Hypertension: Mechanisms and Diagnosis

31

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Introduction

Cardiovascular disease is by far the leading cause of death, in males and females, in industrialized nations. In the United States this year, about a million deaths will be due to diseases of the heart and circulation, more than twice the number for the next most frequent cause of death, cancer. The most common fatal cardiovascular diseases are coronary artery disease, congestive heart failure, and stroke; these, together with renovascular disease, all have hypertension as a major risk factor. High blood pressure (BP), affecting one in three (over 76 million) US adults, is therefore a highly lethal disease.

The relationship between BP and the relative risks of stroke and coronary heart disease is direct, continuous, and independent, and no evidence has been put forward of any "threshold" level of blood pressure below which humans are entirely safe [1].

In general, men are at greater risk for hypertension-related death than women, black persons than white, and older ones than younger ones. The age-adjusted prevalence of hypertension (both diagnosed and undiagnosed) in 2003–2006 was 75 % for older women [2]. With increasing age, the prevalence of isolated systolic hypertension with a normal diastolic blood pressure (DBP) increases considerably, and it is now generally accepted that in adults, systolic blood pressure (SBP) may be a more accurate predictor of cardiovascular risk than diastolic pressure.

An enormous amount of data—experimental, epidemiologic, and clinical—now indicates that reducing elevated BP is beneficial. The first definitive proof of this came from the Veterans Administration (VA) Cooperative Study begun in 1963, and it has been confirmed in a host of studies since, most of which utilized diuretics or β-blockers as antihypertensive agents. Since then, there have been numerous clinical trials of many different classes of antihypertensive drugs, which have shown huge reductions in cardiovascular morbidity and mortality.

In spite of the demonstrated benefits of BP reduction, physicians and other health care professionals who are responsible for identifying and treating patients with hypertension are not doing a great job. In 2006, the percentage of Americans who were aware that they had high BP was 78 and 68 % were on treatment. However, only 64 % of those treated had their hypertension controlled, equivalent to about 43 % of the total hypertensive population. So, of every 100 patients with hypertension, 78 are aware of the fact, 68 are receiving treatment, and only 43 are "controlled," with a BP < 140/90 mmHg [3]. About 13 % of those taking antihypertensive medication meet the criteria for resistant hypertension (BP > 140/90 mmHg, on three different antihypertensive drug classes or on ≥4 antihypertensive drug classes regardless of BP) [4]. Projections show that by 2030, an additional 27 million people could have hypertension, a 9.9 % increase in prevalence from 2010 [5].

Definitions and Classification

BP is a continuous variable in any population, with a distribution along a bell-shaped curve. The difference between "normotensive" and "hypertensive" BP values is, therefore, somewhat arbitrary, but since cardiovascular risk increases with BP, various operational definitions of hypertension have been developed.

The Seventh Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) defined hypertension as an SBP of 140 mmHg or greater or DBP of 90 mmHg or greater [6]. JNC 7 subdivided "hypertension" into two categories: stage 1 with a BP range of 140–159 mmHg (SBP) or 90–99 mmHg (DBP) and stage 2 with BP ≥160 mmHg (SBP) or ≥100 mmHg (DBP). The utility of

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such a classification is, first, to provide an appropriate basis for comparing patients in epidemiologic and clinical studies and, second, as an indicator of the urgency of starting therapy. For example, a patient with a BP of 142/92 mmHg (stage 1) need not be treated with antihypertensive therapy right away; repeat visits to the office or clinic should be arranged to confirm the hypertension and possibly to establish the antihypertensive efficacy of nonpharmacologic interventions (*see* Chap. 32). On the other hand, a patient with a BP of 220/118 mmHg (Stage 2) requires antihypertensive therapy without delay.

Those with a BP of 120–139 mmHg systolic and/or 80–89 mmHg diastolic are classified as "pre-hypertensive," now known to increase the risk of any cardiovascular event compared with a normal BP (<120/80 mmHg), especially if the BP is in the upper half of the pre-hypertensive range, 130–139/85–89 mmHg, and also especially if there is a high cardiovascular risk, indicated by the presence of diabetes, chronic kidney disease, coronary artery disease, coronary artery disease equivalents (stroke, carotid disease, aortic aneurysm, peripheral vascular disease), or by a Framingham Risk Score of >10 %.

Isolated systolic hypertension (ISH), the predominant form of hypertension in the elderly, is defined as an SBP of 140 mmHg or greater in the presence of a DBP of 90 mmHg or lower. The accuracy of diagnosis and staging of hypertension is markedly improved by using SBP rather than DBP as the dominant criterion.

Essential, primary, or idiopathic hypertension, defined as high BP due neither to secondary causes nor to a Mendelian (monogenetic) disorder, accounts for 90 % of all cases. The term "*primary hypertension*" is preferred since "essential hypertension" represents an archaic misunderstanding of pathophysiology, namely, that hypertension is "essential" to maintain blood flow through severely narrowed resistance vessels.

Secondary hypertension is high BP caused by an identifiable and potentially curable disorder. *Refractory or resistant hypertension* is defined as a BP of ≥140/90 mmHg despite three drugs of different classes at maximum approved doses, given at least 1 month to take effect. *Spurious hypertension (pseudohypertension)* is artifactually elevated BP obtained by indirect cuff measurement over a rigid, often calcified, brachial artery.

White coat hypertension describes patients whose BP is high (>140/90 mmHg) in an office or clinic setting, with a normal daytime ambulatory pressure (<135/85 mmHg). This is a condition with higher risk of morbid events than if the BP were normal, <120/80 mmHg. Antihypertensive medication in white coat hypertension patients may decrease clinic BP but produces little or no change in ambulatory BP; thus, drug treatment may not confer substantial benefit.

Masked hypertension is the mirror image of white coat hypertension. Here the clinic BP is normal, but ambulatory or home measurements are high and associated with high risk. Although the prevalence of masked hypertension is low, perhaps only 6 % of the normotensive population, the absolute number in the United States may approach 15–18 million.

The term *hypertensive crisis* encompasses both *hypertensive urgency and hypertensive emergency. Hypertensive urgency* is defined as DBP >120 mmHg in the absence of acute or rapidly worsening target-organ damage. *Hypertensive emergency* is defined as acute or rapidly worsening target-organ damage occurring in a hypertensive patient in association with elevated BP but irrespective of the specific BP level attained. *Malignant hypertension* is a hypertensive emergency associated with papilledema, while *accelerated hypertension* is a hypertensive emergency associated with retinal hemorrhages and exudates.

Measurement of Blood Pressure

In-office BP measurement. BP is usually measured [7] with a mercury sphygmomanometer, an aneroid manometer, or an electronic manometer, with a 12-by-26 cm cuff. The bladder of the cuff should encircle at least 80 % of the arm, so for patients with arms of greater than 30 cm circumference, pressure should be measured with a large cuff (13-by-36 cm). If an aneroid or electronic manometer is used, it should be calibrated against a mercury manometer at regular intervals. BPs should be measured with subjects both lying and standing, or sitting and standing, and repeated 5 min later when possible. The cuff should be placed over the brachial artery and the bell of the stethoscope over the artery distal to the cuff; the environment should be quiet and the patient relaxed. Serial measurements should be taken at the same time of day, preferably in the morning, before the patient has taken any antihypertensive medication (i.e., at the trough of the plasma concentration).

The cuff is pumped up to about 20 mmHg above the systolic level, which point is signaled by the disappearance of the radial pulse, and then the pressure lowered by about 2 mmHg per second. The SBP is the pressure at which the first faint, consistent, tapping sounds are heard (Korotkoff sounds, phase I). The DBP is the level at which the last regular blood pressure sound is heard and after which all sound disappears (Korotkoff sound, phase V). Below Korotkoff phase I, there is sometimes a period of silence referred to as the *auscultatory gap*; otherwise, there is a continuum of sound, including swishing beats (Korotkoff II), crisper and louder sounds (Korotkoff III), and muffling of the sound (Korotkoff IV). If the sounds continue down to zero, Korotkoff IV is recorded as the DBP.

Since BP can vary by as much as 10 mmHg between arms (and more in conditions such as coarctation of the aorta), it should be measured in both arms, at least at the initial visit. The higher pressure is recorded. All BPs should be read to the nearest 2 mmHg, not rounded off to the nearest 5 or 10 mmHg, as is done so often.

There are many sources of variability of the BP. These include poor technique, faulty equipment, a stressful setting or an anxious patient, and a patient who has been smoking or has had caffeine or alcohol. A common error is the failure to remove patients' garments with tight sleeves. The considerable interobserver variability in BP measurements can be minimized by meticulous attention to correct technique.

Home BP Measurement and Automated Ambulatory BP Monitoring. This often helps to verify the diagnosis and assess the severity of hypertension. BP values obtained outside the clinic setting are generally lower and correlate better with target-organ damage and outcomes than BP measurements obtained by health care personnel in the clinic.

Normal mean 24-h ambulatory BP is <125/75 mmHg, with a mean of <130/85 mmHg during the day and <110/70 mmHg at night. Among the biologic variations are short-term ones driven by changes in the autonomic nervous system and a slower circadian variability. BP usually falls about 15 % at night, during sleep, to rise to daytime levels an hour or two before awakening. BP usually peaks in the late afternoon and evening. Some patients (so-called *non-dippers*) have a smaller fall of BP during sleep, sometimes none; these patients are at greater risk for cardiovascular disease, a more rapid progression of hypertensive renal disease, and even cognitive dysfunction. The converse, namely, an excessive fall of nocturnal BP, also carries risk, especially for stroke and myocardial ischemia. The early-morning surge of pressure, after arising from sleep, is also associated with more cardiovascular catastrophes, compared with the remainder of the 24-h period. Obstructive sleep apnea (OSA) is associated with hypertension, and BP can be lowered in patients with OSA by the use of continuous positive airway pressure (CPAP) during sleep.

Initial Workup of the Hypertensive Patient

The initial evaluation of patients with hypertension has three objectives: (1) to find clues to secondary causes of hypertension, (2) to assess target-organ damage, and (3) to determine whether there are other risk factors for cardiovascular disease. This requires careful history taking, a complete physical examination, some basic laboratory tests, and electrocardiography (ECG).

The first step is to establish the diagnosis of sustained hypertension. BP should be measured on at least two occasions. If the hypertension is stage 1, measurements should be made within 1 month of each other; if stage 2, within a week; and if severe, immediate action is necessary to complete the workup and treat the hypertension.

Secondary Hypertension

Table 31.1 lists the common causes of secondary hypertension. If none of these causes is present, the hypertension is primary. Of the secondary causes of hypertension, some are often easy to recognize. For example, by the time Cushing's syndrome is severe enough to cause hypertension, the clinical features are usually obvious on physical examination. The same is true of acromegaly. Many cases of coarctation of the aorta are detected in infancy or childhood. However, most of the causes of secondary hypertension need to be carefully excluded in the history, the physical examination, and the laboratory workup. Tables 31.2 and 31.3 propose a simple and general approach to this process. Some of the

Table 31.1 Causes of secondary hypertension

Renal parenchymal hypertension
Renovascular disease
Coarctation of the aorta
Adrenal disorders
Adrenocortical hypertension:
Mineralocorticoid hypertension (e.g., Conn's syndrome)
Glucocorticoid hypertension (e.g., Cushing's syndrome)
Other hormonal disorders
Hypothyroidism
Hyperthyroidism
Hyperparathyroidism
Acromegaly
Neurologic disorders: increased intracranial pressure
Drugs, especially oral contraceptives, exogenous steroids, erythropoietin, cyclosporine, licorice, sympathomimetic drugs, cocaine, tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, anabolic steroids

Table 31.2 Hypertension workup: history and physical examination

Symptoms and signs	Diagnosis
Secondary hypertension	
Abdominal or flank masses	Polycystic kidneys
Abdominal bruit	Renovascular hypertension
Delayed/absent femoral pulses, blood pressure gradient between arm and leg	Aortic coarctation
Truncal obesity, moon face, purple striae, buffalo hump	Cushing's syndrome
Tachycardia, tremor, pallor, sweating	Pheochromocytoma
Flank pain, frequency, dysuria, hematuria, prostatism, edema	Renal parenchymal disease
Target-organ damage	
Vision, fundoscopy	Retinopathy
Dyspnea, fatigue, signs of left ventricular failure	Left ventricular failure
Angina, previous myocardial infarction	Coronary artery disease
Focal neurologic symptoms and signs	Cerebrovascular disease
Symptoms and signs of renal failure	Hypertensive renal disease
Risk factor profiling	
Hypertension, diabetes, dyslipidemia, age, gender, body mass index, family history, smoking, artery disease, cerebrovascular disease, peripheral vascular disease, left ventricular hypertrophy	

Table 31.3 Hypertension workup: screening laboratory tests

Test	Rationale
Blood chemistry	
Blood urea nitrogen	Impaired renal function
Creatinine	Impaired renal function
Potassium	Primary aldosteronism
	Cushing's syndrome
	Renal failure
Calcium/phosphate	Hyperparathyroidism
Cholesterol (total, HDL and LDL), triglycerides, glucose, C-reactive protein, uric acid	Risk factors for cardiovascular disease
Thyroid-stimulating hormone	Hyperthyroidism
	Hypothyroidism
Urinalysis	Renal disease
Electrocardiography	LVH
Complete blood count	All new patients should have one

commonest causes of secondary hypertension are described in more detail later in this chapter.

Target-Organ Damage

Vascular Hypertrophy

Hypertrophy [8] refers to growth brought about by an increase in cell *size* rather than *number*. (An increase in cell number is hyperplasia.) In adults, the vascular smooth muscle cells (VSMC) are relatively quiescent, having an extremely low (<5 %) mitotic index. In persons with hypertension and atherosclerosis, however, VSMC undergo phenotypic modulation with hypertrophy and/or hyperplasia, altered receptor expression, altered lipid handling, and migration from the vascular media to the subintimal portion of the vessel, and the vessel shows enhanced extracellular matrix deposition. All these result in an increase in stiffness (lower compliance) of the arteries of hypertensive patients. This diffuse arteriosclerosis of hypertension increases with age. Superimposed on this may be accelerated development of atherosclerotic lesions.

Factors that stimulate vascular smooth muscle hypertrophy or hyperplasia in hypertension include endothelin, which activates the ETA subtype of the endothelin receptor to activate an intracellular transduction pathway involving phospholipase C (PLC), inositol 1,4,5-trisphosphate (IP_3), and 1,2-diacylglycerol (DAG); release of cytosolic calcium from the endoplasmic reticulum; and, possibly, the mitogen-activated protein (MAP) kinase system. Angiotensin II, acting via the AT_1 receptor subtype, has a similar intracellular transduction pathway. Other hormones or autocrine or paracrine factors that affect VSMC growth are vasopressin, catecholamines, insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor (TGF)-β, which all stimulate growth, and nitric oxide, atrial natriuretic peptide, estrogens, and prostacyclin, which are inhibitory. This inhibition is thought to be due to an increase in apoptosis, reversing VSMC proliferation. Many studies have shown improvement in VSMC hypertrophy and hyperplasia in hypertensive patients who take drugs that inhibit the action of angiotensin II (ACE inhibitors or AT_1 receptor blockers) or calcium (calcium-channel blockers), and it could be predicted that the same effects would occur with agents that enhance inhibitory factors, such as those neutral endopeptidase inhibitors that reduce the breakdown of atrial natriuretic peptide.

SBP and pulse pressure (PP) increase with advancing age, mainly as a result of reduced elasticity (increased stiffness) of the large conduit arteries. Increased stiffness of these arteries results from collagen deposition and smooth muscle cell hypertrophy, as well as thinning, fragmenting, and fracture of elastin fibers in the media. The distending pressure of conduit vessels is a major determinant of stiffness. The two-phase (elastin and collagen) content of load-bearing elements in the media is responsible for the behavior of these vessels under stress: At low pressures, stress is borne almost entirely by the distensible elastin lamellae, while at higher pressures, less distensible collagenous fibers are recruited, and the vessel appears stiffer. Conduit vessels are relatively unaffected by neurohumoral vasodilator mechanisms.

In addition to these structural abnormalities, endothelial dysfunction, which develops over time as a consequence of both aging and hypertension, contributes functionally to increased arterial stiffness in elderly persons with ISH. Other factors that decrease central arterial compliance by damaging the endothelium include (1) diabetes, (2) tobacco use, (3) high dietary salt intake, (4) elevated homocysteine levels, and (5) estrogen deficiency. Reduced nitric oxide (NO) synthesis and/or release in this setting contributes to increased wall thickness of conduit vessels such as the aorta and common carotid artery. The functional significance of NO deficiency in ISH is supported by the ability of NO donors, such as nitrates or derivatives, to increase arterial compliance and distensibility and reduce SBP without decreasing DBP.

Increased arterial stiffness contributes to the wide pulse pressure (PP) commonly seen in elderly hypertensive patients, in part by causing the pulse wave velocity to increase. With each ejection of blood from the LV, a pressure (pulse) wave is generated and travels from the heart to the periphery at a finite speed that depends on the elastic properties of the conduit arteries. The pulse wave is reflected at any point of discontinuity in the arterial tree and returns to the aorta and LV. The timing of the wave reflection depends on both the elastic properties and the length of the conduit arteries.

In younger persons, pulse wave velocity is sufficiently slow (approximately 5 m/s) so that the reflected wave reaches the aortic valve after closure, leading to a higher DBP and

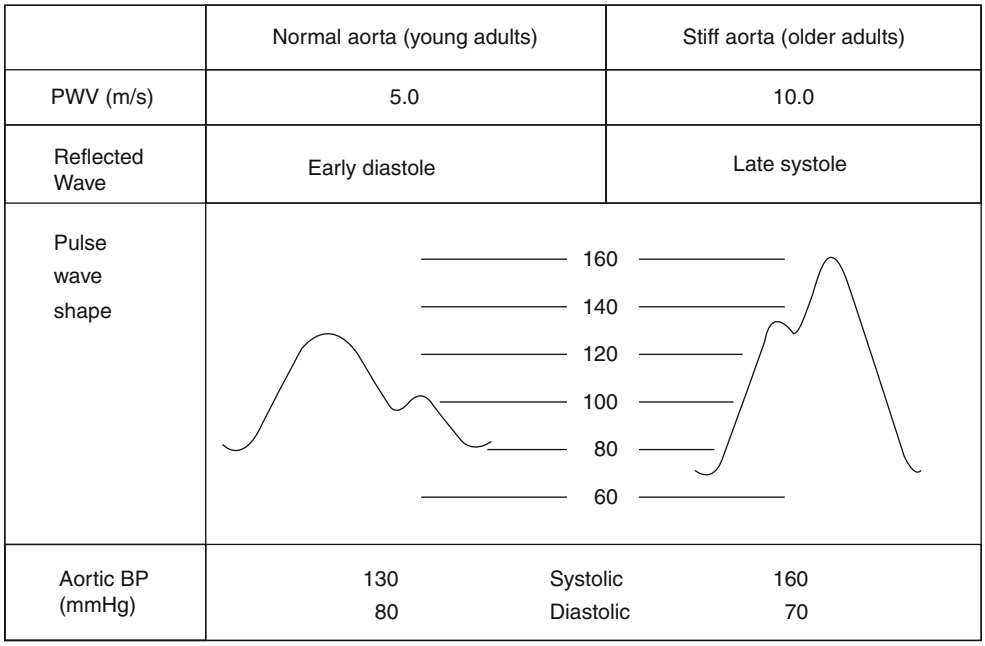

Fig. 31.1 Change in aortic pressure profile due to age-related vascular stiffening and increased pulse wave velocity (*PWV*). *Note*: Increased SBP and decreased DBP due to decreased aortic distensibility, increased PWV as a result of decreased aortic distensibility and increased distal (arteriolar) resistance, return of the reflected primary pulse to the central aorta in systole rather than in diastole due to faster wave travel, and change in aortic pulse wave profile because of early wave reflection. Note the summation of antegrade and retrograde pulse waves to produce a large SBP. This increases LV stroke work and therefore myocardial oxygen demand. There is also a reduction in the diastolic pressure–time (integrated area under the DBP curve) and therefore of the coronary perfusion pressure. This increases the vulnerability of the myocardium to hypoxia (Reprinted from Rosendorff [9]. With permission from Elsevier)

enhancing coronary perfusion by providing a "boosting" effect. In older persons, particularly if they are hypertensive, pulse wave velocity is greatly increased (approximately 10–20 m/s) due to central arterial stiffening. At this speed, the reflected wave reaches the ascending aorta before aortic valve closure, merges with the incident or antegrade wave, and produces a higher SBP (and afterload), PP, and a decreased DBP (Fig. 31.1). This phenomenon accounts for the higher SBP and PP and the lower DBP that is seen in the elderly population. The increase in SBP increases cardiac metabolic requirements and predisposes to the development of LV hypertrophy and heart failure. PP is closely related to SBP and is clearly linked to advanced atherosclerotic disease and cardiovascular events such as fatal and nonfatal MI and stroke. With aging, there is a gradual shift in the BP-risk relationships from diastolic to systolic and pulse pressure.

Most antihypertensive drugs act on peripheral muscular arteries rather than central conduit vessels. They reduce PP via indirect effects on the amplitude and timing of reflected pulse waves. Nitroglycerine causes marked reductions in wave reflection, central SBP, and LV load with smaller changes in SBP or DBP in the periphery. Vasodilator drugs lower BP by decreasing arteriolar tone, but some of them like ACEIs, ARBs, and CCBs also reduce the stiffness of conduit arteries and therefore pulse wave reflection, contributing to their antihypertensive effect.

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) [10] is a consequence of mechanical forces such as chronic increased systolic afterloading of the cardiac myofibrils in hypertension. As they do to VSMC hypertrophy, important neurohormonal stimuli contribute to LVH, particularly the renin–angiotensin system (angiotensin II), the sympathetic nervous system, and the other growth factors listed earlier for VSMC. The clinical significance of the pro-hypertrophic actions of angiotensin II, for instance, is that ACE inhibitors or AT_1 receptor blockers could be expected to prevent, or even reverse, LVH more than antihypertensive drugs that reduce blood pressure by the same amount but have no direct action on myocardial cells. This is important because of the very adverse effect of LVH on the prognosis for patients with hypertension.

Patients with LVH (and many hypertensive patients without LVH) usually have diastolic dysfunction: their left ventricle is stiffer (i.e., less compliant) and thus requires greater distending pressure during diastole. These patients may have dyspnea (secondary to the raised pulmonary venous filling pressure), left atrial hypertrophy, a fourth heart sound, and late diastolic flow across the mitral valve (A wave) that is larger than early diastolic flow (E wave), as well as tissue Doppler features of reduced LV compliance (*see* Chap. 8). LVH may progress toward the syndrome of

systolic dysfunction and dilated cardiomyopathy with congestive heart failure.

Heart Attack and Brain Attack [11, 12]

Hypertension is a significant risk factor for both acute myocardial infarction and stroke. Both situations are marked by hypertension-induced vascular hypertrophy and/or hyperplasia, endothelial dysfunction, and accelerated atherosclerosis, caused by migration of VSMC into the subintima, subendothelial infiltration of monocytes, cholesterol deposition and oxidation, and calcification. Additional elements in acute myocardial infarction are plaque disruption, platelet adhesion and aggregation, and thrombosis. Patients with hypertension are at much greater risk of coronary events because of the malignant combination of decreased oxygen supply and the increased oxygen demand. The limitation of oxygen supply is due to either decreased coronary flow or more commonly, a decreased capacity of the arteriosclerotic coronary arteries to vasodilate (impaired coronary flow reserve) in response to the increased oxygen demand of LVH and the increased output impedance of the left ventricle.

Strokes, however, are more varied in their pathogenesis. Hypertension is the major cause of stroke. In hypertension, about 80 % of strokes are ischemic, and about 15 % are hemorrhagic. Reduction of cerebral blood flow due to arterial stenosis or thrombosis may produce any degree of tissue injury from asymptomatic and isolated neuronal dropout to huge infarction and cavitary necrosis. The extent of the ischemic injury depends on the duration and the intensity of the ischemia, and these, in turn, depend on the efficiency of the collateral circulation and the cardiac output. Hemorrhagic stroke in hypertension is probably due to rupture of microaneurysms of the small intracerebral arteries. Hypertension can also cause focal damage to small intracerebral arteries (lipohyalinosis) marked by occlusion of the vessels and the production of small ischemic cavities in the brain known as *lacunar infarcts*, frequently seen in the MRIs of patients with vascular dementia. Last, hypertension is a risk factor for berry aneurysms and subarachnoid hemorrhage.

Hypertensive Encephalopathy

Hypertensive encephalopathy [13] is an acute syndrome of severe hypertension, cerebrovascular dysfunction, and neurologic impairment that resolves rapidly with treatment. The pathophysiologic mechanism is segmental dilation along the cerebral arterioles (sausage-string appearance); when, in severe hypertension, the autoregulatory capacity of vessels is exceeded, segments of the vessel are stretched and dilated. There is then leakage of fluid into the perivascular tissue causing edema and the syndrome of hypertensive encephalopathy. Clinical features are those of encephalopathy (headache, nausea, projectile vomiting, visual blurring, drowsiness, confusion, seizures, coma) in association with severe hypertension. Papilledema, usually with retinal hemorrhages and exudates, may be present, and the sausage-string arteries may be seen in the retina. The differential diagnosis includes cerebral infarction, intracerebral hemorrhage, subarachnoid hemorrhage, subdural hematoma, brain tumor, encephalitis, and epilepsy. These lesions are usually identified by their distinctive clinical features and by computed tomography (CT). Drugs, such as intravenous amphetamines and cocaine, and ingestion of tyramine by patients taking monoamine oxidase inhibitors can produce a similar clinical picture, as can lupus vasculitis, polyarteritis, or uremic encephalopathy.

Hypertension-Related Renal Damage (*See Also* Chap. 40)

Chronic kidney disease (CKD) is defined as the presence of long-standing injury to the kidney, confirmed by kidney biopsy or a glomerular filtration rate (GFR) of <60 mL/min/1.73/m^2 for longer than 3 months. The clinical associations are a serum creatinine of ≥1.2 mg/dL in women and ≥1.4 mg/dL in men and microalbuminuria (30–300 mg/day) or albuminuria (>300 mg/day). Diabetes and hypertension account for the bulk of patients with end-stage renal failure.

Hypertension is both a cause and complication of CKD, [14, 15] and lowering BP slows the progression of renal disease. In hypertension, there is inappropriately elevated sympathetic nervous system (SNS) activity or activation of the renin–angiotensin–aldosterone system (RAAS) or both. Both SNS overactivity and angiotensin II selectively constrict the efferent arterioles of the kidney, increasing glomerular filtration pressure and therefore filtration fraction. As a consequence, the colloid osmotic pressure of the fluid leaving the glomerular capillary to enter the peritubular network of capillaries is increased, resulting in greater sodium reabsorption through the tubules.

Both the SNS and the RAAS are direct vasoconstrictors of systemic resistance arterioles. Sympathetic nerves also stimulate renin release through activation of β-receptors, resulting in an increase in angiotensin II. Other mechanisms include a direct effect of angiotensin II to enhance the sodium/hydrogen antiporter of the proximal tubule cells to increase sodium reabsorption and the angiotensin II-mediated release of the mineralocorticoid hormone, aldosterone. Angiotensin II also causes morphologic changes in the kidney, mesangial cell proliferation, vascular intimal thickening and fibrosis and hyalinization of arterioles (arteriosclerosis), and the activation and release of pro-inflammatory cytokines in the renal parenchyma. There may be focal glomerulosclerosis with atrophic tubules.

Patients with CKD are at increased risk of CV events [16]. The BP goal in patients with CKD is <130/80 mmHg.

Achievement of this level of BP control in patients with CKD is often difficult, and most patients will require 2–4 antihypertensive drugs in moderate to high doses.

Hypertensive Retinopathy

The optic fundi should be examined in every new hypertensive patient; with some practice, this can often be done without having to dilate the pupils. The features of hypertensive retinopathy [17] are:

1. *Arteriolar narrowing*. The retinal artery: vein diameter ratio is about 3:4 in the normal eye. In hypertension, the artery becomes narrower, with a decrease in the A/V ratio. The arteriosclerotic arteries may have a reddish-brown ("copper-wire") appearance, and as thickening of the wall progresses, the visibility of the blood column diminishes and eventually disappears, leading to the appearance of the artery as a silver thread ("silver wire").
2. *Arteriovenous nicking*. The retinal arteries, with their thickened walls and increased intraluminal pressure, externally compress the low-pressure, thin-walled vein, causing "A/V nicking."
3. *Cotton-wool spots*. Reduced blood flow caused by sclerosis or fibrinoid necrosis of small retinal arteries may cause regions of infarction, the so-called cotton-wool spots or cytoid bodies. They are commonly referred to as exudates, but are not exudates.
4. *Aneurysms*. Although capillary microaneurysms are usually considered to be classic lesions of diabetic retinopathy, they may also occur in hypertension in the absence of diabetes.
5. *Flame hemorrhages*. In severe hypertension, there may be breakdown of the blood–retinal barrier, producing intraretinal hemorrhages that are often flame-shaped.
6. Less common ocular manifestations of hypertension are papilledema, central retinal vein occlusion, and hypertensive changes in the choroidal vessels, the last recognizable only by special techniques such as intravenous fluorescein angiography.

Hypertensive Emergency and Urgency

Hypertensive emergency is a situation in which severe hypertension is associated with acute or rapidly progressive target-organ damage, such as acute cerebrovasular (hypertensive encephalopathy, stroke, transient ischemic attack) or cardiac (acute left ventricular failure with pulmonary edema, myocardial infarction, aortic dissection) lesions or acute renal failure. The mechanism of the often extremely high blood pressure with rapid deterioration of target-organ function is not known; hypotheses include vascular endothelial damage with myointimal proliferation and pressure natriuresis producing hypovolemia with activation of vasoconstrictor hormones such as catecholamines, endothelin, and the renin–angiotensin system. Plasma renin activity is usually high. Obviously, many of these patients require urgent therapy with parenteral antihypertensive agents (*see* Chap. 32), although care should be taken not to drop mean arterial pressure too suddenly or below the lower limit of cerebrovascular autoregulation, which could induce an ischemic stroke. *Hypertensive urgencies* describe situations of very high blood pressure (>180 mmHg SBP or >110 mmHg DBP) not related to severe symptoms or acute progressive target-organ damage. For this condition, the blood pressure should be reduced by oral agents without delay.

Risk Factor Profiling

The third objective of the initial evaluation of a patient with hypertension is to get a full picture of the cardiovascular risk factors, other than hypertension, for that patient. There is a cluster of atherogenic risk factors that often accompanies hypertension, referred to as "metabolic syndrome" [18]. This is defined as hypertension, abdominal obesity (waist circumference: men >40 in [>102 cm], women >35 in [>88 cm]), dyslipidemia (triglycerides >150 mg/dL [>1.7 mmol/L], HDL-cholesterol <40 mg/dL [<1.0 mmol/L] for men and <50 mg/dL [<1.3 mmol/L] for women), insulin resistance or glucose intolerance (fasting blood glucose >110 mg/dL [>6.1 mmol/L]), a pro-inflammatory state (elevated C-reactive protein), and a prothrombotic state (elevated plasma plasminogen activator inhibitor, PAI-1) [18]. Other potent risk factors include age, gender, smoking, LDL-cholesterol, a positive history of premature cardiovascular events in first-degree relatives, left ventricular hypertrophy, and hyperuricemia. More recently, homocysteine, fibrinogen, factor VII, t-PA, and lipoprotein(a) have been shown to predict cardiovascular morbidity and mortality. These are discussed more fully in Chap. 1.

Pathogenesis of Primary Hypertension

Most of the causes of secondary hypertension (*see* section on "Common Causes of Secondary Hypertension") have been well-characterized, and their pathophysiologic mechanisms are reasonably well-understood. These causes, however, account for only 5–10 % of all hypertensive patients seen by physicians, and the remaining 90–95 % of patients with primary hypertension have a disease that is as poorly understood as it is common. Consequently, enormous research efforts have been mobilized to study the pathogenesis of primary hypertension, using animal models, human patients, and more recently, the powerful tools of cell and molecular biology. The result has been a plethora of mechanisms and theories, not all mutually exclusive, that support the concept devised by Irvine Page of a "mosaic" of

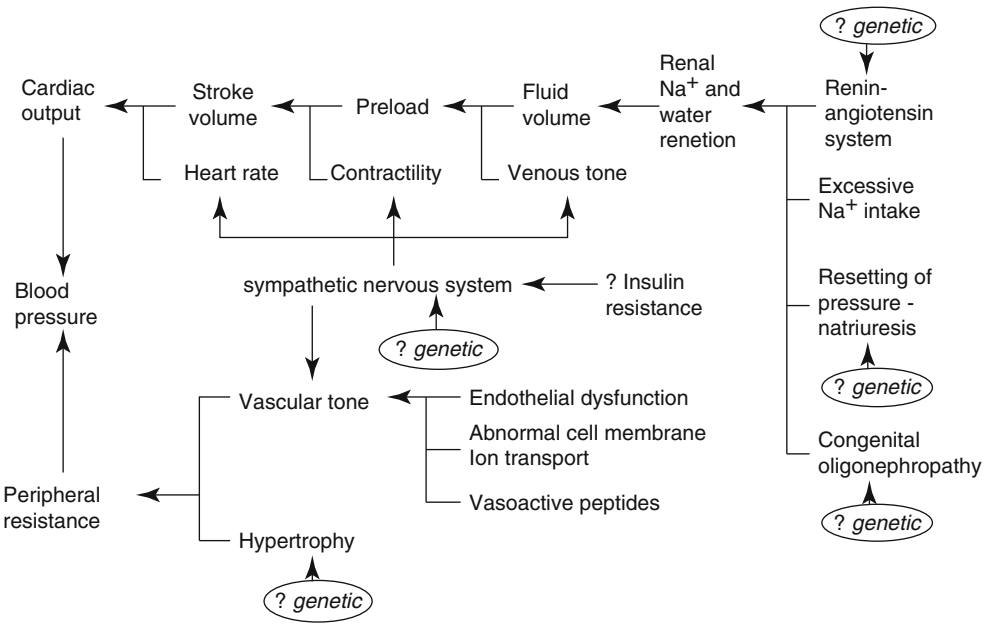

Fig. 31.2 Hemodynamic and renal control of blood pressure

mechanisms, each operating in different organs and at different levels of organization. A brief and selective survey of this topic follows.

Genetic Predisposition

Monogenic syndromes are covered in the section on "Secondary Hypertension." Primary hypertension also tends to cluster in families, but a specific genotype has not been identified. A number of associations have been suggested, but none has been confirmed. These include mutations in the genes for angiotensinogen, renin, 11β-hydroxylase, aldosterone synthase, and the α_1-adrenoreceptors; a negative association with transforming growth factor-β_1 (TGF-β_1) and the adducin protein which affects the assembly of the actin-based cytoskeleton; and polymorphisms in about 25 genes, including those for angiotensinogen, angiotensin-converting enzyme (ACE), and the angiotensin II type 1 receptor.

Increased Cardiac Output

Blood pressure is proportional to cardiac output (CO) and total peripheral resistance (TPR). Some young "borderline hypertensives" have a hyperkinetic circulation with increased heart rate and CO (Fig. 31.2). This, in turn, may be due to increased preload associated with increased blood volume or to increased myocardial contractility. Also, LVH has been described in the still normotensive children of hypertensive parents, an observation that suggests that the LVH is not only a consequence of increased arterial pressure but that it may itself reflect some mechanism, such as hyperactivity of the sympathetic nervous system or the renin–angiotensin system that causes both LVH and hypertension. In mature primary hypertension, the CO is normal and the TPR elevated. The switch from elevated CO to elevated TPR may be due to autoregulatory vasoconstriction in response to organ hyperperfusion; thereafter, the hypertension becomes self-sustaining due to the accelerated arteriosclerosis. Plasma volume is usually normal or slightly lower than normal in established primary hypertension; however, some investigators have suggested that the volumes are still higher than they should be, given the elevated blood pressure, which should produce substantial pressure natriuresis and diuresis.

Excessive Dietary Sodium

We ingest many times more sodium than we need; there is much epidemiologic and experimental evidence to show an association between salt intake and hypertension. Sodium excess activates some pressor mechanisms (such as increases of intracellular calcium and plasma catecholamines and an upregulation of angiotensin II type 1 receptors), and it increases insulin resistance. About half of hypertensive patients are particularly salt-sensitive (as defined by the blood pressure rise induced by sodium loading), as compared with about a quarter of normotensive controls. Sodium sensitivity becomes greater with age and has a strong genetic component. The mechanism of sodium sensitivity may be renal sodium retention (*see* later). Clinical trials have shown an average reduction of blood pressure of 5/2 mmHg in hypertensive patients who lower their sodium intake to approximately 100 mmol/day (roughly equivalent to a daily intake of sodium chloride of less than 0.5 g/day).

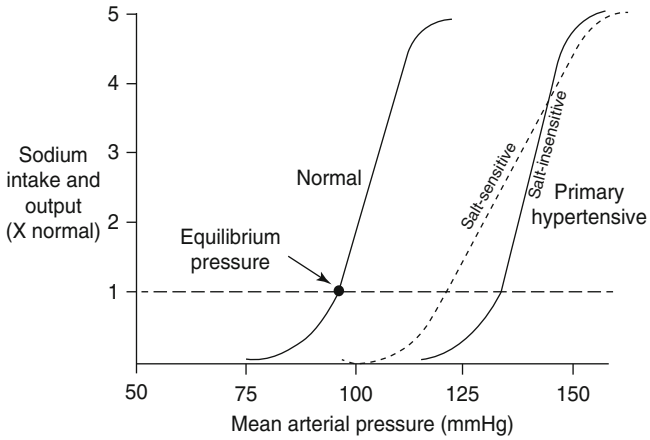

Fig. 31.3 Steady-state relations between blood pressure and sodium intake and output in normotensive subjects and in patients with salt-sensitive or salt-insensitive hypertension. Normally, an increase in sodium intake will result in a small increase in mean arterial pressure that is sufficient to increase sodium output by pressure natriuresis so that the "equilibrium pressure" is restored. In salt-insensitive hypertension, the steep curve is retained but is shifted to the right (i.e., reset at a higher mean arterial pressure). In salt-sensitive hypertension, there is a shift to the right and flattening of the curve so that sodium loading increases blood pressure by a greater amount (Modified from Hall et al. [19]. With permission from Lippincott Williams & Wilkins)

Renal Sodium Retention

Four mechanisms have been advanced to explain renal sodium retention in hypertension, resetting of the renal pressure–natriuresis curve, an endogenous sodium pump inhibitor, inappropriately high renin levels, and reduced nephron number.

Abnormal renal sodium handling may be due to a rightward shift of the pressure–natriuresis curve of the kidney (Fig. 31.3) [20]. When the arterial pressure is raised, the normal kidney excretes more salt and water; balance normally occurs at a mean perfusion pressure of around 100 mmHg, producing sodium excretion of about 150 mEq/day. Increased salt intake transiently raises blood pressure, and the pressure–natriuresis effectively restores total body sodium to normal. In patients with primary hypertension, this pressure–natriuresis curve is reset to a higher blood pressure, preventing return of the blood pressure to normal. There is some evidence in certain animal models and in humans that the rightward shift in the pressure–natriuresis curve is inherited.

A variation on this theme is a hormonal mediator of salt sensitivity, a sodium pump inhibitor, endogenous ouabain [21], which is secreted by the adrenal cortex and is natriuretic in sodium-loaded animals. Renal sodium retention stimulates ouabain release, which, by its inhibition of the sodium pump, increases intracellular sodium. In turn, sodium–calcium exchange is inhibited, and the rise in intracellular calcium causes increased vascular tone and vascular hypertrophy. This is discussed further in the section on "Abnormal Cell Membrane Ion Transport."

Some investigators believe that a more important role for the kidney is the generation of more renin from nephrons that are ischemic, owing to afferent arteriolar vasoconstriction or structural narrowing of the lumen [22]. Some patients with primary hypertension have elevated plasma renin activity, but, even in those with normal levels, it may be inappropriately high, as we would expect the hypertension to suppress renin. Others have developed the idea that hypertension may arise from a congenital reduction in the number of nephrons or in the filtration surface area per glomerulus that limits the ability of the kidney to excrete sodium, raising blood pressure, which destroys more glomeruli, thus setting up a vicious cycle of hypertension and renal glomerular dysfunction [23].

Increased Activity of the Renin–Angiotensin System

The components of the renin–angiotensin system, the biosynthesis and actions of angiotensin II, and angiotensin II signal transduction in VSMC are all described in Chap. 4. Plasma renin activity is nearly always low in association with primary aldosteronism, high with renovascular or accelerated malignant hypertension, and low, normal, or high with primary hypertension. Primary hypertension with sodium retention would be expected to depress plasma renin levels; under these circumstances, "normal" values are inappropriately high. Three explanations for this have been developed. The first, cited earlier, is that a population of ischemic nephrons contributes excess renin. The second is that the sympathetic hyperactivity associated with primary hypertension stimulates β-adrenergic receptors in the juxtaglomerular apparatus of the nephron to activate renin release. The third proposes that many of the patients with inappropriately normal or even high renin levels have defective regulation of the relationship of sodium and the renin–angiotensin system—that they are "non-modulators." This results in abnormal adrenal and renal responses to salt loads; in particular, salt loading does not reduce angiotensin II [24]. In low-renin hypertension, the hypertension is primarily due to volume overload but may in rarer cases be explained by hyperaldosteronism (*see* below), or excess 18-hydroxylated steroids, or with high levels of cortisone from inhibition of 11β-hydroxysteroid dehydrogenase. High- or normal-renin hypertensives have a higher rate of cardiovascular complications than those with low renin. Also it has been suggested that, since high- and normal-renin hypertensives are vasoconstricted, the drug of first choice in their treatment should be one that antagonizes the renin–angiotensin system, and because low-renin hypertensives are volume-overloaded, they should be treated in the first instance with a diuretic.

Increased Sympathetic Activity

There is much evidence of sympathetic hyperactivity in patients with primary hypertension. Heart rate and stroke volume are increased, at least in the early, labile, phase of blood pressure elevation and at least part of the increased vascular resistance of the established phase of hypertension may be due to the increased sympathetic tone. It is not surprising that psychogenic stress seems to predispose to high blood pressure, tension causing hypertension. Baroreceptor sensitivity is reduced in some patients with hypertension, presumably because of the arteriosclerotic stiffness of the vessels that house baroreceptors, so that a given increase in blood pressure decreases heart rate less than it normally would. In other patients, there is resetting of the baroreceptor reflex, with baroreceptor reflexes operating normally, but around a higher set point of arterial pressure.

Increased Peripheral Resistance

Small arteries and arterioles are responsible for most of the peripheral resistance, but the microvasculature is difficult to study in humans. It is much easier to study larger arteries, especially by noninvasive methods such as ultrasonography. We can make measurements of morphology such as wall thickness and wall–lumen ratio, and of physiologic processes, such as compliance or distensibility (lumen cross-sectional diameter or area change per unit pressure change). Patients with hypertension very frequently have large arteries (e.g., brachial, carotid, femoral) that are thick (owing to hypertrophy, increased wall–lumen ratio) and stiff (owing to decreased compliance). These effects are due to vascular smooth muscle cell hypertrophy in the media. Smaller arteries probably undergo either hyperplasia or remodeling, which is a rearrangement of existing cells around a smaller lumen. Increased large artery stiffness may be quantified by measuring the pulse wave velocity (PWV). PWV measurement utilizes the feature of the arterial waveform that during early systole, there is no, or minimal, interference of the incident pressure wave by the reflected pressure wave. With this assumption, PWV can be measured between two sites, a known distance apart using the pressure "foot" of the waveform to calculate the transit time. PWV is then calculated as the distance divided by the time. The augmentation index (AIx) is another noninvasive measure, this time of both large artery stiffness and small artery constriction. The AIx is the "boost" given to the peak systolic pressure waveform by a reflected wave that arrives back at the aorta more quickly than normal. The growth factors responsible for these changes are summarized in Fig. 31.4 and are discussed in more detail in Chap. 4.

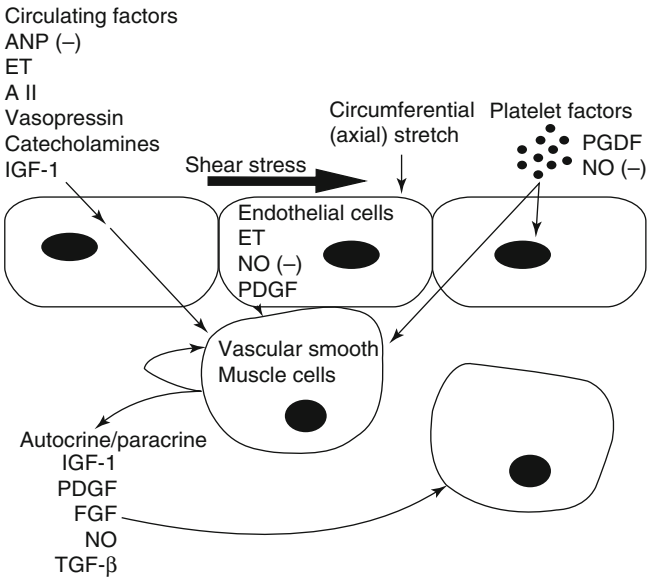

Fig. 31.4 Stimuli to vascular smooth muscle growth. *ANP* atrial natriuretic peptide, *ET* endothelin, *AII* angiotensin II, *PDGF* platelet-derived growth factor, *NO* nitric oxide, *IGF-1* insulin-like growth factor-1, *FGF* fibroblast growth factor, *TGF-β* transforming growth factor β, (–), inhibitory to hypertrophy/hyperplasia

Abnormal Cell Membrane Ion Transport

Because it is so easy to measure red cell cation concentrations and therefore the kinetics of transmembrane cation flux, the literature on abnormalities of these in primary hypertension is voluminous. There seems to be general agreement that there is decreased activity of the Na^+–K^+–ATPase pump (which pumps Na^+ *out* of the cell), possibly the result of an excess of the endogenous inhibitor ouabain (*see* earlier in the section on "Renal Sodium Retention"). There may also be increased activity of the Na^+–H^+ exchange antiporter (which pumps Na^+ *into* the cell). Both mechanisms increase intracellular sodium. This high intracellular sodium concentration (and low intracellular pH) inhibits Na^+–Ca^{2+} exchange (normally Na^+ *in* and Ca^{2+} *out*) to increase intracellular Ca^{2+}, which increases vascular tone and stimulates hypertrophy. Hyperactivity of the Na^+–H^+ exchanger in the renal proximal tubule cells may also cause increased sodium reabsorption and intravascular volume expansion [25].

Endothelial Dysfunction

Impaired biosynthesis or release of nitric oxide, the vascular endothelium-derived relaxing factor, has been described in animal models of hypertension and in human hypertension. Endothelin, a 21-amino-acid vasoconstrictor made by endothelial cells, is present in increased amounts in the

plasma of hypertensives. There may also be paracrine release of endothelin from the endothelial cells, where it is made, toward the VSMC, where it acts [26]. Hypertensives have an increased vasoconstrictor response to endothelin, as well as an enhanced expression of the endothelin gene. Prostaglandin H_2 and thromboxane A_2 are other vasoconstrictors made by endothelial cells (*see* Chap. 4).

Insulin Resistance and Hyperinsulinemia

Hypertension is more common in obese persons, possibly because of insulin resistance and the resulting hyperinsulinemia [27]. The mechanism by which insulin resistance or hyperinsulinemia increases blood pressure is obscure; possibilities include enhanced renal sodium and water reabsorption, increased renin–angiotensin or sympathetic nervous system activity, and vascular hypertrophy, all firmly established actions of insulin. While the physiologic role of insulin resistance and hyperinsulinemia has been studied most intensively in the syndrome of obesity, hypertension, and diabetes, similar abnormalities of insulin action have been described in lean hypertensives who are not diabetic. Leptin, a hormone produced by fat cells, stimulates the sympathetic nervous and renin–angiotensin systems and also promotes insulin resistance, vascular inflammation, and endothelial dysfunction.

Other Possible Mechanisms

The many other possible mechanisms that have been investigated are supported by more or less solid evidence. Notable ones are abnormal patterns of biosynthesis or secretion of adrenocortical hormones in response to various stimuli; adrenomedullin (an adrenomedullary vasodilator peptide); the kallikrein–kinin system, including bradykinin; other vasoactive peptides (natriuretic peptide, calcitonin gene-related peptide, neuropeptide Y, opioid peptides, vasopressin); dopamine; serotonin; prostaglandins; and medullipin (a renomedullary vasodepressor lipid). In addition to all the postulated mechanisms for primary hypertension, many other factors may contribute to high blood pressure in susceptible persons. Examples are increased urinary calcium with a low plasma calcium concentration, potassium and magnesium deficiency, smoking, excessive consumption of caffeine or alcohol, physical inactivity, and hyperuricemia.

Common Causes of Secondary Hypertension

"Common" is an overstatement. As a rough estimate, only about 5 % of all patients who present with hypertension have a demonstrable cause that qualify the condition as secondary. It is, however, critically important to recognize these conditions when they occur, as many are curable—by surgery or some other means.

Renovascular Hypertension

Renal hypoperfusion as a result of renovascular disease (renal artery stenosis—RAS) accounts for about 1 % of all cases of hypertension, but it is much more likely to be the cause when hypertension is rapidly progressive, accelerated, or malignant or is associated with coronary, carotid, or peripheral vascular disease [28, 29].

The mechanism of renovascular hypertension has been firmly established in animal models (based on those developed by Harry Goldblatt in the 1930s). When both renal arteries in the dog are partially occluded by clamps or when one artery is clamped and the other kidney removed, sustained hypertension develops. The two-clip–two-kidney model resembles bilateral renovascular hypertension, and the one-clip–one-kidney animal is a model for renovascular hypertension plus chronic renal parenchymal disease. A more useful model for the common form of renovascular hypertension, unilateral renal artery stenosis, is the one-clip–two-kidney model.

Mechanisms

Bilateral renovascular hypertension and *renovascular hypertension* (*unilateral or bilateral*) *with chronic renal parenchymal disease* have similar mechanisms. The decreased intrarenal vascular pressure results in increased secretion of renin from the juxtaglomerular apparatus and, consequently, increased activity of angiotensin II and aldosterone. The systemic vasoconstriction produced by angiotensin II raises the blood pressure (renin-dependent hypertension). With time, however, the renin–angiotensin dependency of the systemic hypertension wanes because of progressive retention of sodium and water, which leads to increases in extracellular fluid volume, blood volume, and blood pressure. Sodium and water retention are consequences of a reduction in the functional renal mass subjected to reduced perfusion pressure, with the associated rightward shift of the pressure–natriuresis curve (*see* Fig. 31.2), and are secondary to the effects of angiotensin II, namely, intrarenal vasoconstriction, increased net tubular sodium reabsorption, and increased aldosterone levels. At this stage, the hypertension is mainly volume-dependent. With progressive diminution in renin release and in circulating angiotensin II levels, salt and water balance is restored but at the expense of high arterial blood pressure.

This dual mechanism has important therapeutic implications. Therapy with vasodilators reduces the renal perfusion pressure even further and exacerbates volume retention. Diuretics reduce the extracellular fluid volume and enhance the activity of the renin–angiotensin system. Vasodilator

drugs in combination with volume depletion can decrease the glomerular filtration rate and can even cause acute renal failure. ACE inhibitors or angiotensin II receptor blockers may also be dangerous in renovascular hypertension because they remove the selective vasoconstrictor action of angiotensin II on efferent arterioles to maintain glomerular filtration pressure.

Unilateral renovascular hypertension is much more common than bilateral stenosis in humans. Here, the stenotic kidney releases renin, elevating circulating levels of angiotensin II to increase blood pressure. This hypertension should increase sodium excretion in the nonstenotic kidney to restore blood pressure to normal; however, this pressure–natriuresis effect (*see* Fig. 31.3) is blunted by the increased angiotensin II levels because of angiotensin II and aldosterone-mediated sodium reabsorption and because of angiotensin II renal vasoconstriction with reduction in renal plasma flow and glomerular filtration rate (GFR). Since the pressure distal to the stenosis is never completely restored to normal, even with high systemic blood pressure, the levels of renin and angiotensin II remain high, and the hypertension is "renin-dependent."

Treatment of unilateral renovascular hypertension with ACE inhibitors or angiotensin II receptor blockers reduces glomerular filtration pressure and GFR in the stenotic kidney but increases renal blood flow and GFR in the nonstenotic kidney. In some patients, the sustained hypertension of unilateral renovascular disease can cause hypertensive glomerular injury in the nonstenotic kidney, which further compromises renal function and exacerbates the hypertension. In these patients, ACE inhibitors and angiotensin II receptor blockers may further impair renal function for the reasons described earlier.

Pathology

The most common cause of renovascular hypertension is atherosclerotic stenosis of a main renal artery. Affected patients are relatively older and usually have vascular disease elsewhere. The second condition is fibromuscular dysplasia, which can be subdivided into intimal fibroplasia, medial fibromuscular dysplasia, and periadventitial fibrosis. Of these, the most common is medial fibromuscular dysplasia (or medial fibroplasia), usually a condition of young women. Other, rare, causes are renal artery aneurysms, emboli, and Takayasu's arteritis and other vasculitides.

Clinical Features

The only unique clinical finding, an abdominal bruit, is heard in about half of those who have renal artery stenosis. In general, renal artery stenosis should be suspected in severe hypertension associated with any one of the following: progressive renal insufficiency, refractoriness to aggressive treatment, and other evidence of occlusive vascular disease in young women or in patients whose serum creatinine value rises quickly after they start taking an ACE inhibitor. Laboratory findings often include proteinuria, elevated renin and aldosterone levels, and a low serum potassium value.

Diagnosis

A workup for atherosclerotic renal artery stenosis [30] should be done only if there is resistant hypertension or if there is worsening of renal function. The most cost-effective screening test is color Doppler ultrasonography. A more traditional modality of screening is the captopril renal scan. Reduced renal uptake of technetium 99 m diethylenetriamine penta acetic acid (^{99m}Tc-DTPA) and reduced renal excretion of iodine 121 (^{121}I) hippurate or ^{99m}Tc-mercaptoacetyltriglycine (^{99m}Tc-MAG$_3$) are measures of renal function in stenotic kidneys. Renal function can be reduced further after a single dose of the ACE inhibitor captopril.

If the ultrasonogram or the captopril scan is positive, then magnetic resonance angiography (MRA) or CT angiography should be done. Other useful imaging tests include digital subtraction intravenous angiography and renal arteriography. Various tests detect hypersecretion of renin from the hypoperfused kidney: these are peripheral blood plasma renin activity (PRA) and the renal vein renin ratio (ratio of PRA between the two renal veins; a ratio >1.5:1 is diagnostic).

Therapy

Most patients with atherosclerotic RAS require only medical antihypertensive therapy as either primary therapy or following some revascularization procedure because revascularization alone is seldom sufficient to control the BP in middle-aged or elderly patients with RAS. The reason for this may be residual ischemic nephropathy in the affected kidney, restenosis of the affected kidney, concomitant hypertensive parenchymal damage to the contralateral kidney, or progression of atherosclerotic disease in the contralateral kidney. In contrast, percutaneous trans-renal angioplasty (PTRA), with or without stenting, is the treatment of choice in patients with fibromuscular dysplasia. Surgical revascularization of the kidney should be reserved for the rare cases of failed medical management and PTRA. ACE inhibitors or angiotensin II receptor antagonists should not be used.

Renal Parenchymal Hypertension [31, 32]

Renal parenchymal hypertension is discussed in more detail in Chap. 40. Chronic kidney disease (CKD) is the most common cause of secondary hypertension, which is present in about 80 % of patients with chronic renal failure (CRF). Primary hypertension also damages the kidneys; in the United States, hypertension ranks just below diabetes among causes of end-stage renal disease. Hypertension is, therefore, both a cause and a consequence of CKD, and often there is a

vicious circle: hypertension causes renal damage, which exacerbates hypertension.

Pathophysiologic Mechanisms

The following mechanisms have been identified.

Glomerular Hypertension

A high systemic blood pressure may be transmitted to the glomerular capillaries, particularly if the autoregulatory vasoconstrictor response of the afferent arterioles is defective. This causes an increased filtration pressure and an increased filtration rate of individual glomeruli, increased pressure within Bowman's capsule, and damage to glomerular epithelial cells. This results in a protein leak through the glomerular membrane, and the protein may then damage tubule cells. The renal damage will eventually result in a decrease of whole-kidney glomerular filtration rate, sodium and water retention, and worsening of the hypertension.

Sodium and Volume Status

A severely reduced GFR (<50 mL/min) causes sodium retention and volume expansion and, therefore, increased cardiac output. The disorder of sodium homeostasis may also be due to increased amounts of an endogenous ouabain-like natriuretic factor that inhibits the Na^+–K^+–ATPase pump.

Renin–Angiotensin–Aldosterone System

The renin–angiotensin–aldosterone system is activated in CRF because of diffuse intrarenal ischemia. The aldosterone contributes to sodium retention. Eventually, however, the expanded fluid volume inhibits renin release, and plasma renin activity may become normal. Even "normal" plasma concentrations of renin are, however, inappropriately high in relation to the state of sodium and water balance, and the hypertension remains partly due to an angiotensin-dependent increase in peripheral vascular resistance.

Autonomic Nervous System

CRF activates renal baroreceptors, which effect increases sympathetic nervous system activity and elevates plasma norepinephrine levels (as does reduced catecholamine clearance).

Other Mechanisms

In uremic patients, increased plasma levels of an endogenous compound, asymmetrical dimethylarginine (ADMA), a nitric oxide synthase inhibitor, contribute to the hypertension. Recombinant human erythropoietin (rHu-EPO), used extensively to treat the anemia of CRF, exacerbates hypertension, though how it does so is not known. The secondary hyperparathyroidism of CRF makes the hypertension worse. The mechanism, as yet undefined, is somehow related to the increase in intracellular calcium concentration.

Management

The problem in treating hypertension in patients with CRF is that diuretics and other antihypertensive agents often produce a transient drop in renal blood flow and GFR and an increase in serum creatinine; thus, management is often a delicate balancing act between achieving blood pressure control and maintaining whatever renal function is left. In general, ACE inhibitors or angiotensin receptor blockers are the antihypertensive drugs of choice (*see* Chap. 32).

Pheochromocytoma

About 0.5 % of hypertensives have pheochromocytoma as the cause of the high blood pressure. Pheochromocytomas [33, 34] can occur at any age, and they arise from neuroectodermal chromaffin cells, mostly in the adrenal medulla (85 %) but sometimes elsewhere, usually in the abdomen or pelvis (15 %). About 10 % of adrenal and about 30–40 % of extraadrenal tumors are malignant. Ten percent are familial and autosomal-dominant. The familial form seems to be due to mutations of the RET protooncogene on chromosome 10 and may be intercurrent with other tumors as a syndrome of multiple endocrine neoplasia (MEN). In MEN 2A, pheochromocytoma is associated with medullary thyroid carcinoma (MTC) and hyperparathyroidism, whereas in MEN 2B, there is no parathyroid disease but there is a characteristic phenotype (marfanoid appearance, neuromas of the lips and tongue, thickened corneal nerves, intestinal ganglioneuromatosis). Other familial syndromes with pheochromocytoma include von-Hippel–Lindau syndrome and von Recklinghausen's disease.

Pheochromocytomas secrete mainly norepinephrine (NE) and less epinephrine, plus a variety of peptide hormones, adrenocorticotropin (ACTH), erythropoietin, parathyroid hormone, calcitonin gene-related protein, atrial natriuretic peptide, vasoactive intestinal peptide, and others. Most patients have hypertension; in about half, it is sustained, with or without paroxysms, and in the other half, blood pressure is normal between paroxysms. Paroxysms of hypertension may be signaled by severe headaches, sweating, palpitations with tachycardia, pallor, anxiety, and tremor. Also described are orthostatic hypotension, nausea and vomiting, and weight loss. Any patient with this symptom complex should be screened for pheochromocytoma with measurement of the plasma or urinary concentrations of the catecholamine metabolites, metanephrine and normetanephrine. There are, however, some problems with these tests. Results can be normal in patients with paroxysmal hypertension if the test is done during a normotensive interval. Plasma or urinary metabolites of an antihypertensive drug, labetalol, may cause a false-positive result. Other medications, particularly tricyclic antidepressants, may also give false-positive results.

If plasma catecholamines are only moderately elevated (600–2,000 pg/mL), the differential diagnosis includes neurogenic hypertension and hypertension associated with increased sympathetic activity. Here, the clonidine suppression test is useful; clonidine decreases plasma catecholamine levels to normal in neurogenic hypertension, but not in pheochromocytoma. If blood or urine test findings are positive, the next step is to localize the tumor using CT or MRI. In patients with elevated metanephrines but a negative CT or MRI, scintigraphy using ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) should be done. Definitive treatment is surgery, but great care must be taken to prevent severe hypertension or hypotension during the operation or in the immediate postoperative period, utilizing α- and β-adrenergic blocking drugs and careful management of fluid balance.

Mineralocorticoid Hypertension

Aldosterone, the most abundant mineralocorticoid hormone, is synthesized by aldosterone synthase in the outer zone of the adrenal cortex (zona glomerulosa). Its synthesis and release are controlled by adrenocorticotropic hormone (ACTH), and blood levels peak in the early morning. Aldosterone blood levels are also increased by angiotensin II and lowered by an increased plasma potassium concentration. Aldosterone increases distal tubular reabsorption of sodium and chloride and secretion of potassium and hydrogen ions. Another mineralocorticoid hormone, deoxycorticosterone, produced by the inner zone of the adrenal cortex (zona fasciculata), is a much weaker mineralocorticoid than aldosterone, but it can cause hypertension when produced in large quantities.

The hypertension produced by mineralocorticoid excess is due to the increase in total exchangeable sodium, but many patients with chronic mineralocorticoid excess have normal plasma volume because the initial increase in extracellular fluid volume is restored to normal by an increased natriuresis and diuresis due to decreased sodium reabsorption in segments of the nephron other than the distal tubule (mineralocorticoid escape). The hypertension is sustained by increased vascular resistance (possibly due to augmented vascular sensitivity to catecholamines) or by central nervous system mineralocorticoid receptors, which activate the sympathetic nervous system.

Primary hyperaldosteronism (PA) [35, 36] is due either to a benign aldosterone-producing adenoma (APA) or, more rarely, to bilateral hyperplasia (BH). The classic clinical features of PA are hypertension, excessive urinary potassium excretion, hypokalemia (serum K^+ <3.5 mEq/L), hypernatremia (serum Na+ >145 mEq/L), and metabolic alkalosis. The 24-h urinary potassium excretion exceeds 30 mEq/day, and the plasma aldosterone will be high and the renin low. A hypertensive patient who is treated with diuretics or who has diarrhea may also have a low serum potassium concentration. In this situation, the serum potassium value returns to normal after recovery from the diarrhea or a few weeks after the diuretic is discontinued. Diuretics raise both PRA and aldosterone levels.

The morning ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA), the PAC: PRA ratio, is the screening test of choice for PA. A ratio of >20 with a PAC of at least 12 ng/dL should prompt confirmatory testing. A ratio > 70 with a PAC of ≥15 ng/dL and a PRA of ≤1 ng/mL/h is virtually diagnostic. Another test sometimes done to confirm the diagnosis is based on the failure of volume expansion to suppress aldosterone (plasma aldosterone is >10 ng/dL after 2 L normal saline iv over 4 h; alternatively, urinary aldosterone >12 mcg/24 h after 3 days of 4–6 g/day of sodium chloride orally). CT or MRI of the adrenal glands completes the workup. Bilateral adrenal venous sampling is a highly specialized procedure that may reveal a unilateral source of excess aldosterone.

Glucocorticoid Hypertension [37]

The principal glucocorticoid in humans, cortisol, is synthesized in the zona fasciculata under the control of ACTH. While cortisol has only a weak mineralocorticoid effect, the circulating levels of the hormone in Cushing's syndrome are usually hundreds of times the normal value. Since most patients with Cushing's syndrome, however, do not have other findings of hypermineralocorticoidism, particularly hypokalemia, and since spironolactone, a mineralocorticoid antagonist, does not blunt the hypertensive effect of cortisol, other mechanisms must be operating. Possibilities include the glucocorticoids activating the gene transcription of angiotensinogen in the liver or increasing vascular reactivity to vasoconstrictor amines or inhibition of the extraneuronal uptake and degradation of norepinephrine or inhibition of vasodilators such as endothelial nitric oxide, kinins, and some prostaglandins, or a shift of sodium from cells to the extracellular compartment with an increase in plasma volume and, thus, in cardiac output. Also, in Cushing's syndrome, the ACTH excess may stimulate production and release of endogenous mineralocorticoids, especially 11-deoxycorticosterone (Fig. 31.5).

Other Clinical Syndromes of Adrenocortical Hypertension [38, 39]

Glucocorticoid-Remediable Hyperaldosteronism (GRA)

GRA is an autosomal-dominant disorder in which the classic features of primary hyperaldosteronism are completely relieved by glucocorticoids such as dexamethasone. Because

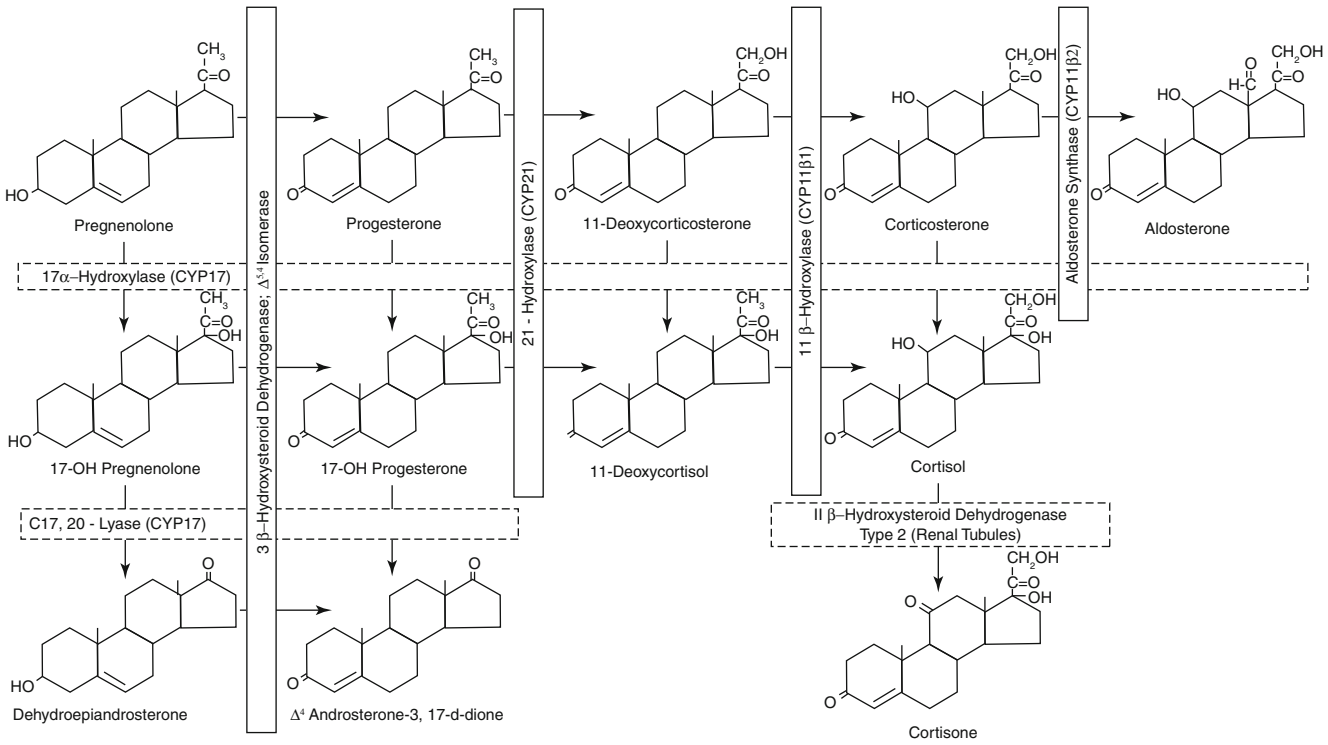

Fig. 31.5 Pathways of steroid biosynthesis in the adrenal cortex

dexamethasone suppresses ACTH, the concept was developed of increased adrenal sensitivity to the aldosterone-stimulating effects of ACTH. Recently, it has been shown that this syndrome is due to a chimeric gene produced by unequal crossing over of the 5′ regulatory region of 11β-hydroxylase (CYP11β1) and the 3′ coding sequence of aldosterone synthase (CYP11β2) (Fig. 31.5). As a result, aldosterone synthase, normally found in the zona glomerulosa, is expressed in the zona fasciculata under the control of the ACTH-sensitive 11β-hydroxylase regulatory sequence, which accounts for the aldosterone elevation and the excess formation of products of 11β-hydroxylase activity, such as cortisol. This was the first description of a gene mutation as a cause of hypertension in humans.

Pseudohyperaldosteronism (Liddle's Syndrome)

In 1963, Liddle described members of a family with hypertension and hypokalemic alkalosis who had low levels of aldosterone and no elevations of other mineralocorticoids. Treatment with the mineralocorticoid antagonist spironolactone or with other inhibitors of mineralocorticoid biosynthesis had no effect, but amiloride and triamterene, both inhibitors of distal nephron sodium reabsorption, improved hypertension and hypokalemia. Affected patients have a mutation of the β- or γ-subunits of the renal epithelial sodium channel that increases sodium reabsorption in the distal nephron.

11β-Hydroxylase (CYP11β1) Deficiency

11β-Hydroxylase converts 11-deoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol (Fig. 31.5). Deficiency of this enzyme leads to reduced cortisol levels, increased ACTH secretion, and increased production of 11-deoxycorticosterone in the zona fasciculata. The 11-deoxycorticosterone induces volume expansion and hypertension. The adrenal steroid pathway is also redirected toward androgen production so that these patients also have virilization, usually recognized in infancy.

17α-Hydroxylase (CYP17) Deficiency

17α-Hydroxylase converts pregnenolone to 17-hydroxypregnenolone, progesterone to 17-hydroxyprogesterone, 11-deoxycorticosterone to 11-deoxycortisol, and corticosterone to cortisol (Fig. 31.5). Deficiency of 17α-hydroxylase reduces cortisol levels, causing increased ACTH and increased 11-deoxycorticosterone, corticosterone, and aldosterone levels. There is an absence of sex hormones.

11β-Hydroxysteroid Dehydrogenase Type 2 Deficiency

The normal renal mineralocorticoid receptor binds glucocorticoids with a similar affinity to mineralocorticoids. The 11β-hydroxysteroid dehydrogenase type 2 isoform enzyme in the renal tubules normally converts the large amounts of fully active cortisol to the inactive cortisone (Fig. 31.5),

thereby leaving the renal mineralocorticoid receptors open to the effects of aldosterone. A deficiency of this enzyme in the kidney allows for high renal levels of cortisol, producing all of the features of the hypermineralocorticoid state but with low mineralocorticoid levels (the syndrome of *apparent mineralocorticoid excess*). An acquired form of this syndrome develops in adults who eat large quantities of licorice. The active alkaloid in licorice, glycyrrhetinic acid, is an inhibitor of 11β-hydroxysteroid dehydrogenase.

Miscellaneous Causes of Secondary Hypertension

Other causes of secondary hypertension include coarctation of the aorta, hypo- and hyperthyroidism, hyperparathyroidism, sleep apnea, brain tumors and increased intracranial pressure, erythropoietin, polycythemia, inappropriate antidiuretic hormone, and a host of drugs and other chemical agents, notably exogenous steroids, cyclosporine, tacrolimus, pseudoephedrine (in nasal decongestants), monoamine oxidase inhibitors, tricyclic antidepressants, nonsteroidal anti-inflammatory drugs, herbal remedies containing ephedrine, yohimbine, or licorice, and street drugs such as amphetamines and cocaine.

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