodium balance can be maintained at reduced blood pressure.[19] However, blockade of the RAS also reduces the slope of pressure natriuresis and makes blood pressure salt sensitive.[30]
Thus, the effectiveness of RAS blockers in lowering blood pressure is greatly diminished by high salt intake and, in many patients, effectiveness is improved by the addition of a diuretic.

Inappropriately high levels of ANG II reduce renal excretory capability and impair pressure natriuresis, thereby reducing the slope and necessitating increased blood pressure to maintain sodium balance. The mechanisms mediating the potent antinatriuretic effects of ANG II include renal hemodynamic effects as well as direct and indirect effects to increase tubular reabsorption.[30]

ANG II-Mediated Efferent Arteriolar Constriction Attenuates Reductions in GFR When Renal Perfusion is Threatened Physiologic activation of the RAS usually occurs as a compensation for conditions that cause underperfusion of the kidneys, such as sodium depletion or hemorrhage. The RAS acts in concert with other autoregulatory mechanisms, such as tubuloglomerular feedback (TGF) and myogenic activity, to maintain a relatively constant GFR when perfusion of the kidney is threatened.[19,30] In these cases, administration of ARBs or ACE inhibitors may actually reduce GFR further, even though renal blood flow is preserved. The impairment of GFR after RAS blockade is caused, in part, by inhibition of the constrictor effects of ANG II on efferent arterioles as well as reduced blood pressure.[30]

The vasoconstrictor effect of ANG II on efferent arterioles is most important when renal perfusion pressure is reduced to low levels, near the limits of autoregulation, or when other disturbances such as sodium depletion are superimposed on low perfusion pressure. Clinically, the constrictor effects of ANG II on efferent arterioles become especially important in patients with renal artery stenosis and/or sodium depletion or with heart failure who may have substantial decreases in GFR when treated with RAS blockers.[30]

The relatively weak constrictor action of ANG II on preglomerular vessels is related, in part, to selective protection of these vessels by autacoid mechanisms such as

prostaglandins or endothelial-derived nitric oxide (NO). After blockade of prostaglandin synthesis or inhibition of NO, ANG II infusion causes marked constriction of preglomerular as well as postglomerular vessels.[30] When the ability of the kidneys to produce these autocoids is impaired by treatment with nonsteroidal antiinflammatory drugs or by chronic vascular disease (e.g., atherosclerosis), increased levels of ANG II may reduce GFR by constricting afferent arterioles.

Increased ANG II May Mediate Glomerular Injury in Overperfused Kidneys Although blockade of the vasoconstrictor effects of ANG II on the efferent arterioles may cause a further decline in GFR in ischemic nephrons, RAS blockade may be beneficial when nephrons are hyperfiltering, especially if ANG II is not appropriately suppressed. For example, in diabetes mellitus and in certain forms of hypertension associated with glomerulosclerosis and nephron loss, ANG II blockade, by decreasing efferent arteriolar resistance and arterial pressure, lowers glomerular hydrostatic pressure and attenuates glomerular hyperfiltration.[46,47] Clinical and experimental studies indicate that RAS blockers are more effective than other antihypertensive agents in preventing glomerular injury, even with similar reductions in blood pressure;[48-50] this appears to be partly caused by a greater reduction in glomerular hydrostatic pressure as a result of vasodilation of efferent arterioles after blockade of the RAS.

Do Nonhemodynamic Effects of ANG II Cause Target-Organ Injury?

It also has been suggested that ANG II causes injury to the kidneys and other organs through direct actions that promote vascular smooth muscle migration and proliferation, increased collagen formation, and production of extracellular matrix, in addition to its hemodynamic effect. Much of the evidence supporting this hypothesis comes from in vitro studies, often using supraphysiologic concentrations of ANG II. Although in vivo studies have demonstrated greater renal protective effects of RAS blockers compared to other antihypertensive drugs, decreases in glomerular hydrostatic pressure because of efferent arteriolar vasodilation may have contributed to these beneficial effects. In studies where blood pressure was measured very accurately, using 24-hour telemetry, the renal protective effects of RAS blockade appear to be largely a result of reductions in blood pressure.[51]

An observation that is difficult to reconcile with the concept that ANG II directly mediates target-organ injury, independent of blood pressure, is the finding that physiologic activation of the RAS is not associated with vascular or renal injury as long as the blood pressure is not elevated. For example, sodium depletion does not cause renal, cardiac or vascular injury despite marked increases in renal ANG II levels. Also, the clipped kidney of the two-kidney, one-clip Goldblatt model of hypertension
is exposed to very high ANG II levels but is protected from increased arterial pressure by the clip on the renal artery and has no visible injury as long as the stenosis is not too severe. However, the nonclipped kidney, exposed to lower ANG II concentrations but higher blood pressure, has marked focal segmental glomerular sclerosis as well as tubulointerstitial changes characteristic of hypertension.[52] These observations suggest that the hemodynamic effects of ANG II are necessary for most of the vascular and renal injury that occur in ANG II-dependent hypertension.

[**Figure 69-9.**
Steady-state relationships between arterial pressure and sodium intake and excretion under normal conditions with a fully functional renin-angiotensin system, after blockade of ANG II formation with an angiotensin-converting enzyme (ACE) inhibitor, and after ANG II infusion at a low dose to prevent ANG II levels from being suppressed when sodium intake was increased. The numbers in parentheses are estimated ANG II levels expressed as times normal.]

ANG II Stimulates Renal Tubular Sodium Reabsorption

ANG II increases renal tubular sodium reabsorption through stimulation of aldosterone secretion, by direct effects on epithelial transport, and by hemodynamic effects. ANG II-mediated constriction of efferent arterioles reduces renal blood flow and peritubular capillary hydrostatic pressure, and increases peritubular colloid osmotic pressure as a result of increased filtration fraction.[30] These changes, in turn, increase the driving force for fluid reabsorption across tubular epithelial cells. Reductions in renal medullary blood flow caused by efferent arteriolar constriction or by direct effects of ANG II on the vasa recta may also enhance reabsorption in the loop of Henle and collecting ducts.[30]

ANG II also directly stimulates proximal tubular sodium reabsorption. This effect occurs at very low ANG II concentrations and is mediated by actions on the luminal and basolateral membranes (Fig. 69-10).[30,46] ANG II stimulates the Na^+-H^+ antiporter on the luminal membrane and increases sodium-potassium-adenosine triphosphatase (ATPase) activity, as well as sodium bicarbonate cotransport on the basolateral membrane.[46,53] These effects appear to be partly a result of inhibition of an adenyl cyclase and increased phospholipase C activity.

Sodium reabsorption in the loop of Henle, macula densa, and distal nephron segments is also stimulated by ANG II. At physiologic concentrations, ANG II increases bicarbonate reabsorption in the loop of Henle and stimulates Na^+-K^+-2 Cl transport in the medullary thick ascending loop of Henle.[46,53] ANG II stimulates multiple

ion transporters in the distal parts of the nephron, including H^+-ATPase activity, as well as epithelial sodium channel activity in the cortical collecting ducts.[46,53]

ANG II also amplifies TGF sensitivity by increasing ion transport in the macula densa epithelial cells.[53] The macula densa operates to maintain a relatively constant delivery of sodium chloride to the distal tubules by feedback regulation of afferent and efferent arteriolar resistances and, therefore, GFR. ANG II-mediated enhanced TGF sensitivity permits a decrease in distal sodium chloride delivery without compensatory increases in GFR via TGF. Decreased distal tubular NaCl delivery, caused by the multiple proximal tubule and vascular actions of ANG II, combines with other actions of ANG II on the distal nephron sites to reduce sodium excretion and exert powerful antinatriuretic effects. It is for this reason that ANG II is one of the most powerful sodium-retaining hormones in the body, and it exerts important effects on renal pressure natriuresis and long-term blood pressure regulation. Conversely, blockade of ANG II provides a means of enhancing renal excretory capability, thereby allowing sodium balance to be maintained at greatly reduced arterial blood pressures.

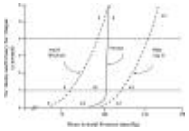

Figure 69-9. Steady-state relationships between arterial pressure and sodium intake and excretion under normal conditions with a fully functional renin-angiotensin system, after blockade of ANG II formation with an angiotensin-converting enzyme (ACE) inhibitor, and after ANG II infusion at a low dose to prevent ANG II levels from being suppressed when sodium intake was increased. The numbers in parentheses are estimated ANG II levels expressed as times normal. *Source: Redrawn from Hall JE, Guyton AC, Smith MJ Jr, et al. Blood pressure and renal function during chronic changes in sodium intake: role of angiotensin. Am J Physiol 1980;239:F271-F280.*

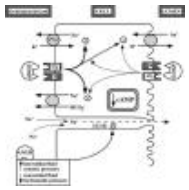

Figure 69-10. Angiotensin (ANG) II increases proximal tubular reabsorption by binding to receptors on the luminal and basolateral membranes and stimulating Na^+/H^+ antiporter, Na^+/HCO_3 cotransport, and Na^+/K^+ adenosine triphosphatase (ATPase) activity. ANG II also increases reabsorption by increasing interstitial fluid colloid osmotic pressure and decreasing interstitial fluid hydrostatic pressure. *Source: Redrawn from Hall JE, Brands MW, Henegar JR. Angiotensin II and long-term arterial pressure regulation: the overriding dominance of the kidney. J Am Soc Nephrol 1999;10:S258-S265.*

Aldosterone

Aldosterone is a powerful sodium-retaining hormone and consequently has important effects on renal pressure natriuresis and blood pressure regulation. The primary sites of actions of aldosterone on sodium reabsorption are the principal cells of the distal tubules, cortical collecting tubules, and collecting ducts where aldosterone stimulates sodium reabsorption and potassium secretion. Aldosterone binds to intracellular mineralocorticoid receptors (MRs) and activates transcription by target genes which, in turn, stimulate synthesis or activation of the Na^+-K^+-ATPase pump on the basolateral epithelial membrane and activation of amiloride-sensitive sodium channels on the luminal side of the epithelial membrane.[54] These effects are termed *genomic* because they are mediated by activation of gene transcription and require 60 to 90 minutes to occur after administration of aldosterone.

[**Figure 69-10.** Angiotensin (ANG) II increases proximal tubular reabsorption by binding to receptors on the luminal and basolateral membranes and stimulating Na^+/H^+ antiporter, Na^+/HCO_3 cotransport, and Na^+/K^+ adenosine triphosphatase (ATPase) activity. ANG II also increases reabsorption by increasing interstitial fluid colloid osmotic pressure and decreasing interstitial fluid hydrostatic pressure.]

Aldosterone also exerts rapid *nongenomic* effects on the cardiovascular and renal systems.[55,56] Aldosterone increases the sodium current in principal cells of the cortical collecting tubule through activation of the amiloride-sensitive channel and stimulates the Na^+-H^+ exchanger in a few minutes after application.[55,56] In vascular smooth muscle cells, aldosterone stimulates sodium influx by activating the Na^+-H^+ exchanger in less than 4 minutes. Acute aldosterone administration may rapidly reduce forearm blood flow in humans, although some investigators have found either no change or an increase in blood flow (see references 55 and 56 for review). The putative membrane receptor and the cell-signaling mechanisms responsible for these rapid nongenomic actions of aldosterone have not been identified, especially with physiologic levels of aldosterone. Thus, the importance of the nongenomic effects of aldosterone on long-term regulation of renal pressure natriuresis and blood pressure are still unclear.

The overall effects of aldosterone on renal pressure natriuresis are similar to those observed for ANG II. With low sodium intake, increased aldosterone helps prevent

sodium loss and reductions in blood pressure. Conversely, during high sodium intake, suppression of aldosterone helps to prevent excessive sodium retention and attenuates an increase in blood pressure.

Excess aldosterone secretion reduces the slope of pressure natriuresis so that blood pressure becomes very salt sensitive. Consequently, increasing plasma aldosterone 6- to 10-fold causes marked hypertension when sodium intake is normal or elevated, but there is very little effect on blood pressure when sodium intake is low.[17,57]

The role of aldosterone and activation of MRs in human hypertension is a topic of renewed interest in recent years. Some investigators suggest that hyperaldosteronism or excess activation of MRs may be more common than previously believed, especially in patients with hypertension that is resistant to treatment with the usual antihypertensive medications. For example, the prevalence of primary aldosteronism is reported to be almost 20 percent among patients referred to specialty clinics for resistant hypertension. Many of these patients, however, are overweight or obese.[58]

Regardless of the prevalence of primary aldosteronism, there is emerging evidence that antagonism of MRs may provide an important therapeutic tool for preventing target-organ injury and reducing blood pressure in hypertension[58,59]; for example, antagonism of MR attenuated sodium retention, hypertension, and glomerular hyperfiltration in obese dogs fed a high-fat diet.[60] This finding was somewhat surprising in view of the fact that plasma aldosterone concentration was only slightly elevated in obesity. However, even mild increases of plasma aldosterone may increase blood pressure when accompanied by high sodium intake and volume expansion because aldosterone greatly enhances salt sensitivity of blood pressure.

In obese, insulin-resistant patients there may also be enhanced sensitivity to the effects of aldosterone because of increased abundance of epithelial sodium channels (ENaCs) which would amplify the effects of MR activation on sodium reabsorption and blood pressure. It is also possible that glucocorticoids may contribute to activation of the MRs in obese, insulin-resistant patients. Normally the MR is "protected" from activation by glucocorticoids as a consequence of the effects of 11β-hydroxysteroid dehydrogenase-2 (11β-HSD2) which converts active cortisol into inactive cortisone. Consequently, reductions in 11β-HSD2 in the renal tubules would lead to increased MR activation by cortisol, causing sodium retention, hypokalemia, and hypertension. Although studies in some experimental models of hypertension, such as the Dahl salt-sensitive rat, have shown reduced expression of 11β-HSD2 in the kidney, few studies have assessed the potential role of this mechanism in human hypertension.

The Endothelin System

Endothelin-1 (ET-1), the most powerful vasoconstrictor produced in humans, is derived from a 203-amino-acid peptide precursor, preproendothelin, which is cleaved after translation to form proendothelin.[61] A converting enzyme located within the endothelial cells cleaves proendothelin (or big endothelin) to produce the 21-amino-acid peptide, endothelin.[62-65]

Cardiovascular and Renal Effects of ET-1

ET-1 receptor binding sites have been identified throughout the body, with the greatest numbers of receptors in the kidneys and lungs.[62-65] Although the biochemical and molecular nature of endothelin is well characterized, its physiologic importance in regulating renal and cardiovascular function has yet to be fully elucidated.[62-65] ET-1 can either elicit a hypertensive effect by activating endothelin type A (ET_A) receptors in the kidneys or an antihypertensive effect via endothelin type B (ET_B) receptor activation. Thus, the ability of ET-1 to influence blood pressure regulation is highly dependent on where ET-1 is produced and which ET receptor type is activated (Fig. 69-11).

Endothelin-1 produces vasoconstriction, impairs renal pressure natriuresis, and increases blood pressure via ET_A receptor activation. ET_A receptors are located primarily on vascular smooth muscle cells and are thought to mediate ET-1 vasoconstriction and cellular proliferation in various disease states.[62-65] Although ET_A receptors may play a role in certain forms of hypertension, they do not appear to have a major influence on cardiovascular and renal function under normal physiologic conditions.

ET-1, via ET_A receptor activation exerts multiple actions within the kidney that, if sustained chronically, could contribute to the development of hypertension and progressive renal injury. ET-1 decreases GFR and renal plasma flow through stimulation of vascular smooth muscle and mesangial cell contraction. Long-term effects of ET-1 on the kidney include stimulation of mesangial cell proliferation and extracellular matrix deposition, as well as vascular smooth muscle hypertrophy in renal resistance vessels.[62-64]

Expression of ET-1 is greatly enhanced in several animal models of severe hypertension with renal vascular hypertrophy and in models of progressive renal injury.[66-74] In addition, treatment with endothelin receptor antagonists attenuated the hypertension and small artery morphologic changes, and improved kidney function in these models.[68-72]

Role of ET-1 in Salt-Sensitive Hypertension

Several lines of evidence suggest that ET-1 may contribute to salt-sensitive hypertension. Dahl salt-sensitive (DS) rats placed on a high-sodium diet are characterized by attenuated pressure natriuresis, development of hypertension, extensive glomerulosclerosis, renal arteriolar, and tubular injury, as well as progressive renal injury. There is growing evidence that ET-1, acting via an ET_A receptor, may play a role in mediating the renal injury of DS hypertension. Prepro-ET-1 mRNA and vascular responsiveness to ET-1 are increased in the renal cortex of DS rats compared with Dahl salt-resistant (DR) rats and a positive correlation between ET-1 generation in the renal cortex and the extent of glomerulosclerosis has been reported in DS hypertensive rats.[67] Also supporting a role of ET-1 in DS hypertension is the finding that acute infusion of a nonselective ET_A-ET_B receptor antagonist directly into the renal interstitium improved renal hemodynamic and excretory function in DS rats but not in DR rats.[68] Moreover, chronic blockade of ET_A receptors attenuated the hypertension and proteinuria and ameliorated the glomerular and tubular damage associated with high salt intake in DS rats.[69] An important unanswered question is whether the beneficial effect of the ET_A blockade in reducing renal injury is mediated through lower blood pressure or through direct renal mechanisms.

Interaction between ET-1 and the RAS

Recent studies also suggest an important interaction between ET-1 and the RAS. Renal ET-1 synthesis is enhanced in various animal

[**Figure 69-11.**
Summary of the pro- and antihypertensive actions of endothelin-1 (ET-1). The ability of ET-1 to influence blood pressure regulation and renal pressure natriuresis is highly dependent on where ET-1 is produced and which renal ET receptor type is activated. ET-1 can elicit a prohypertensive antinatriuretic effect by activating ET_A receptors in the kidneys. Activation of renal ET_A receptors increases renal vascular resistance (RVR), which decreases renal plasma flow (RPF) and glomerular filtration rate (GFR), and enhances sodium reabsorption by decreasing peritubular capillary hydrostatic pressure (Pc). The net effect of renal ET_A receptor activation is decreased sodium excretion and increased blood pressure. Conversely, ET-1 can elicit an antihypertensive natriuretic effect via ET_B receptor activation. Activation of the renal ET_B receptor leads to enhanced synthesis of nitric oxide (NO) and prostaglandin (PG) E_2 and suppression of the renin-angiotensin system. The net effect of renal ET_B receptor activation is increased sodium excretion and decreased blood pressure.]

models of chronic ANG II-induced hypertension,[70-72] and the renal and hypertensive effects of ANG II in rats are markedly attenuated or completely abolished by ET_A receptor antagonists.[70-74] The quantitative importance of ET-1 in mediating the chronic hypertensive actions of ANG II may depend on the level of dietary sodium intake.

Possible Role of ET-1 in Preeclampsia

Preeclampsia is associated with hypertension, proteinuria, and endothelial dysfunction.[75,76] Because endothelial damage is a known stimulus for ET-1 synthesis, increases in the production of ET-1 and activation of ET_A receptors may participate in the pathophysiology of hypertension during preeclampsia. Alexander and coworkers found that renal expression of preproendothelin was significantly elevated in the renal medulla and the cortex in a rat model of preeclampsia induced by chronic reductions in uterine perfusion pressure.[77,78] Moreover, they reported that chronic administration of the selective ET_A receptor antagonist markedly attenuated the increase in blood pressure in pregnant rats with chronic reductions in uterine perfusion pressure. In sharp contrast to the response in reduced uterine perfusion pressure rats, ET_A receptor blockade had no significant effect on blood pressure in normal pregnant animal.[77] These findings suggest that ET-1 plays a major role in mediating the hypertension produced by chronic reductions in uterine perfusion pressure in pregnant rats. The role of ET-1 in mediating the cardiovascular and renal disorders in women with preeclampsia, however, is unknown.

Endothelin type B receptor activation causes vasodilation, enhances renal pressure natriuresis, and decreases blood pressure. While much attention has been given to ET_A receptor activation in the pathophysiology of cardiovascular and renal disease, recent studies indicate an important antihypertensive role for ET_B receptor.[79,80] The most compelling evidence for a major role of ET_B receptors in regulating renal function and blood pressure comes from reports that transgenic mice deficient in

ET_B receptors develop a severe salt-sensitive hypertension and that pharmacologic antagonism of ET_B receptors produces significant hypertension in rats.[80,81]

Because ET_B
receptors are located on multiple cell types throughout the body, including endothelial cells and renal epithelial cells, both intrarenal and extrarenal mechanisms could theoretically mediate the hypertension produced by chronic disruption of ET_B receptors. Bagnall et al. reported that ablation of ET_B receptors exclusively from endothelial cells produced endothelial dysfunction but did not cause hypertension.[82] In contrast to models of total ET_B receptor ablation, the blood pressure response to a high-salt diet was unchanged in endothelial cell-specific ET_B receptor knockouts compared to control mice. These findings suggest that ET_B receptors in nonendothelial cells are important for blood pressure regulation. Supporting this concept is the finding that collecting duct ET_B knockout (KO) mice on a normal sodium diet were hypertensive and that a high-sodium diet had worsened the hypertension.[83] These findings provide strong evidence that the intrarenal effect of ET_B receptor activation on the collecting duct is an important physiologic regulator that increases renal sodium excretion and reduces blood pressure.

Role of Endothelin in Human Hypertension

Although ET-1 clearly plays a significant role in the pathogenesis of some forms of experimental hypertension, especially salt-sensitive models, its role in human primary hypertension is unclear. Bosentan, a combined ET_A-ET_B receptor antagonist, significantly lowered blood pressure in a large, double-blind, clinical trial, indicating that endothelin system helps maintain blood pressure in human hypertension.[84] However, the magnitude of the blood pressure reduction by bosentan was almost the same as that observed in normotensive humans. Although this observation suggests that endothelin probably does not play a major role in raising blood pressure in most patients with essential hypertension, interpretation of the results is complicated by the fact that bosentan blocks both ET_A and ET_B receptors; blockade of the antihypertensive ET_B receptor may have masked an important role of endothelin in essential hypertension via ET_A receptor activation. Therefore, the importance of ET-1 in human essential hypertension deserves further investigation.

Role of Endothelin in Pulmonary Arterial Hypertension

Although the importance of ET-1 in human essential hypertension remains unclear, ET-1 appears to play an important role in pulmonary arterial hypertension (PAH). PAH is characterized by a progressive increase in pulmonary vascular resistance resulting from vascular remodeling, vasoconstriction, and cellular proliferation.[85] Depending on the severity of the disease, PAH may progress to right ventricular failure and death. Studies in animal models of PAH and in humans suggest that ET-1 plays an important role in mediating the vascular remodeling, vasoconstriction, and cellular proliferation associated with PAH.[85] Thus, ET-1 receptor antagonists have proven to be efficacious in treatment of patients with PAH.

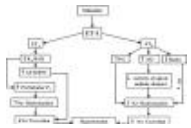

Figure 69-11. Summary of the pro- and antihypertensive actions of endothelin-1 (ET-1). The ability of ET-1 to influence blood pressure regulation and renal pressure natriuresis is highly dependent on where ET-1 is produced and which renal ET receptor type is activated. ET-1 can elicit a prohypertensive antinatriuretic effect by activating ET_A receptors in the kidneys. Activation of renal ET_A receptors increases renal vascular resistance (RVR), which decreases renal plasma flow (RPF) and glomerular filtration rate (GFR), and enhances sodium reabsorption by decreasing peritubular capillary hydrostatic pressure (Pc). The net effect of renal ET_A receptor activation is decreased sodium excretion and increased blood pressure. Conversely, ET-1 can elicit an antihypertensive natriuretic effect via ET_B receptor activation. Activation of the renal ET_B receptor leads to enhanced synthesis of nitric oxide (NO) and prostaglandin (PG) E_2 and suppression of the renin-angiotensin system. The net effect of renal ET_B receptor activation is increased sodium excretion and decreased blood pressure.

Nitric Oxide

Tonic release of NO by the vascular endothelium plays a major role in regulating vascular function and long-term inhibition of nitric oxide synthase models causes sustained hypertension associated with increases in total peripheral resistance and impaired renal pressure natriuresis.[86] The magnitude of the increase in blood pressure during NO inhibition depends on the sodium intake, indicating that NO also regulates sodium balance and renal pressure natriuresis.

NO Enhancement of Pressure Natriuresis

The renal mechanisms whereby reductions in NO synthesis enhance pressure natriuresis can be divided into hemodynamic and tubular components, each of which may be modulated by processes that are intrinsic or extrinsic to the kidneys (Fig. 69-12). For example, reductions in NO synthesis may decrease renal sodium excretory function by increasing renal vascular resistance directly or by enhancing the renal vascular responsiveness to vasoconstrictors such as ANG II or norepinephrine.[86]
Reductions in NO synthesis also increase renal tubular sodium reabsorption via direct effects on renal tubular transport and through changes in intrarenal physical factors, such as renal interstitial hydrostatic pressure and medullary blood flow.[86-90] Inhibition of NO synthesis reduces renal interstitial fluid hydrostatic pressure (RIHP) and urinary sodium excretion.[86] Stimulation of NO production normalizes the blunted pressure natriuretic response in DS rats as a result of improvement in the kidney's ability to generate increased RIHP in response to increased renal perfusion pressure.[86]

Most investigators attribute the alterations in RIHP to changes in flow and pressure in the renal medullary circulation.[88,89] Consistent with this hypothesis is the observation that acute infusion of an NO synthase inhibitor directly into the renal medulla significantly reduces papillary blood flow, RIHP, and urinary sodium and water excretion without affecting GFR or systemic arterial pressure.[88] Chronic renal medullary interstitial infusion of NO synthase inhibitors in conscious rats caused sustained reductions in medullary blood flow, sodium and water retention, and hypertension, which were reversed when the infusion was discontinued.[88] These findings suggest that reductions in medullary blood flow may be another important mechanism whereby inhibition of NO in the kidney leads to a hypertensive impairment of pressure natriuresis.

NO and the SNS

Several studies show that renal sympathetic nerve activity is suppressed following stimulation of NO production and increased after systemic administration of NO synthesis inhibitors. As changes in SNS activity are known to alter both renal hemodynamics and sodium reabsorption, changes in renal sympathetic activity may also contribute to the blunted pressure natriuresis observed in conditions of impaired NO production. However, not all studies support this concept[91] and the importance of interactions between NO and the SNS in long-term blood pressure control is still unclear.

NO Interacts with the RAS

Inhibition of NO production enhances renin release from juxtaglomerular cells directly as well as through a macula densa mediated mechanism.[92] Moreover, activation of the RAS accounts for a significant part of the hypertensive effects of impaired NO release.

Impaired NO Production Produces Salt-Sensitive Hypertension

Several lines of evidence suggest that NO plays an important role in the regulation of sodium balance and in the pathogenesis of salt-sensitive hypertension.[93] Increased renal NO production or

[**Figure 69-12.**
Renal mechanisms whereby reduced nitric oxide (NO) synthesis decreases pressure natriuresis and increases blood pressure. Decreased endothelial-derived nitric oxide (EDNO) synthesis impairs renal sodium excretory function by increasing basal renal vascular resistance, enhancing the renal vascular responsiveness to vasoconstrictors such as ANG II or norepinephrine, or activating the renin-angiotensin system. Reductions in NO synthesis also impair sodium excretory function either by directly increasing tubular reabsorption or by altering intrarenal physical factors, such as renal interstitial hydrostatic pressure or medullary blood flow.]

release, as evidenced by increased urinary excretion of NO metabolites or the NO second messenger, cyclic guanosine monophosphate, has been reported to be essential for the maintenance of normotension during a dietary salt challenge. Prevention of this increase in renal NO production resulted in salt-sensitive hypertension.[93]

There is also evidence that NO synthesis is impaired in some vascular beds in human primary hypertension. The extent to which these changes are secondary to increased blood pressure or reflect important mechanisms for the pathogenesis of hypertension, however, remains unclear.

Figure 69-12. Renal mechanisms whereby reduced nitric oxide (NO) synthesis decreases pressure natriuresis and increases blood pressure. Decreased endothelial-derived nitric oxide (EDNO) synthesis impairs renal sodium excretory function by

blood pressure. Decreased endothelial derived nitric oxide (EDNO) synthesis impairs renal sodium excretory function by increasing basal renal vascular resistance, enhancing the renal vascular responsiveness to vasoconstrictors such as ANG II or norepinephrine, or activating the renin-angiotensin system. Reductions in NO synthesis also impair sodium excretory function either by directly increasing tubular reabsorption or by altering intrarenal physical factors, such as renal interstitial hydrostatic pressure or medullary blood flow.

Oxidative Stress

Oxidative stress occurs when total oxidant production exceeds antioxidant capacity. Recent studies suggest that reactive oxygen species (ROS) may play a role in the initiation and progression of cardiovascular dysfunction associated with hyperlipidemia, diabetes mellitus, and hypertension.[94] In many forms of hypertension, the increased ROS appear to be derived mainly from nicotinamide adenine dinucleotide phosphate oxidases, which could serve as a triggering mechanism for uncoupling endothelial nitrous oxide synthase (NOS) by oxidants.[94]

ROS produced by migrating inflammatory cells and/or vascular cells have distinct effects on different cell types.[94] These effects include endothelial dysfunction, increased renal tubule sodium transport, cell growth and migration, inflammatory gene expression, and stimulation of extracellular matrix formation. ROS, by affecting vascular and renal tubule function, can also impair renal pressure natriuresis, alter systemic hemodynamics, and raise blood pressure (Fig. 69-13).[95-100]

Considerable evidence supports a role for ROS in various animal models of sodium-sensitive hypertension.[95-100] The DS rat, for example, has increased vascular and renal superoxide production and increased levels of H_2O_2. The renal expression of superoxide dismutase is decreased in the kidneys of DS rats, and long-term administration of Tempol, a superoxide dismutase mimetic, significantly decreases blood pressure and attenuates renal damage. Another salt-sensitive model, the stroke-prone spontaneously hypertensive rats, has elevated levels of superoxide and decreased total plasma antioxidant capacity. Superoxide production is also increased in the deoxycorticosterone acetate (DOCA)-salt hypertensive rat and treatment with apocynin, an nicotinamide adenine dinucleotide phosphate oxidase inhibitor, decreases arterial pressure.

The importance of oxidative stress in human hypertension is unclear. An imbalance between total oxidant production and the antioxidant capacity in human primary hypertension has been reported to occur in some but not all studies.[95] The equivocal findings in human studies are most likely a result of the difficulty of assessing oxidative stress in humans. However, most of the recent human studies have found that vitamin E and C supplementation has little or no effect on blood pressure.[95]

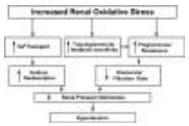

Figure 69-13. Renal mechanisms whereby reactive oxygen species impair pressure natriuresis and increase blood pressure. An increase in renal oxidative stress impairs renal pressure natriuresis by increasing renal vascular resistance or enhancing tubuloglomerular feedback, both of which decrease the glomerular filtration rate. Renal oxidative stress also reduces sodium excretion by direct effects to increase renal tubular reabsorption.

Inflammatory Cytokines

Epidemiologic and experimental studies reveal an association between biochemical markers of systemic inflammation and cardiovascular disorders such as atherosclerosis, heart failure, and hypertension. Although significant progress has been made in understanding the role of inflammatory cytokines in pathogenesis of atherosclerotic disease, the quantitative importance of cytokines in the pathogenesis and progression of hypertension has yet to be fully elucidated.

[**Figure 69-13.**
Renal mechanisms whereby reactive oxygen species impair pressure natriuresis and increase blood pressure. An increase in renal oxidative stress impairs renal pressure natriuresis by increasing renal vascular resistance or enhancing tubuloglomerular feedback, both of which decrease the glomerular filtration rate. Renal oxidative stress also reduces sodium excretion by direct effects to increase renal tubular reabsorption.]

Inflammatory Cytokines Interact with Important Blood Pressure Regulatory Systems Important blood pressure regulatory systems, such as the RAS and SNS, interact with the proinflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor-α (TNF-α). The SNS stimulates the release of proinflammatory

cytokines and sympathetic nerves may also serve as a source of cytokines.[101-105] There is also experimental evidence that proinflammatory cytokines may activate the sympathetic nervous system. ANG II enhances the synthesis of TNF-α and IL-6 and stimulates chemokine monocyte chemoattractant protein-1 and nuclear factor kappa B. ANG II also increases the production of ROS, including hydrogen peroxide, that participate in the process of inflammation.

Inflammatory Cytokines Interact with Endothelium-Derived Factors Proinflammatory cytokines also affect vascular function and endothelium-derived factors involved in the regulation of blood pressure. TNF-α and IL-6 induce both structural and functional alterations in endothelial cells. These cytokines enhance the formation of a number of endothelial cell substances, such as endothelin, reduce acetylcholine-induced vasodilatation, and destabilize the mRNA of endothelial nitric oxide synthase. Thus, endothelial dysfunction associated with many forms of hypertension may, in part, be mediated by proinflammatory cytokines.

Inflammatory Cytokines in Human and Experimental Hypertension Also supporting a potential role for cytokines in the regulation of blood pressure are findings that plasma levels of proinflammatory cytokines correlate with increased blood pressure in human hypertension and in some experimental animal models of hypertension.[106-108] Moreover, several recent studies have demonstrated that chronic increases in plasma cytokines, comparable to concentrations observed in the hypertension associated with preeclampsia, cause significant and sustained increases in blood pressure. For example, Alexander and coworkers[106] and LaMarca and coworkers[107]
reported that a twofold elevation in the plasma levels of TNF-α significantly increased blood pressure and renal vascular resistance in pregnant rats. Orshal and coworkers[108]
reported similar findings during IL-6 infusion for 5 days in pregnant rats. These studies are consistent with the hypothesis that increasing plasma levels of cytokines may contribute to pregnancy-induced hypertension.

A recent study by Lee and coworkers[109] also suggests that the hypertension caused by chronic ANG II excess may depend, at least in part, on the presence of IL-6. Mice with knockout of IL-6 had significantly lower blood pressure than wild-type mice during 2 weeks of ANG II infusion. Although these findings demonstrate a significant role for IL-6 in mediating the chronic hypertensive response to ANG II in mice, the importance of inflammatory cytokines in the pathogenesis and progression of the various forms of human hypertension is unclear and is currently an area of active investigation.

Eicosanoids

Eicosanoids are thought to be important regulators of vascular function, platelet aggregation, and sodium and water homeostasis.[110,111] Cyclooxygenase metabolizes arachidonic acid into prostaglandin (PG) G_2 and subsequently to PGH_2, which is then further metabolized by tissue-specific isomerases to PGs such as prostacyclin and thromboxane.

Although PGs play an important role in regulating vascular function in many vascular beds, the renal actions of PGs are thought to have a critical role in long-term blood pressure regulation under certain physiologic and pathophysiologic conditions. The kidneys produce many types of prostaglandins with multiple functions, including prostacyclin, thromboxane, 20-hydroxyeicosatetraenoic acid (20-HETE), and epoxyeicosatetraenoic acids (EETs), all of which have been reported to influence renal pressure natriuresis and blood pressure. However, the major renal prostaglandin controlling sodium excretion is probably PGE_2.[110] The largest production of PGE_2 occurs in the renal medulla with decreasing synthesis in the cortex. PGE_2 is synthesized and rapidly inactivated, and once synthesized, is released, not stored. Once released, PGE_2 inhibits sodium reabsorption by several mechanisms, including direct effects on the renal tubules.

Despite numerous reports that PGs may contribute to the natriuresis of acute physiologic perturbations, the importance of endogenous renal PGs in the long-term regulation of sodium balance under normal physiologic conditions remains unclear.[110] Increases in sodium intake have little or no effect on urinary PG excretion. In addition, nonspecific cyclooxygenase (COX) inhibitors do not affect sodium excretion or blood pressure responses to chronic alterations in dietary sodium intake. Thus, endogenous renal PGs may not play a major role in regulating sodium excretion during chronic changes in sodium intake.[110]

Even though long-term administration of PG synthesis inhibitors has very little effect on volume and/or blood pressure regulation under normal physiologic conditions, renal PGs may be important in pathophysiologic states associated with enhanced activity of the RAS.[110] In vitro and in vivo studies indicate that renal PGs protect the preglomerular vessels from excessive ANG II-induced vasoconstriction.[110] In the absence of this protective mechanism, the renal vasculature could be exposed to the potent vasoconstrictor actions of ANG II in various conditions, such as sodium and volume depletion. This could, in turn, lead to significant impairment of renal hemodynamics and excretory function.

Inhibitors of the COX-2 enzyme reduce renal pressure natriuresis, cause vasoconstriction, and increase blood pressure. There are at least two distinct

inhibitors of the COX-2 enzyme reduce renal pressure natriuresis, cause vasoconstriction, and increase blood pressure. There are at least two distinct cyclooxygenases—COX-1 and COX-2.[111] COX-1 is called the *constitutive enzyme* because of its wide tissue distribution, whereas COX-2 has been termed as *inducible* because of its more restricted basal expression and its upregulation by inflammatory and/or proliferative stimuli.[111] Based on the concept that COX-1 performs cellular housekeeping functions for normal physiologic activity and COX-2 acts at inflammatory sites, it was initially hypothesized that the blood pressure and renal effects of nonsteroidal antiinflammatory drugs might be linked to COX-1 inhibition.[111] However, increasing experimental and clinical evidence indicates that COX-2 metabolites may play a role in the regulation of vascular and renal function under various physiologic and pathophysiologic conditions.[111]

Selective COX-2 inhibitors were designed to minimize gastrointestinal complications of traditional NSAIDs—adverse effects attributed to suppression of COX-1-derived PGE_2 and prostacyclin. Randomized controlled-outcome trials of inhibitors of COX-2 indicate that such compounds may elevate the risk of hypertension, myocardial infarction, and stroke, possibly by removing the protective action of prostacyclin in counteracting thrombogenesis, hypertension, and atherogenesis.[112]

Eicosanoids Produced by Cytochrome P450 Monooxygenase Metabolism of Arachidonic Acid Alter Vascular Function and Renal Pressure Natriuresis

In addition to the PGs generated via the COX pathway, other eicosanoids that affect vascular function and/or renal sodium transport are produced by cytochrome P450 (CYP) monooxygenase metabolism of arachidonic acid. CYP enzymes metabolize arachidonic acid primarily to 20-HETE and EETs. 20-HETE is a potent vasoconstrictor that may have an important role in regulation vascular tone and in autoregulation of renal blood flow.[113] 20-HETE and EETs also inhibit sodium reabsorption in the proximal tubule and thick ascending limb of the loop of Henle. Compelling evidence suggests that the renal production of CYP metabolites of arachidonic acid is altered in genetic and experimental models of hypertension and that this system contributes to the resetting of pressure natriuresis and the development of hypertension. In the spontaneously hypertensive rat, renal production of 20-HETE is increased and inhibitors of the formation of 20-HETE decrease blood pressure.[113] Blockade of 20-HETE synthesis also reduces blood pressure and improves renal function in DOCA-salt, ANG II-infused, and Lyon hypertensive rats.[113] In contrast, 20-HETE formation is reduced in the thick ascending limb of DS rats, which contributes to elevated sodium reabsorption.[113] Enhanced 20-HETE synthesis improves pressure natriuresis and lowers blood pressure in DS rats, whereas inhibitors of 20-HETE production promote the development of hypertension in Lewis rats.[113]

Studies in humans also suggest that CYP metabolites may play a role in sodium homeostasis. Urinary 20-HETE excretion is regulated by salt intake and is differentially regulated in salt-sensitive versus salt-resistant individuals.[114] Moreover, there appears to be a strong negative relationship between the excretion of 20-HETE and body mass index (BMI), suggesting that some factor related to obesity may be responsible for decreased synthesis or excretion of this eicosanoid in hypertension.[115] These observations support the possibility that attenuated renal production of 20-HETE could contribute to impaired renal pressure natriuresis in human hypertension, especially when associated with obesity. However, further mechanistic studies are needed to test the importance of 20-HETE in human hypertension.

Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANP) is a 28-amino-acid peptide synthesized and released from atrial cardiocytes in response to stretch. ANP is released from the atria and reduces vascular resistance while enhancing sodium excretion through extrarenal and intrarenal mechanisms.[110] ANP increases GFR but has little effect on renal blood flow. However, an increase in GFR is not a prerequisite for ANP to enhance sodium excretion. ANP may also inhibit renal tubular sodium reabsorption either directly by inhibiting active tubular transport of sodium or indirectly via alterations in medullary blood flow, physical factors, and intrarenal hormones.[110,116]

ANP Inhibits Renin and Aldosterone Secretion ANP has important actions at several sites of the RAS cascade.[110] Intrarenal or intravenous infusion of ANP reduces the renin secretion rate by a macula densa mechanism, and reductions in intrarenal ANG II levels likely contribute to ANP-induced natriuresis. When intrarenal levels of ANG II were prevented from decreasing, the natriuretic effects of ANP were blunted.[110]

ANP also decreases aldosterone release from the adrenal zona glomerulosa cells.[110] Two mechanisms for ANP-induced suppression of aldosterone release have been suggested: (1) a direct action on adrenal glomerulosa cells, and (2) reduced circulating levels of ANG II because of suppressed renin secretion.[110] Although the suppression of aldosterone release does not mediate the acute natriuretic responses to ANP, decreases in circulating levels of aldosterone could contribute to the long-term actions of ANP on sodium balance and blood pressure regulation.

ANP Plays a Role in Short- and Long-Term Volume Regulation Plasma levels of ANP are elevated in numerous physiologic conditions associated with enhanced

sodium excretion.[110] Acute blood volume expansion consistently elevates circulating levels of ANP. Some, but not all, investigators report that chronic increases in dietary sodium intake also raise circulating levels of ANP. Infusions of exogenous ANP at rates that result in physiologically relevant plasma concentrations, comparable to those observed during volume expansion, elicit significant natriuresis, especially in the presence of other natriuretic stimuli, such as high renal perfusion pressure.[110] Long-term physiologic elevations in plasma ANP also enhance renal pressure natriuresis and reduce blood pressure.[117]

Blockade of the ANP System Produces Salt-Sensitive Hypertension The development of genetic mouse models that exhibit altered expression of ANP or its receptors (NPR-A, NPR-C) have provided compelling evidence for a role of ANP in chronic regulation of renal pressure natriuresis and blood pressure.[118] Transgenic mice overexpressing ANP are hypotensive relative to their wild-type littermates, whereas mice harboring functional disruptions of the ANP or NPR-A genes are hypertensive. ANP gene knockout mice develop salt-sensitive form of hypertension in association with failure to adequately suppress the RAS. These findings suggest that genetic deficiencies in ANP or its receptors could play a role in the pathogenesis of salt-sensitive hypertension.

SECONDARY CAUSES OF HYPERTENSION

Introduction

In a small percentage of patients, the clinical features, history, and physical examination point to a specific cause of increased blood pressure and the hypertension is therefore said to be *secondary*. Some types of secondary hypertension have a definite genetic basis, whereas others are caused by cardiovascular diseases and target-organ injury associated with various disorders such as diabetes and kidney disease, and in some instances, hypertension can be caused by drugs or treatments that the patient receives. Nearly all forms of secondary hypertension, however, are characterized by impaired renal function or altered activity of the SNS or hormones that, in turn, impair the ability of the kidneys to excrete salt and water.

Table 69-3 lists some of the most frequently diagnosed causes of secondary hypertension, including those caused by drugs that either themselves raise blood pressure or exacerbate underlying disorders that contribute to hypertension. These drugs include nonsteroidal antiinflammatory drugs, oral contraceptive agents, glucocorticoids, and sympathomimetics that are used as cold remedies. This chapter discusses only a few of the more common causes of secondary hypertension.

Renovascular Hypertension

Renovascular hypertension, although accounting for only 2 to 3 percent of all hypertension, is one of the most common causes of secondary hypertension. The pathophysiology of renovascular hypertension is related directly to the reduction in renal perfusion that occurs as a result of stenosis of the main renal artery, one of its branches, or stenosis/injury of other smaller preglomerular blood vessels and glomeruli. The majority of renal vascular lesions reflect either fibromuscular dysplasia or atherosclerosis.[119] The predominant lesion found in the main renal artery or its branches in patients older than 50 years of age is atherosclerotic disease. More subtle functional (constriction) or structural changes in smaller blood vessels (e.g., afferent arterioles, glomeruli), however, are difficult to detect clinically and can contribute to increased blood pressure.

Renovascular hypertension can be unilateral, involving only one kidney, or bilateral, and can result in a homogeneous or a nonhomogeneous ischemia of nephrons. As discussed earlier in the chapter, there are some important differences in the pathophysiology of homogeneous compared to nonhomogenous impairment of renal perfusion. Experimental counterparts of these two clinical forms of renovascular hypertension can be found in the one-kidney, one-clip and the two-kidney, one-clip models of Goldblatt hypertension, respectively.

One-Kidney, One-Clip Model of Goldblatt Hypertension, or Stenosis of a Single Remaining Kidney

In the one-kidney, one-clip model of Goldblatt hypertension, and in patients with stenosis of a single remaining kidney, there is a fairly homogeneous reduction in perfusion of all nephrons leading to an elevation of blood pressure that is proportional to the severity of the stenosis. In experimental one-kidney, one-clip Goldblatt hypertension, the blood pressure increases rapidly after clipping the renal artery and remains stable as long as the stenosis does not worsen. Moreover, blood pressure returns to normal when the stenosis is removed.

Renal artery constriction, if severe enough to reduce renal perfusion pressure below the range of autoregulation (approximately 70 mmHg), initially decreases renal blood flow, GFR, and sodium excretion, while increasing renin secretion. However, sodium excretion returns to normal and if sodium intake is normal and adequate volume is available, renin secretion also returns to nearly normal in the established phase of hypertension if the stenosis is not too severe.[18,120] At this point, the hypertension is stable and most indices of renal function are relatively normal, including pressure distal to the stenosis.

hypertension is stable and most indices of renal function are relatively normal, including pressure distal to the stenosis.

[**TABLE 69-3. Some Secondary Causes of Hypertension**]

Increased ANG II accounts for most of the rapid increase in blood pressure after stenosis of the renal artery. However, even after blocking the RAS, blood pressure still increases (although more slowly) until renal perfusion pressure returns to nearly normal. This increase in renal perfusion pressure, at the expense of systemic arterial hypertension, permits normal excretion of sodium and water to be maintained. As long as the sodium intake is normal, activation of the RAS serves mainly to increase the rate at which blood pressure is elevated. In the established phase of hypertension, blockade of the RAS causes only small reductions in blood pressure, similar to the decreases observed in normal subjects after ANG II blockade.[121]

The importance of volume expansion in elevating blood pressure in one-kidney, one-clip Goldblatt hypertension depends on the sodium intake. With normal or high sodium intake, significant extracellular volume expansion occurs, whereas a low-sodium diet converts this model of hypertension from one that is volume dependent to one that is highly ANG II dependent. Thus, a combination of low-sodium diet and blockade of ANG II formation often normalizes blood pressure in one-kidney, one-clip Goldblatt hypertension.[122]

When the stenosis is severe and adequate renal perfusion cannot be restored even with increased systemic arterial pressure, renin secretion continues to increase, as does arterial pressure, leading eventually to malignant hypertension and renal failure. Thus, the ability to return renal perfusion pressure to normal, or nearly normal, by volume retention or activation of the RAS is critical to maintaining homeostasis when there is a stenosis of a single remaining kidney.

The same sequence as described above occurs when there are widespread homogeneous increases in preglomerular resistance caused by bilateral renal artery stenosis or aortic coarctation above both renal arteries.[18,21]

Two-Kidney, One-Clip Model of Goldblatt Hypertension (Nonhomogeneous Increases in Preglomerular Resistance)

In the two-kidney, one-clip model of Goldblatt hypertension, or in patients with nonhomogeneous increases in preglomerular resistance, the pathophysiology of hypertension
is more complicated. Nonhomogeneous increases in preglomerular resistance can be a result of stenosis of one renal artery and normal perfusion of the contralateral kidney or of patchy increases in preglomerular resistance within the kidneys, with some nephrons being underperfused and others having normal or increased blood flow. Thus, these models of hypertension are characterized by underperfusion of some nephrons and normal or increased blood flow in adjacent nephrons or in the nonstenotic kidney.

In experimental models with unilateral renal artery stenosis, the increase in blood pressure is less predictable as long as the contralateral kidney does not become injured because of the hypertension. In this situation, the underperfused nephrons (or the entire underperfused kidney in the case of a unilateral renal artery stenosis) are exposed to reduced perfusion pressure, secrete increased amounts of renin, and excrete less sodium and water than kidneys with normal blood flow. In contrast, the nonischemic nephrons (or nonstenotic kidney) are exposed to increased renal perfusion pressure causing renin secretion to fall to very low levels and increasing sodium excretion above normal. However, even with increased perfusion pressure the function of the nonischemic nephrons (or unclipped, nonstenotic kidney) is impaired because of increased circulating levels of ANG II which exert an antinatriuretic effect and help to sustain hypertension.

The higher blood pressures experienced by the nonstenotic kidney may eventually cause damage to its nephrons. If sufficient damage occurs, unclipping the stenotic kidney (in the case of the experimental two-kidney, one-clip Goldblatt model) or repair of a unilateral renal artery stenosis in humans, may not completely normalize blood pressure. Thus, the contralateral, nonstenotic kidney in these instances may, because of injury, sustain increased blood pressure even after correction of the stenosis in the other kidney. However, correction of the stenosis plus nephrectomy of the nonstenotic kidney usually normalizes blood pressure.[123]

As discussed previously, the two-kidney, one-clip hypertension is *salt sensitive*, whereas the one-kidney, one-clip model is *salt insensitive*. The main reason for the differences in salt sensitivity relate to the reactivity of the RAS in these two models. In one-kidney, one-clip hypertension, renin secretion is normal after hypertension is established and high salt intake results in normal suppression of renin release. In two-kidney, one-clip hypertension, however, the stenotic kidney has a high level of renin secretion that cannot be adequately suppressed when salt intake is raised. The contralateral nonstenotic kidney already has suppressed renin secretion as a consequence of the high blood pressure and therefore cannot suppress renin secretion further when salt intake is raised. Thus, blood pressure in the two-kidney, one-clip model of Goldblatt becomes sensitive to increased salt intake because of impaired responsiveness of the RAS.

Administration of ACE inhibitors or ARBs as a treatment for renovascular hypertension may improve the structure and function of the nonstenotic kidney, but can also produce shrinkage of the stenotic kidney, resulting in fibrosis and deterioration of its function. This is partly a result of the fall in blood pressure, which may reduce

produce shrinkage of the stenotic kidney, resulting in fibrosis and deterioration of its function. This is partly a result of the fall in blood pressure, which may reduce renal perfusion pressure distal to the lesion to a level below the range of autoregulation. However, blockade of the RAS also causes vasodilation of efferent arterioles, which contributes to a decline in GFR in the stenotic kidney. In some patients with severe renal vascular lesions, administration of ACE inhibitors or ARBs may cause severe decreases in renal function, especially when there is also volume depletion because of concomitant use of diuretics. Therefore, renal function should be monitored frequently after administration of RAS inhibitors in patients suspected of having renovascular hypertension. Fortunately, these effects appear to be reversible upon cessation of ACE inhibition or ARB, and in many patients the beneficial effects of RAS blockade in reducing blood pressure can be achieved without precipitating further loss of kidney function.

Adrenal Cortex Hypertension

Aldosterone normally exerts nearly 90 percent of the mineralocorticoid activity of the adrenocortical secretions. However, cortisol, the major glucocorticoid secreted by the adrenal cortex, can also provide significant amount of mineralocorticoid activity in some conditions. Aldosterone's mineralocorticoid activity is about 3000 times greater than that of cortisol, but the plasma concentration of cortisol is nearly 2000 times that of aldosterone. As discussed previously, the renal MR is normally protected from activation by cortisol as a result of the effects of 11β-HSD2, which converts active cortisol into inactive cortisone, but when activity of this enzyme is reduced or when cortisol levels are very high, the MR can be activated by cortisol.

Primary Aldosteronism (Conn Syndrome)

Primary aldosteronism, also called *Conn Syndrome* in honor of Jerome Conn who first described this condition in 1955, is the syndrome that results from hypersecretion of aldosterone in the absence of a known stimulus. The excess aldosterone secretion almost always comes from the adrenal cortex and is usually associated with a solitary adenoma or bilateral hyperplasia of the adrenal cortex. *Secondary aldosteronism* refers to increased aldosterone secretion that occurs secondary to a know stimulus, such as activation of the RAS. This is the most common form of aldosteronism seen in clinical practice and occurs in various conditions associated with stimulation of renin secretion, such as congestive heart failure, sodium depletion, or renal artery stenosis.[124]

Primary aldosteronism can occur as a result of an aldosterone-producing adenoma (APA) or because of unilateral or bilateral adrenal hyperplasia.[125] The effects of excess aldosterone were discussed earlier, but the most important with regard to chronic blood pressure regulation are increased sodium reabsorption and increased potassium secretion by the principal cells of the renal tubules. This leads to expansion of extracellular fluid volume, hypertension, suppression of renin secretion, hypokalemia, and metabolic alkalosis, hallmarks of primary aldosteronism. Most of these effects are highly salt sensitive and low sodium intake can greatly attenuate the hypertension and hypokalemia associated with primary aldosteronism.

Adrenal adenomas and bilateral adrenal hyperplasia account for more than 95 percent of primary aldosteronism. However, this is a rare form of hypertension, and in most studies of unselected patients, the classic form of primary aldosteronism was found in less than 1 percent of hypertensive patients.[124] Some adrenal glands in patients with primary aldosteronism may have varying degrees of hyperplasticity and the term *idiopathic hyperaldosteronism* (IHA) was coined to describe this condition. Clinically, APA and IHA are difficult to distinguish, although patients with APA often have more severe hypertension and hypokalemia compared to those with IHA.

The measurement of the aldosterone-renin ratio has been used is recent years in an attempt to define more subtle cases of primary aldosteronism.[125,126] This approach has lead to the suggestion that excess aldosterone secretion may account for as much as 5 to 10 percent of essential hypertension.[125] However, there is considerable debate about whether patients with an increased aldosterone-renin ratio truly have primary aldosteronism, as first described by Conn. In many of these patients, the major reason for the increased aldosterone-renin ratio is the low level of renin, rather than excess aldosterone secretion.[124]

Increased Arterial Pressure and "Escape" from Sodium Retention during Hyperaldosteronism

Although aldosterone is one of the body's most powerful sodium-retaining hormones, sodium excretion eventually returns to match sodium intake even in patients with APA and very high levels of aldosterone. This "escape" from sodium retention is secondary to increases in extracellular fluid volume and arterial pressure, which in turn increases renal excretion of salt and water via the pressure natriuresis and diuresis mechanisms.[57] Thus, after the extracellular fluid volume increases 5 to 15 percent above normal, arterial pressure also increases 15 to 25 mmHg and this elevated blood pressure returns the renal output of salt and water to normal despite the excess aldosterone (Fig. 69-14). However, this escape occurs at the expense of hypertension, which lasts as long as the person is exposed to the high levels of aldosterone. The importance of pressure natriuresis in permitting aldosterone escape has been demonstrated experimentally by servocontrolling renal perfusion pressure; when renal perfusion pressure was servocontrolled, aldosterone infusion caused continued sodium retention and progressive increases in cumulative

sodium balance and extracellular fluid volume, resulting in severe circulatory congestion and edema.[37] Failure of the kidneys to escape from aldoster-one-induced sodium retention can also be observed in patients with heart failure who, because of a severely weakened heart, cannot increase arterial pressure sufficiently to reestablish salt and water balance.

Sustained Hypokalemia and Metabolic Alkalosis with Hyperaldosteronism

Excess aldosterone not only increases secretion of potassium ions by the principal cells of the renal tubules, but also stimulates transport of potassium from the extracellular fluid into most cells of the body. This shift of potassium from the extracellular to intracellular fluid accounts for a significant part of the hypokalemia that occurs with excess aldosterone secretion.

Excess aldosterone secretion also stimulates secretion of hydrogen ions in exchange for sodium in the intercalated cells of the renal cortical collecting tubules. This decreases the hydrogen ion concentration in the extracellular fluid causing metabolic alkalosis.

Patients with IHA often have a milder form of aldosteronism than those with APA, although there may be overlap in severity of the clinical features of these two groups.[124,125]
In patients with APA, plasma aldosterone concentration is not usually increased in response to upright posture because of marked suppression of the RAS and insensitivity of the aldosterone-secreting adenoma to ANG II. In contrast, patients with IHA usually have a significant increase in aldosterone concentration during upright posture suggesting that adrenal sensitivity to ANG II is maintained.[125] These differences between IHA and APA in adrenal responsiveness to RAS activation have been used to discriminate these two forms of primary aldosteronism.[124]

Cushing Syndrome (Glucocorticoid Excess)

Cushing syndrome is a serious disorder characterized by excess glucocorticoids. Hypertension occurs in approximately 80 percent of patients with Cushing syndrome and is difficult to control.[127]

Cushing syndrome can be caused by either administration of excess cortisol (e.g., for treatment of various inflammatory disorders) or by excess endogenous cortisol secretion. The most common cause of endogenous cortisol excess is overproduction of adrenocorticotrophic hormone (ACTH) from a pituitary adenoma, a condition referred to as *Cushing disease*. The increased ACTH causes adrenal hyperplasia and stimulates cortisol secretion. Cushing disease can also occur as a result of ectopic secretion of ACTH by tumors outside the pituitary, such as an abdominal carcinoma.

ACTH-independent hypercortisolism can occur as a result of adenomas of the adrenal cortex. Primary overproduction of cortisol by the adrenal glands, independent of ACTH, accounts for approximately 20 to 25 percent of Cushing syndrome and is usually associated with suppressed ACTH levels caused by cortisol-induced feedback inhibition of ACTH secretion by the anterior pituitary gland. Administration of large doses of dexamethasone, a synthetic glucocorticoid, can be used to distinguish between ACTH-dependent and ACTH-independent Cushing syndrome. In patients with overproduction of cortisol because of an ACTH-secreting pituitary adenoma or hypothalamic-pituitary dysfunction, even large doses of dexamethasone usually do not suppress ACTH secretion. In contrast, patients with primary adrenal overproduction of cortisol (ACTH independent) usually have low or undetectable levels of ACTH. However, the dexamethasone test may occasionally give an incorrect diagnosis because some ACTH-secreting pituitary tumors respond to dexamethasone with suppression of ACTH secretion.

Glucocorticoids modulate a wide variety of cell processes and the precise mechanisms by which hypercortisolism causes hypertension are incompletely understood. One potential mechanism is activation of the MR; the high levels of cortisol in Cushing syndrome may simply overwhelm the ability of the renal 11β-HSD2 to convert active cortisol into inactive cortisone at the MR receptor, so that cortisol stimulates the MR and causes sodium retention, volume expansion, hypertension, and hypokalemia. High levels of cortisol also increase levels of angiotensinogen and may increase the responsiveness to various pressor stimuli, including ANG II and norepinephrine.[128]

Studies in experimental animals suggest that excess cortisol may also raise blood pressure through mechanisms that may be at least partially independent of activation of classical glucocorticoid or MR.[128] Most of the available evidence, however, suggests that sodium retention may play a key role, although the precise mechanisms that lead to sodium retention are incompletely understood. Regardless of the precise mechanisms of hypertension, the morbidity associated with cortisol excess is substantial, and the risk for death is largely a result of excess cardiovascular events, including heart attack and stroke.

Other Forms of Adrenocortical Hypertension

There are several other rare forms of adrenocortical hypertension, as discussed in Genetic Causes of Hypertension below. Some of these are genetic disorders and include familial hyperaldosteronism, glucocorticoid

[**Figure 69-14.** Effects of chronic aldosterone infusion when renal perfusion pressure was servo-controlled (*dashed lines*) or allowed to increase (*solid lines*). When real perfusion pressure was prevented from increasing, "escape" from sodium retention did not occur and cumulative sodium balance and systemic arterial pressure continued to increase.]

remediable aldosteronism, deoxycorticosterone-secreting tumors, and the syndrome of apparent mineralocorticoid excess where glucocorticoids activate the mineralocorticoid receptor because of a deficiency of 11β-HSD2. In each of these conditions, the clinical characteristics are similar to those observed with primary increases in aldosterone secretion caused by adrenal adenomas or idiopathic primary aldosteronism.

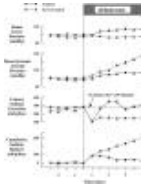

Figure 69-14. Effects of chronic aldosterone infusion when renal perfusion pressure was servo-controlled (*dashed lines*) or allowed to increase (*solid lines*). When real perfusion pressure was prevented from increasing, "escape" from sodium retention did not occur and cumulative sodium balance and systemic arterial pressure continued to increase. *Source: Redrawn from Hall JE, Granger JP, Smith MJ Jr, et al. Role of renal hemodynamics and arterial pressure in aldosterone "escape." Hypertension 1984;6(Suppl I):I183-I192.*

Pheochromocytoma

Pheochromocytoma is a rare form of secondary hypertension occurring in approximately 0.05 percent of hypertensive patients.[124,129] Although rare, pheochromocytoma can provoke fatal hypertensive crises if unrecognized and untreated. Pheochromocytoma can arise from neuroectodermal chromaffin cells, which are part of the sympathoadrenal system. The chromaffin cells have the capacity to synthesize and store catecholamines and are normally found mainly in the adrenal medulla. Although most chromaffin cell tumors are found in the adrenal medulla, as many as 15 to 30 percent may be extraadrenal, located along the sympathetic chain or, rarely, in other sites.[124,129]

The symptoms and severity of hypertension associated with pheochromocytoma are highly variable, depending on the secretory pattern and amount of catecholamines released.[124,129,130] With tumors that continuously release large amounts of catecholamines, there may be sustained hypertension with few paroxysms, or sudden bursts of very high levels of blood pressure. Tumors that are less active may have cyclical release of catecholamines stores that induce paroxysms of hypertension.

The clinical presentation also depends on whether the predominant catecholamine that is secreted is norepinephrine or epinephrine. Norepinephrine produces α-adrenergically mediated vasoconstriction with diastolic hypertension, whereas epinephrine produces β-adrenergically mediated cardiac stimulation with mainly systolic hypertension and tachycardia, along with sweating, tremors, and flushing. Patients with predominantly epinephrine-secreting tumors sometimes have hypertension alternating with hypotension, and approximately 5 percent of patients with pheochromocytoma remain normotensive.[124]

Pheochromocytoma patients often have decreased blood volume, consistent with the potent effects of norepinephrine to cause peripheral vasoconstriction. This observation, and the finding that chronic excess catecholamines often increase sodium excretion, could be interpreted as evidence that the hypertensive effects of catecholamines are unrelated to any impairment of renal excretory capability. However, the natriuretic effect of catecholamines and volume contraction appear to be secondary to peripheral vasoconstriction, decreased vascular capacitance, and increased arterial pressure, which causes a pressure natriuresis.[15,18] Chronic intrarenal infusion of norepinephrine causes sustained hypertension, indicating important direct effects of catecholamines on the kidney to cause hypertension.

Figure 69-15 shows the relationship between blood pressure and sodium excretion after chronic intravenous infusion of norepinephrine, which has a relatively weak antinatriuretic effect but a powerful peripheral vasoconstrictor action. The antinatriuretic effect of norepinephrine shifts the pressure natriuresis curve to higher blood pressures, thereby necessitating a small increase in blood pressure to maintain sodium balance. However, because norepinephrine has a weak antinatriuretic effect, compared to its potent peripheral vasoconstrictor effect, arterial pressure initially increases above the renal setpoint for regulation of sodium balance and causes transient natriuresis. The sodium loss is transient because extracellular fluid volume decreases and arterial pressure eventually stabilizes at a point where sodium intake and output are balanced.

Orthostatic hypotension is common among patients with pheochromocytoma and is related not only to the reduction of blood volume but perhaps also to desensitization of adrenergic receptors secondary to the chronic excess of catecholamines.

Although a high level of circulating catecholamine is the ultimate cause of hypertension in pheochromocytoma, blood pressure is often only modestly correlated with the level of plasma catecholamines. However, the periodic burst of catecholamine release may cause moderate to severe hypertension and lead to target-organ injury. Consequently, diagnosis and effective treatment of pheochromocytoma is essential.

Figure 69-15. Long-term effects of norepinephrine, a powerful vasoconstrictor that has a relatively weak effect to impair pressure natriuresis. The normal curve (*solid line*) is compared with the vasoconstrictor curve (*dashed line*). Initially the vasoconstrictor raises blood pressure (from *point A* to *point B*) above the renal set point for sodium balance. Increased arterial pressure, however, causes a transient natriuresis and decreases extracellular fluid volume until blood pressure eventually stabilizes at a level (*point C*) at which sodium intake and output are balanced at a reduced extracellular fluid volume. *Source: Redrawn from Hall JE. The kidney, hypertension, and obesity. Hypertension 2003;41:625-633.*

Preeclampsia

Preeclampsia in women is characterized by hypertension and proteinuria. Progression of the disease may lead to eclampsia in which seizures develop in association with a high risk for fetal and maternal mortality. Despite being a leading cause of maternal death and a major contributor of maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of preeclampsia have not yet been fully elucidated. Hypertension associated with preeclampsia develops during pregnancy and remits after delivery, implicating the placenta as a central culprit in the disease.

Although numerous factors including genetic, immunologic, behavioral, and environmental factors have been implicated in the pathogenesis of preeclampsia, reduced uteroplacental perfusion as a result of abnormal cytotrophoblast invasion of spiral arterioles appears to play a key role.[131] Placental ischemia is thought to lead to widespread activation/dysfunction of the maternal vascular endothelium, which results in enhanced formation of endothelin, thromboxane, and superoxide, increased vascular sensitivity to ANG II, and decreased formation of vasodilators such as nitric oxide and prostacyclin. These endothelial abnormalities, in turn, cause hypertension by impairing renal function and increasing total peripheral resistance.[131,132]

Inflammatory cytokines such as IL-6 and TNF-α are thought to be important links between placental ischemia and cardiovascular and renal dysfunction.[131] Supporting a potential role of cytokines are findings that plasma levels of TNF-α and IL-6 are elevated in women with preeclampsia. Important blood pressure regulatory systems such as the RAS, sympathetic nervous system, and endothelial factors interact with proinflammatory cytokines such as IL-6 and TNF-α to raise blood pressure. Proinflammatory cytokines also affect vascular function and endothelium-derived factors involved in blood pressure regulation. Thus, endothelial dysfunction associated with preeclampsia may be mediated, at least in part, by cytokines.

Recent studies indicate that chronic reductions in placental perfusion in pregnant animals are associated with enhanced production

[**Figure 69-15.** Long-term effects of norepinephrine, a powerful vasoconstrictor that has a relatively weak effect to impair pressure natriuresis. The normal curve (*solid line*) is compared with the vasoconstrictor curve (*dashed line*). Initially the vasoconstrictor raises blood pressure (from *point A* to *point B*) above the renal set point for sodium balance. Increased arterial pressure, however, causes a transient natriuresis and decreases extracellular fluid volume until blood pressure eventually stabilizes at a level (*point C*) at which sodium intake and output are balanced at a reduced extracellular fluid volume.]

of inflammatory cytokines, such as TNF-α and IL-6.[133-135] In addition, chronic infusion of either TNF-α or IL-6 into normal pregnant rats results in significant increases in blood pressure and a decrease in renal hemodynamics. TNF-α activates the endothelin system in placenta, renal, and vascular tissues, whereas IL-6 stimulates the renin-angiotensin system.[133-135] Collectively, these findings suggest that inflammatory cytokines play a role in causing hypertension in response to chronic reductions in uterine perfusion during pregnancy by activating multiple vasoactive pathways.

Although recent studies support a role for cytokines such TNF-α and IL-6 as potential mediators of endothelial dysfunction, identification of novel factors that link placental ischemia and maternal endothelial and vascular abnormalities in preeclampsia remains an important area of investigation. Recent studies in preeclamptic

women have demonstrated increased soluble fms-like tyrosine kinase-1 (sFlt-1), a naturally occurring antagonist of circulating vascular endothelial growth factor and placental growth factor.[136] Increased sFlt-1 during preeclampsia is associated with decreased free vascular endothelial growth factor and free placental growth factor in the blood. Moreover, sFlt-1 administration to pregnant rats decreases free vascular endothelial growth factor and free placental growth factor in the blood and produces hypertension and proteinuria.[137]

Another novel placenta-derived factor, soluble endoglin (sEng), was recently implicated in pathogenesis of preeclampsia.[138] sEng, a TGF-β coreceptor, is elevated in preeclamptic women and falls after delivery. sEng causes hypertension in vivo and its effects in pregnant rats are amplified by coadministration of sFlt-1, leading to severe preeclampsia including the hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. sEng is thought to impair binding of TGF-β_1 to its receptors and downstream signaling, including effects on activation of endothelial nitric oxide synthase and vasodilation. These findings suggest that sEng may act in concert with sFlt-1 to induce severe preeclampsia.

Unfortunately, effective treatments for preeclampsia remain elusive. In light of the recent developments in our understanding of the pathophysiology of preeclampsia, treatment strategies aimed at improving endothelial dysfunction, safely lowering blood pressure, and reducing maternal and perinatal morbidity should be further explored.

GENETIC CAUSES OF HYPERTENSION

Gene Variants and Human Primary Hypertension

With the development of superb tools for genetic studies and sequencing of the human genome, there has been great enthusiasm for the possibility that genetic causes of primary hypertension can be identified. Proponents of the genetic basis for primary hypertension have implied that the recent advances in genetics will offer unparalleled insights into the pathophysiology of hypertension and the development of more effective individualized treatments for hypertension. However, despite the expenditure of great financial resources and effort, there have been no clear successes in identifying genes that cause human primary hypertension. The success that has been achieved thus far has been limited to identification of monogenic forms of hypertension. A detailed discussion of this topic is beyond the scope of the chapter but Luft has discussed some reasons why the "geneticism of hypertension" approach has had limited success.[139]

When one considers the complexity of the multiple neural, hormonal, renal, and vascular mechanisms that contribute to short-term and long-term blood pressure regulation, it is perhaps unsurprising that finding a few variant genes (alleles) to account for a substantial portion of blood pressure variation has been difficult. The complexity of the problem is further amplified by the fact that genetic variation of blood pressure is unlikely caused by only single-gene variations, but also by polymorphic genetic differences, complex interactions among several genes, and interaction among genetic and environmental factors. The observation that increases in blood pressure do not occur with significant frequency in multiple populations living in nonindustrialized regions of the world suggests that environmental influences play a major role in the development of common forms of hypertension.

What is the evidence that gene variants play a major role in human primary hypertension? Multiple studies provide evidence that the closer the genetic relatedness, the greater the similarity of blood pressure.[140-143] For monozygotic twins (with genetic similarity of 100 percent), the correlation coefficient for systolic blood pressure has ranged from 0.5 to 0.8 (average: 0.6), for dizygotic twins it has ranged from 0.19 to 0.46 (average: 0.35), and for nontwin siblings (genetic similarity of around 50 percent) the correlation coefficient has averaged around 0.23. There is also a better correlation of blood pressure values in biologic children than in adopted children. However, the importance of shared family environment is also evident from the blood pressure correlations observed in genetically unrelated adopted siblings.

Comprehensive familial analyses that include other relatives in addition to twins suggest that environment may contribute to as much as 30 percent of blood pressure variance, and genetic factors may contribute 40 to 50 percent of blood pressure variance.[140-143] However, despite the use of sophisticated mathematical models for these calculations, the possibility of nonlinear gene-environmental interactions makes it difficult to quantify the precise roles of genes and environment in blood pressure variation.

Hypertension
has been suggested to result from the additive effects of multiple variant genes acting in concert to elevate blood pressure. Each gene variant is presumed to have a relatively weak impact on blood pressure but may produce significant hypertension when they act together in the presence of the necessary environmental conditions. This *polygenic*
model also applies to other complex diseases (such as diabetes or cancer) where multiple genes and environmental factors may play a role in the development of the

model also applies to other complex diseases (such as diabetes or cancer) where multiple genes and environmental factors may play a role in the development of the disease.

Although the hypertension research literature is replete with studies showing associations of gene polymorphisms and blood pressure, the genetic alterations that contribute to primary hypertension remain unknown.[143,144] Most of these genetic studies have produced mixed results, even for widely studied polymorphisms such as the ACE insertion/deletion and angiotensinogen polymorphisms.[143,144] Polymorphisms and mutations in other genes such as α-adducin, atrial natriuretic factor, the insulin receptor, β_2-adrenergic receptor, calcitonin gene-related peptide, angiotensinase C, renin-binding protein, endothelin-1 precursor, G-protein β_3-subunit have also been associated with the development of hypertension in some studies;[139,143-145] however, all of these polymorphisms show weak associations, if any, with blood pressure, and many of the early studies showing statistically significant associations have not been confirmed. At best, the gene variations discovered thus far explain only a small part of the blood pressure variation found in humans.

Monogenic Disorders that Cause Hypertension

At least 10 monogenic disorders have been identified that have either high blood pressure or low blood pressure as part of the phenotype.[146,147] Table 69-4 shows some of the monogenic disorders that are associated with high blood pressure. An interesting feature of these genetic disorders is that most of them affect either electrolyte transport in the renal tubule or the synthesis and/or activity of mineralocorticoid hormones. In all monogenic hypertensive disorders thus far, the final common pathway to hypertension appears to be increased sodium reabsorption and volume expansion. Monogenic hypertension, however, is rare and all of the known forms together account for less than 1 percent of human hypertension.

Familial Hyperaldosteronism Type I

Also called *glucocorticoid remediable aldosteronism*, familial hyperaldosteronism type I (FH-I) is inherited as an autosomal dominant trait caused by a chimeric gene derived from a meiotic mismatch and unequal crossing between the promoter of the 11β-hydroxylase (*CYP11B1*) controlled by the structural portion of the aldosterone synthase gene (*CYP11B2*).[148] This causes aldosterone secretion to be regulated by ACTH. Because ACTH is suppressed by glucocorticoids, administration of excess glucocorticoids is effective in reducing aldosterone secretion in patients with FH-I.

Patients with FH-I exhibit many of the same characteristics as those with primary aldosteronism, including high aldosterone, hypokalemia, volume expansion, metabolic alkalosis, and low plasma renin. Although some patients with FH-I have severe hypertension, others have only moderate hypertension or may even be normotensive.[149]
The reasons for this wide range of blood pressure in patients are unclear but could be related to variable expression of the chimeric gene or to other differences in genetic background that would place their inherited blood pressure in the low or normal range in the absence of the FH-I mutation. The final blood pressure could therefore be the combined result of the low or normal inherited blood pressure, the hypertensive effect of the FH-I mutation, and other environmental factors, such as salt intake. When sodium intake is high, even moderate increases in aldosterone raise blood pressure, whereas low sodium intake markedly attenuates the hypertensive

[**TABLE 69-4. Known Genetic Causes of Hypertension**]

effects of excess aldosterone secretion. Patients with FH-I respond well to both thiazide diuretics and spironolactone.

Familial Hyperaldosteronism Type II

Familial hyperaldosteronism type II (FH-II) is a rare cause of hypertension in which the hypertension is caused by excessive secretion of aldosterone that is not suppressed by glucocorticoid administration, distinguishing it from FH-I.[150,151] Patients with FH-II have the same clinical symptoms as patients with primary hyperaldosteronism caused by bilateral adrenal hyperplasia. The genetic abnormality causing FH-II has been localized to chromosome 7p22.[151] Although hypertension in FH-II is unresponsive to glucocorticoids, spironolactone is effective in reducing blood pressure and correcting the metabolic disturbances.

Congenital Adrenal Hyperplasia

This disorder describes a group of syndromes caused by defects in cortisol biosynthesis.[152] Congenital adrenal hyperplasia is an autosomal recessive disorder. When 21-hydroxylase (*CYP21A2*) is deficient, the most common cause of congenital adrenal hyperplasia, patients are normotensive.[150,152] When 11ß-hydroxylase

21-hydroxylase (*CYP21A2*) is deficient, the most common cause of congenital adrenal hyperplasia, patients are normotensive.[151,152] When 11β-hydroxylase (*CYP11B1*) and 17α-hydroxylase (*CYP17*) are deficient, production of deoxycorticosterone, which has mineralocorticoid activity, is increased, leading to hypertension. Defects in *CYP11B1* and *CYP17* cause inhibition of cortisol production with a subsequent reduction in feedback inhibition of ACTH secretion by the anterior pituitary and hypothalamus. Increased ACTH secretion then stimulates production of steroid precursors proximal to the blocked step, leading to excessive levels of deoxycorticosterone.

Both forms of congenital adrenal hyperplasia are associated with early onset hypertension and hypokalemia. Signs of androgen excess distinguish the two disorders: 11β-hydroxylase deficiency causes virilization in girls and precocious puberty in boys, whereas 17α-hydroxylase deficiency causes sex hormone deficiency, primary amenorrhea, and delayed sexual development in girls, and ambiguous genitalia in boys. Genetic diagnosis of both conditions relies on testing for mutations that either severely depress or abolish enzyme activity. Both conditions can be effectively treated by administering glucocorticoids that normalize ACTH secretion and ACTH-mediated buildup of cortisol precursors proximal to the enzymatic deficiency, including deoxycorticosterone.

Liddle's Syndrome

This is an autosomal dominant form of monogenic hypertension that results from mutations in the amiloride-sensitive ENaC. Several mutations that result in the elimination of 45 to 75 amino acids from the cytoplasmic carboxyl terminus of β- or γ-subunits of the channel have been reported. Mutations that increase ENaC activity, in turn, cause excessive distal and collecting tubule sodium reabsorption and hypertension.[150,153]

Liddle's syndrome is characterized by the early onset of hypertension with hypokalemia and suppression of plasma renin activity and aldosterone. The suppression of aldosterone and lack of responsiveness to MR antagonists differentiates this syndrome from primary aldosteronism. Both the hypertension and the hypokalemia vary in severity, depending on salt intake, and can be treated with amiloride or triamterene, specific inhibitors of the ENaC.

Apparent Mineralocorticoid Excess

Apparent mineralocorticoid excess is an autosomal recessive form of monogenic hypertension that results from a mutation in the renal-specific isoform of the 11β-hydroxysteroid dehydrogenase gene.[154] This enzyme normally converts cortisol to the inactive metabolite cortisone and "protects" the MR from being activated by cortisol. This is important because the renal epithelial MR receptor in the distal and collecting tubules has a similar affinity for aldosterone and cortisol, while cortisol concentrations are normally much higher than aldosterone. Deficiency of 11β-hydroxysteroid dehydrogenase allows the tubular MR to be occupied and activated by cortisol, causing sodium retention and volume expansion, low renin, low aldosterone, and a form of hypertension that is salt sensitive.

A nongenetic form of the apparent mineralocorticoid excess syndrome can be observed in persons ingesting large amounts of licorice, which contains glycyrrhetinic acid, an inhibitor of the enzyme 11β-hydroxysteroid dehydrogenase. Both forms of apparent mineralocorticoid excess are effectively treated with MR antagonists such as spironolactone or eplerenone.

Pseudohypoaldosteronism Type II

Also called *Gordon's syndrome*, pseudohypoaldosteronism type II is a rare mendelian form of hypertension that is salt sensitive and is associated with hyperkalemia (despite normal glomerular filtration rate), hyperchloremia, metabolic acidosis, and suppressed plasma renin and aldosterone levels. The disorder is caused by mutations in two genes encoding the serine/threonine protein kinases: WNK1 and WNK4.[155]

The phenotypes of excessive salt retention and hypertension are caused by loss of normal inhibition or to constitutive activation of the renal tubular NaCl cotransporter by mutant WNK1 or WNK4 genes; thiazide diuretics, which inhibit distal nephron NaCl reabsorption, are especially effective in reducing blood pressure in patients with pseudohypoaldosteronism type II. The mutant WNKs may also have a direct effect on ROMK1, the major potassium secretory channel in the distal nephron, as hyperkalemia is another major feature of pseudohypoaldosteronism type II.[150,155] The fact that hyperkalemia is invariably present in pseudohypoaldosteronism type II is often used to distinguish it from other monogenic forms of hypertension.

Mineralocorticoid Receptor Activating Mutation

This monogenic disorder is caused by a substitution of leucine for serine at codon 810 of the MR.[156] This mutation alters the shape and the specificity of the MR and eliminates the usual requirement for the 21-hydroxyl group of aldosterone to interact with the MR. This explains why other steroids, such as progesterone, activate the MR and why spironolactone, which is normally an antagonist of the MR, acts as an agonist for the MR in this disorder. Thus treatment of these patients with spironolactone or increased levels of progesterone, as occurs in pregnancy, worsens the sodium retention, hypokalemia, and hypertension.

spironolactone or increased levels of progesterone, as occurs in pregnancy, worsens the sodium retention, hypokalemia, and hypertension.

PATHOPHYSIOLOGY OF PRIMARY (ESSENTIAL) HYPERTENSION

Introduction

Widespread human primary (essential) hypertension appears to be a relatively modern disorder associated with industrialization and the ready availability of food. Nearly all studies of westernized, industrialized populations have demonstrated that blood pressure, and therefore the prevalence of hypertension, rises with age.[157] Hunter-gatherers living in nonindustrialized societies, however, rarely develop hypertension or progressive increases in systolic and mean pressures that occur in the majority of individuals living in industrialized societies.[157-159] This observation suggests that environmental factors play a major role in raising blood pressure in many patients with primary hypertension. This does not, however, imply that genetic factors are unimportant in primary hypertension. Genetic variation almost certainly is responsible for differences in baseline blood pressure that result in normal distribution of blood pressure in a population. When hypertension-producing environmental factors are added to the population baseline blood pressure, the normal distribution is shifted toward higher blood pressure. Moreover, variations in the impact of environmental factors flatten the blood pressure curve and cause even greater variability in the overall population blood pressure.

What are the elements of industrialized societies that cause blood pressure to rise in the majority of people as they age? How do they affect the physiologic controllers of blood pressure? As discussed earlier, many of the long-term blood pressure controllers either directly or indirectly influence renal function. In all patients with primary hypertension there is a resetting of renal pressure natriuresis so that sodium balance is maintained at higher blood pressures.[16,18] In some individuals, this resetting is related to increased renal tubular reabsorption, because of abnormalities intrinsic to the kidneys or to altered neurohumoral control of the kidneys.[16,19]
In other instances, resetting of pressure natriuresis is associated with renal vasoconstriction and reductions in GFR, as a result of intrarenal mechanisms or of nervous and hormonal mechanisms acting on the kidneys.[16,19] After hypertension is established, many of these changes in kidney function are difficult to detect because increased blood pressure often returns renal function to normal.

Experimental, clinical, and population studies suggest some of the key environmental factors that affect blood pressure include excess weight gain, excess sodium intake, and excess alcohol intake.

Obesity is a Major Cause of Primary Hypertension

The prevalence of obesity has risen dramatically in the past two to three decades and has rapidly become the most important public health problem in most industrialized countries. Current estimates indicate that more than 1 *billion* people in the world are overweight or obese.[160,161] In the United States, more than 64 percent of adults are overweight and almost one-third of the adult population is obese with a BMI greater than 30.[162] Population studies show that excess weight gain is perhaps the best predictor we have for the development of hypertension, and the relationship between BMI and systolic and diastolic blood pressure appears to be nearly linear in diverse populations throughout the world.[163] Risk estimates from the Framingham Heart Study, for example, suggest that approximately 78 percent of primary hypertension in men and 65 percent in women can be ascribed to excess weight gain.[164] Clinical studies also indicate that weight loss is effective in reducing blood pressure in most hypertensive subjects and have also shown the effectiveness of weight loss in primary prevention of hypertension.[165,166]

One question often raised is why some overweight or obese persons are not hypertensive by the usual standards (i.e., blood pressure greater than 140/90 mmHg) if obesity is a major cause of hypertension. Perhaps this is not surprising if one considers that blood pressure is normally distributed, and accepts the assumption that excess weight gain shifts the frequency distribution of blood pressure toward higher levels. Although obesity increases the probability that a person's blood pressure will register in the hypertensive range, not all obese people will have a blood pressure greater than 140/90 mmHg (Fig. 69-16). However, even those obese individuals who are classified as "normotensive" have higher blood pressure than they would at a lower body weight. This assumption is supported by the fact that weight loss lowers blood pressure in normotensive as well as hypertensive obese subjects.[167]

Although the importance of obesity as a cause of primary hypertension is well established, the physiologic mechanisms by which excess weight gain alters renal function and raises blood pressure are only beginning to be elucidated. Table 69-5 summarizes some of the changes in hemodynamics, neurohumoral systems, and renal function that occur with excess weight gain in humans and experimental animals.

Effect on Tissue Blood Flow and Cardiac Output

Obesity is associated with expansion of extracellular fluid volume, as well as increased tissue blood flow and cardiac output.[168-171] Studies in experimental animals and in humans indicate that blood flow is increased in many tissues, including the heart, kidneys, gastrointestinal tract, and skeletal muscles.[168-171] Some of the increased flow is caused by tissue growth in organs in response to increased workload and the metabolic demands associated with obesity. However, obesity also causes a functional vasodilation,

[**Figure 69-16.**
Effect of weight gain to shift the frequency distribution of blood pressure to higher levels. Not all obese subjects have blood pressures in the hypertensive range (>140/90 mmHg), but excess weight gain raises blood pressure above the baseline level for an individual.]

perhaps as a consequence of an increased metabolic rate, higher oxygen consumption, and accumulation of vasodilator metabolites. Despite higher resting blood flows in many tissues, there also appears to be reduced blood flow "reserve" during exercise or during reactive hyperemia in obese, compared to lean, individuals.[15,171] There is also a decreased cardiac reserve in obesity despite higher resting cardiac outputs.

Mechanisms of Impaired Renal Pressure Natriuresis in Obesity Hypertension

Increased renal tubular sodium reabsorption appears to play a major role in initiating the rise in blood pressure associated with excess weight gain and obese individuals require higher-than-normal blood pressures to maintain sodium balance, indicating impaired renal pressure natriuresis. Three mechanisms appear to be especially important in mediating increased sodium reabsorption and impaired pressure natriuresis in obesity hypertension: (1) increased SNS activity, (2) activation of the RAS, and (3) physical compression of the kidneys by fat accumulation within and around the kidneys and by increased abdominal pressure (Fig. 69-17).

SNS Activation in Obesity Hypertension

Several observations indicate that increased SNS activity contributes to obesity hypertension[16,44]: (1) SNS activation, especially renal sympathetic activity, is increased in obese subjects; (2) pharmacologic blockade of adrenergic activity lowers blood pressure to a greater extent in obese, compared to lean, individuals; and (3) renal denervation markedly attenuates sodium retention and hypertension associated with a high-fat diet in experimental animals.

Increased SNS activity appears to be highly differentiated in obesity. For example, cardiac sympathetic activity does not appear to be substantially elevated, whereas SNS activity is usually increased in the kidneys and skeletal muscles of obese subjects.[172-174] Genetic factors may be important in modulating the SNS response to excess weight gain. In Pima Indians who have a high prevalence of obesity but a relatively low prevalence of hypertension, muscle SNS activity is lower than in whites and does not track well with adiposity.[175] In black men, SNS activity is higher and hypertension is more prevalent than in white men despite comparable levels of obesity.[176] In young, overweight, black women, adiposity is associated with sympathetic hyperactivity.[176] Factors such as differences in fat mass distribution may contribute to some of the racial variation in SNS responses to increasing adiposity. For reasons that are still unclear, abdominal obesity elicits a much greater sympathetic activation than does subcutaneous or lower body obesity.[177]

The mechanisms of SNS activation in obesity have not been fully elucidated, but as discussed earlier, one of the more promising candidates is hyperleptinemia (Fig. 69-18). Leptin is released from adipocytes and acts on the hypothalamus and other regions of the brain, such as the brainstem to reduce appetite and increase SNS activity.[44]
In rodents, increasing plasma leptin concentration to levels comparable to those found in severe obesity not only increases SNS activity, but also raises blood pressure.[178,179] Moreover, the hypertensive effects of leptin are enhanced when NO synthesis is inhibited,[180] as often occurs in obese subjects with endothelial dysfunction.

Another observation that points toward leptin as a potential link between obesity and hypertension is the finding that leptin-deficient, obese mice and obese mice with mutations of the leptin receptor usually have little or no increase in blood pressure compared to their lean controls.[181] Similar results have been found in obese children with leptin gene mutations. Ozata and coworkers[182] reported that in young patients with homozygous missense mutations of the leptin gene there was no indication of hypertension despite early onset morbid obesity. These children also had decreased, rather than increased SNS activity, as well as postural hypotension and attenuated RAS responses to upright posture. Moreover, children with leptin gene mutations did not have hypertension despite having many other characteristics of the metabolic syndrome, including severe insulin resistance, hyperinsulinemia, and hyperlipidemia.[182] These observations are consistent with those observed in

rodents and suggest that the functional effects of leptin appear to be important in linking obesity with SNS activation and hypertension.

Leptin's stimulatory effect on SNS activity appears to be mediated with interaction with other hypothalamic factors, especially the proopiomelanocortin pathway. Antagonism of the melanocortin 3/4 receptor (MC3/4-R) completely abolished leptin's chronic blood pressure effects.[183] The chronic hypertensive effects of leptin

[**TABLE 69-5. Hemodynamic, Neurohumoral, and Renal Changes in Experimental Obesity Caused by a High-Fat Diet and in Human Obesity**]

[**Figure 69-17.**
Summary of potential mechanisms by which obesity causes hypertension and renal injury. Visceral obesity increases blood pressure by activation of the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), and by physical compression of the kidneys from the fat surrounding the kidneys. SNS activation may be caused by, in large part, the effects of leptin, which acts on proopiomelanocortin (POMC) neurons in the hypothalamus and brainstem. Obesity-induced hypertension and glomerular hyperfiltration may cause renal injury, especially when combined with dyslipidemia and hyperglycemia. Renal injury then exacerbates the hypertension and makes it more difficult to control.]

were also completely abolished in MC4-R knockout mice, suggesting that the MC4-R may mediate most of the effects of leptin to activate SNS activity.[184] However, the importance of the proopiomelanocortin pathway in regulating SNS activity and raising blood pressure in humans has not been elucidated.

Renin-Angiotensin-Aldosterone System Activation in Obesity

Obese individuals, especially those with visceral obesity, often have mild to moderate increases in plasma renin activity, angiotensinogen, ACE activity, ANG II, and aldosterone levels.[185,186] Activation of the RAS in obese subject occurs despite sodium retention, volume expansion, and hypertension, all of which would normally tend to suppress renin secretion and ANG II formation.

An important role for ANG II in stimulating renal sodium reabsorption and in mediating obesity hypertension is supported by studies in experimental animals demonstrating that ANG II receptor blockade or ACE inhibition blunts sodium retention, volume expansion, and increased blood pressure during the development of obesity.[187,188]
Unfortunately, there have been no large-scale clinical studies comparing the effectiveness of RAS blockers in obese and lean hypertensive patients, although smaller clinical trials have shown that both ARBs and ACE inhibitors are effective in lowering blood pressure in obese hypertensive patients.[189,190]

Increased aldosterone and MR activation also appear to contribute to obesity-induced hypertension. Antagonism of MR in obese dogs markedly attenuated sodium retention, hypertension, and glomerular hyperfiltration.[191] Moreover, this protection against hypertension occurred in spite of marked increases in plasma renin activity, suggesting that combined blockade of MR and ANG II might be especially effective in treating obesity hypertension. The observation that MR antagonism attenuated glomerular hyperfiltration may also have important implications for renal protection in obesity, although there are no studies, to our knowledge, that have directly tested this in obese humans. Administration of the MR antagonists does appear to provide significant antihypertensive benefit in resistant obese patients.[192] The reductions in blood pressure caused by MR antagonism in resistant obese patients occurred despite concurrent therapy with ACE inhibitor or ARB, calcium channel blocker, and thiazide diuretic, suggesting that MR activation in obesity can occur independently of ANG II-mediated stimulation of aldosterone secretion.

Renal Compression Caused by Visceral Obesity

Visceral obesity initiates several changes that may lead to compression of the kidneys, increased intrarenal pressures, impaired renal pressure natriuresis, and hypertension.[15] For example, intraabdominal

[**Figure 69-18.**
Possible links among leptin and its effects on the hypothalamus, sympathetic activation, and hypertension. Within the hypothalamus, one of the key pathways of leptin's action on appetite, SNS activity, and blood pressure is stimulation of the proopiomelanocortin (POMC) neurons in the arcuate nucleus. These neurons send projections to the paraventricular nucleus and lateral hypothalamus, releasing α-melanocyte-stimulating hormone (α-MSH), which then acts as an agonist for melanocortin 3/4-receptors (MC3/4-R). These neurons then send projections to the nucleus of the solitary tract to effect changes in appetite, SNS activity, and blood pressure. Leptin also suppresses the NPY/AGRP neurons, but their role in controlling SNS activity and blood pressure are still unclear.]

pressure rises in proportion to the abdominal diameter, reaching levels as high as 35 to 40 mmHg in some individuals.[193] In addition, retroperitoneal adipose tissue

often encapsulates the kidney and penetrates the renal hilum into the renal medullary sinuses, causing additional compression and increased intrarenal pressures.[194]

Obesity also causes changes in renal medullary histology and increased extracellular matrix that could exacerbate intrarenal compression and hypertension.[195] The increased intrarenal hydrostatic pressure may, in turn, cause compression of the loops of Henle and vasa recta, thereby increasing tubular sodium and water reabsorption. Although these physical changes in the kidneys cannot account for the initial increase in blood pressure that occurs with rapid weight gain, they may help to explain why abdominal obesity is much more closely associated with hypertension than subcutaneous obesity.[194,195]

Glomerular Injury and Nephron Loss in Obesity Hypertension

Obese patients often develop proteinuria, frequently in the nephrotic range that is followed by progressive loss of kidney function in a significant number of patients.[196] The most common types of renal lesions observed in renal biopsies are of obese subjects are focal and segmental glomerular sclerosis and glomerulomegaly.[197]

Animals placed on a high-fat diet for only a few weeks demonstrate significant structural changes in the kidneys, including enlargement of the Bowman space, glomerular cell proliferation, increased mesangial matrix, and increased expression of glomerular TGF-β.[198] These early changes occur with only modest hypertension, no evidence of diabetes, and only mild metabolic abnormalities that may be the precursors of more severe renal injury as obesity is sustained.

Population studies indicate that obesity is a major cause of renal disease even after adjustment for hypertension, diabetes, or preexisting renal disease.[199] Moreover, obesity also amplifies the effect of other primary renal insults, even those that are usually considered to be relatively benign, such as unilateral nephrectomy. Praga and coworkers[200]
reported that of patients with a BMI greater than 30 who had undergone unilateral nephrectomy, 92 percent developed proteinuria or renal insufficiency, whereas only 12 percent of patients with a BMI less than 30 developed these disorders. Similar findings have also been reported for patients with immunoglobulin A nephropathy.[201]
These observations indicate that obesity greatly exacerbates the loss of kidney function in patients with preexisting glomerulopathies and that weight loss may lessen the impact of renal injury from other causes.

The gradual loss of kidney function, as well as the hypertension and diabetes that commonly coexist with obesity, lead to progressive impairment of pressure natriuresis, increasing salt sensitivity, and greater increases in blood pressure (Fig. 69-19). Thus renal injury in obese subjects not only makes the hypertension more severe, but also more difficult to control with antihypertensive drugs.

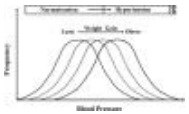

Figure 69-16. Effect of weight gain to shift the frequency distribution of blood pressure to higher levels. Not all obese subjects have blood pressures in the hypertensive range (>140/90 mmHg), but excess weight gain raises blood pressure above the baseline level for an individual.

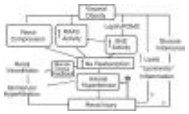

Figure 69-17. Summary of potential mechanisms by which obesity causes hypertension and renal injury. Visceral obesity increases blood pressure by activation of the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), and by physical compression of the kidneys from the fat surrounding the kidneys. SNS activation may be caused by, in large part, the effects of leptin, which acts on proopiomelanocortin (POMC) neurons in the hypothalamus and brainstem. Obesity-induced hypertension and glomerular hyperfiltration may cause renal injury, especially when combined with dyslipidemia and hyperglycemia. Renal injury then exacerbates the hypertension and makes it more difficult to control.

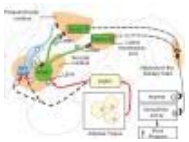

Figure 69-18. Possible links among leptin and its effects on the hypothalamus, sympathetic activation, and hypertension. Within the hypothalamus, one of the key pathways of leptin's action on appetite, SNS activity, and blood pressure is stimulation of the proopiomelanocortin (POMC) neurons in the arcuate nucleus. These neurons send projections to the paraventricular nucleus and lateral hypothalamus, releasing α-melanocyte-stimulating hormone (α-MSH), which then acts as an agonist for melanocortin 3/4-receptors (MC3/4-R). These neurons then send projections to the nucleus of the solitary tract

to effect changes in appetite, SNS activity, and blood pressure. Leptin also suppresses the NPY/AGRP neurons, but their role in controlling SNS activity and blood pressure are still unclear.

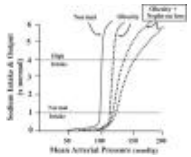

Figure 69-19. Effect of obesity to shift renal pressure natriuresis curve to higher arterial pressure. With chronic obesity lasting for many years, there may be a gradual loss of nephron function, further impairment of pressure natriuresis, increasing salt sensitivity, and higher arterial pressures.

What is the Role of Metabolic Syndrome / Insulin Resistance in Primary Hypertension?

In 1988, Gerald Reaven hypothesized that insulin resistance and compensatory hyperinsulinemia are the underlying causes of hypertension, hyperlipidemia, and diabetes, and thus are major causes of CVD.[202] He coined the term *syndrome X* to describe this cluster of CVD risk factors. Subsequently, many other investigators observed that dyslipidemia, hyperinsulinemia, and hyperglycemia often occurred concurrently with hypertension, leading to the proposal of a unique pathophysiologic condition that is now called the *metabolic syndrome*. Definitions of the metabolic syndrome have been proposed by the World Health Organization (WHO),[203] the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (ATP III),[204] and other organizations.[205] All of these definitions include disordered glucose homeostasis or measures of insulin resistance, dyslipidemia, hypertension and obesity, as discussed in more detail in Chap. 91.

[**Figure 69-19.**
Effect of obesity to shift renal pressure natriuresis curve to higher arterial pressure. With chronic obesity lasting for many years, there may be a gradual loss of nephron function, further impairment of pressure natriuresis, increasing salt sensitivity, and higher arterial pressures.]

Questions have been asked about whether the diagnosis of metabolic syndrome has much clinical usefulness. Some researchers suggest that a defect in insulin action is the main cause of all the CVD risk factors that constitute the different versions of the metabolic syndrome.[206] Broadly defined, insulin resistance refers to a subnormal tissue response to a given concentration of insulin or an impairment of insulin's action of overall glucose homeostasis. However, the term *insulin resistance*
can have several different meanings, depending on the methods of assessment and the type of abnormalities that cause impaired insulin action. For example, when insulin resistance is defined by fasting hyperinsulinemia, the most likely cause is impaired insulin-mediated suppression of hepatic glucose output.[207] However, when insulin resistance is defined by methods that assess the ability of insulin to increase glucose disposal (e.g., glucose tolerance test, euglycemic clamp), the most likely cause is decreased action of insulin on skeletal muscle glucose uptake.[207] Presently, it is not clear which of these measures of insulin resistance (if any) best predicts risk for CVD.

Recent analyses of the metabolic syndrome have questioned whether insulin resistance and hyperinsulinemia are, in fact, the underlying causes of this complex cluster of cardiovascular risk factors.[208] As discussed below, most of the available evidence indicates that insulin resistance and hyperinsulinemia, although clearly important features of the metabolic syndrome, are not directly involved in mediating hypertension.

Does Hyperinsulinemia Cause Hypertension in Humans?

Hyperinsulinemia, which occurs as a compensation for insulin resistance, is postulated to mediate increased blood pressure in essential hypertension via multiple mechanisms, such as stimulation of SNS activity and renal tubular sodium reabsorption.[202,209] Evidence supporting this hypothesis comes mainly from epidemiologic studies showing correlations between insulin resistance, hyperinsulinemia, and blood pressure, and from short-term studies indicating that insulin has renal and sympathetic effects that, if sustained, could theoretically raise blood pressure. For example, acute infusions of insulin cause modest sodium retention and increased SNS activity, and these observations have been extrapolated to infer that hyperinsulinemia may be an important cause of hypertension in insulin-resistant states such as obesity.[202,209]
However, insulin also has vasodilator effects that tend to lower blood pressure and, as discussed earlier, results of short-term studies cannot be extrapolated to form an understanding of chronic hypertension.[210]

Chronic hyperinsulinemia, in the absence of obesity, does not raise blood pressure in either dogs or humans (see references 210 and 211 for reviews). For example

Chronic hyperinsulinemia, in the absence of obesity, does not raise blood pressure in either dogs or humans (see references 210 and 211 for reviews). For example, infusion of insulin for several weeks at rates that raised plasma insulin concentration above those found in obesity reduced, rather than increased, blood pressure as a consequence of the peripheral vasodilator effects of insulin.[212] Moreover, chronic insulin infusions did not raise blood pressure even when there was preexisting impairment of renal function caused by a 70 percent reduction of kidney mass.[212] Hyperinsulinemia also did not enhance the hypertensive effects of other pressor substances such as norepinephrine or ANG II.[210,212] Chronic hyperinsulinemia also did not raise blood pressure in insulin-resistant obese dogs that were resistant to the vasodilator effects of insulin.[213] Multiple studies in humans also have shown that chronic treatment with insulin injections does not raise blood pressure and patients with severe hyperinsulinemia as a result of insulinoma are not hypertensive.[211,214,215] These observations suggest that hyperinsulinemia per se is insufficient to cause chronic hypertension.

Does Insulin Resistance Cause Hypertension Independent of Hyperinsulinemia?

Insulin resistance has also been suggested to cause hypertension by raising total peripheral vascular resistance through mechanisms that are independent of hyperinsulinemia. One interesting hypothesis is that insulin's vasodilator action normally helps to prevent hypertension initiated by other stimuli and that decreased vascular sensitivity to insulin contributes to increased blood pressure in insulin-resistant individuals.[216]

It seems unlikely, however, that decreased action of a hormone that is primarily responsible for glucose regulation and that remains in relatively low concentrations except after meals would be capable of disrupting the multiple mechanisms that operate to maintain normal blood pressure. Moreover, there are several disorders associated with severe insulin resistance in humans and experimental animal models that are not associated with hypertension. For example, experimental models of obesity caused by mutations of the leptin gene or the leptin receptor, or by mutations of the MC4-R, have severe insulin resistance and many of the characteristics of the metabolic syndrome, but do not have increased blood pressure compared to wild-type controls.[181,184] Likewise, humans with leptin gene mutations have severe insulin resistance but no indication of SNS activation or hypertension.[182] These observations argue against a direct role for insulin resistance in causing hypertension.

Several reports indicate that antihyperglycemic agents that increase insulin sensitivity, such as the thiazolidinediones, also lower blood pressure. However, these drugs also influence the expression of multiple genes by binding to the peroxisome proliferator-activated receptor-γ (PPARγ) a nuclear receptor. Thiazolidinediones may also inhibit L-type calcium channels, and they reduce blood pressure in renovascular hypertension that is not associated with insulin resistance or hyperinsulinemia.[217-219] Therefore, it appears that the blood pressure-lowering effects of these drugs are not directly related to improvement of insulin sensitivity but to other actions.

Although a direct causal relationship between insulin resistance and hypertension has not been established, abnormalities of glucose and lipid metabolism associated with insulin resistance may, over a period of many years, lead to vascular and renal injury, and in this way contribute indirectly to increased blood pressure. For example, insulin normally decreases mobilization of fatty acids and promotes fat storage via multiple mechanisms, including inhibition of hormone-sensitive lipase, which decreases lipolysis of triglycerides and prevents release of fatty acids from adipocytes into the circulation. When adipocytes are resistant to insulin's actions, hormone-sensitive lipase activity is reduced, thereby decreasing lipid storage and increasing plasma concentration of fatty acids. These changes, if prolonged, could contribute to atherosclerosis and increased blood pressure, especially if the renal blood vessels and glomeruli are damaged. Also, resistance to insulin's actions on glucose homeostasis would cause glucose intolerance and hyperglycemia, which, if sustained, could cause glycosylation of glomerular proteins, increased production of extracellular matrix, and loss of nephron function. Progressive loss of kidney function, as discussed previously, could contribute to the development of hypertension. Thus, the metabolic disturbances associated with severe insulin resistance could exacerbate hypertension by causing renal injury, although the importance of these effects, in the absence of diabetes, is still unclear.

Does Hypertension Cause Insulin Resistance?

It also has been suggested that insulin resistance is secondary to vascular changes that occur in hypertension.[220] According to this concept, insulin resistance may occur as a result of increased peripheral vascular resistance, decreased tissue blood flow, and vascular rarefaction, which decrease the delivery of insulin and glucose and therefore impair glucose uptake in tissues such as skeletal muscle.[220] This hypothesis is intuitively pleasing because hypertension is often associated with increased peripheral vascular resistance and vascular rarefaction is common in long-standing hypertension. It is likely that tissue blood flow and substrate delivery can be important determinants of glucose uptake under some acute conditions, such as during transients of glucose disposal after a carbohydrate meal or glucose tolerance test. However, it is important to keep in mind the chronic nature of hypertension and that increased blood pressure and insulin resistance are both found under long-term, steady state conditions, not simply when the system is acutely challenged.

For the hemodynamic hypothesis of insulin resistance to be valid, at least two conditions must be met: (1) there must be a sustained reduction in tissue blood flow,

or a failure of blood flow to increase appropriately at the sites at which insulin resistance occurs; and (2) reductions in tissue blood flow, to the levels observed in hypertension, must impair glucose uptake by the tissues. However, neither of these conditions occurs in most patients with essential hypertension. Although peripheral vascular resistance is elevated in hypertension, most tissues, including skeletal muscles, do not appear to be underperfused.[12,207] Also, multiple studies and mathematical models indicate that underperfusion of peripheral tissues cannot explain, quantitatively, chronic hyperinsulinemia observed under fasting conditions as long as the sensitivity of the liver to insulin is normal.[207] Also, mathematical models of glucose homeostasis suggest that mild tissue underperfusion, or the lack of vasodilation, does not account for impaired glucose homeostasis during hyperinsulinemic euglycemic clamp conditions.[207] Finally, most models of secondary hypertension, such as mineralocorticoid or renovascular hypertension, are characterized by increased peripheral vascular resistance and vascular rarefaction but are not associated with the development of insulin resistance (see references 207 and 211 for reviews). These observations indicate that hypertension per se is not a primary cause of insulin resistance.

Although insulin resistance and hypertension are often closely correlated, much of the available evidence suggests that this association is largely a consequence of the fact that obesity causes both insulin resistance and high blood pressure through parallel mechanisms. There is little doubt that obesity, especially visceral obesity, is a major cause of the entire cluster of CVD risk factors associated with the metabolic syndrome (Fig. 69-20).[205,207] Most patients with metabolic syndrome and insulin resistance are overweight or obese and the increasing prevalence of metabolic syndrome has closely paralleled the increasing prevalence of obesity. Importantly, all of the disorders associated with the metabolic syndrome can be reversed in most patients by weight loss.

Thus, although hypertension is a well-recognized component of the metabolic syndrome, there is little direct evidence that insulin resistance or hyperinsulinemia actually cause hypertension. Excess weight gain and visceral obesity appear to be the primary driving forces for all of the major disorders associated with the metabolic syndrome, including hypertension. Available evidence suggests that as much as 65 to 75 percent of primary (essential) hypertension may be attributed to excess weight gain.

Until effective antiobesity drugs are developed, the impact of obesity on hypertension and related cardiovascular, renal, and metabolic disorders is likely to become even more important in the future as the prevalence of obesity continues to increase. In the meantime, effective control of blood pressure is essential in treating patients with metabolic syndrome and preventing CVD. Weight reduction is an essential first step in the effective management of most patients with metabolic syndrome and hypertension, and more emphasis should be placed on lifestyle modifications that help patients to maintain a healthier weight and prevent CVD.

[**Figure 69-20.**
Cardiovascular, metabolic and renal disease associated with visceral obesity which appears to be a primary cause of all of cluster of CVD risk factors in the metabolic syndrome. CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAI, platelet activator inhibitor; PP, postprandial; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; TG, triglycerides.]

Figure 69-20. Cardiovascular, metabolic and renal disease associated with visceral obesity which appears to be a primary cause of all of cluster of CVD risk factors in the metabolic syndrome. CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PAI, platelet activator inhibitor; PP, postprandial; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system; TG, triglycerides.

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