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Hypertension

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Hypertension is a common disease that contributes importantly to the high cardiovascular morbidity and mortality observed in industrialized countries. The proper diagnosis and management of this disorder affords considerable reduction of the risk of developing cardiac, cerebral, and renal complications. Approximately 95% of patients with high blood pressure exhibit the so-called essential or primary form of hypertension. Various mechanisms are involved in the pathogenesis of this type of hypertension. This heterogeneity accounts for the diverse therapeutic approaches that have been utilized and for the rationale for individualizing treatment programs. In a small fraction of patients, the elevation of blood pressure is due to a specific cause (secondary hypertension). The recognition of such patients has improved markedly in recent years. This is relevant since secondary hypertension can often be cured by appropriate interventions.

The diagnosis of hypertension has been based entirely on the demonstration of a measured blood pressure above the normal range of values. Although this measurement clearly identifies individuals at an increased risk of developing morbid cardiovascular events, the disease is not the blood pressure but rather is the vascular abnormality that results in these morbid events. Indeed, morbid vascular events occur in many individuals whose blood pressures are within the normal range, and many individuals with frankly elevated blood pressures do not experience morbid events. Consequently, there is a growing sense that measured blood pressure is not by itself an adequate marker for the presence of the vascular disease that requires aggressive treatment. Efforts to develop methods to assess more specifically the blood vessels that are the site of abnormality in hypertension are advancing to the point that such noninvasive measurements may now be introduced into clinical practice. These approaches, which can supplement pressure measurement, may eventually provide a more precise guide to the disease and its treatment. Nonetheless, we shall focus in this chapter on blood pressure, with full recognition that the disease represents a blood vessel abnormality and its treatment is aimed at preventing vascular events, not merely lowering an elevated pressure.

Pathophysiology

Monogenic Forms of Hypertension

The genetic and molecular basis of several mendelian, single-gene forms of hypertension has been identified recently.[1,2] The better understanding of the pathways involved in the pathogenesis of these rare forms of hypertension may help in the future to recognize new pathophysiologic mechanisms involved in the pathogenesis of essential hypertension. The well-defined monogenic, mendelian forms of hypertension are the glucocorticoid-remediable aldosteronism (GRA), the syndrome of apparent mineralocorticoid excess (AME), and the Liddle's syndrome (LS). Some characteristics of these diseases are given in Table 86.1.

Patients with GRA (autosomal dominant transmission) have a chimeric gene in the adrenal fasciculata encoding at the same time aldosterone synthase (the rate-limiting enzyme for aldosterone biosynthesis) and 11β-hydroxylase (an enzyme involved in cortisol biosynthesis), whose expression is regulated by adrenocorticotropic hormone (ACTH). In normal individuals, aldosterone synthase is found only in the adrenal glomerulosa. In patients with GRA, because aldosterone synthase is ectopically expressed, aldosterone secretion becomes dependent on ACTH. This form of hypertension is associated with hyperaldosteronism, and dexamethasone treatment, by suppressing ACTH secretion, reduces aldosterone secretion.

In patients with AME (autosomal recessive transmission) the enzyme 11β-hydroxysteroid dehydrogenase (type 2) is mutated, leading to an impaired aldosterone synthesis. This enzyme normally metabolizes cortisol (able to activate the mineralocorticoid receptor) to cortisone (devoid of mineralocorticoid activity). The impaired degradation of cortisol, therefore, leads to an increased activation of the mineralocorticoid receptor. Aldosterone secretion is suppressed.

The amiloride-sensitive epithelial Na^+ channel (ENaC) is a rate-limiting step of sodium reabsorption regulated by aldosterone. This channel is composed of three subunits (α, β, and γ). Patients with LS (autosomal dominant transmission) have mutations in genes encoding either the β or γ subunits,

TABLE 86.1. Principal characteristics of monogenic forms of hypertension

	Transmission	*Gene abnormality*	*Pathophysiologic mechanism*
GRA	Autosomal dominant	Chimeric gene encoding aldosterone synthase and 11β-hydroxylase	Increased ACTH-dependent secretion of aldosterone → salt and water retention
AME	Autosomal recessive	11β-hydroxysteroid dehydrogenase deficiency	Decreased metabolism of cortisol, increased activation of the mineralocorticoid receptor by cortisol → salt and water retention
LS	Autosomal dominant	Mutations in genes encoding either the β or γ subunits of the ENaC	Increased activity of the ENaC → salt and water retention

AME, syndrome of apparent mineralocorticoid excess; ENaC, amiloride sensitive epithelial Na^+ channel; GRA, glucocorticoid-remediable aldosteronism; LS, Liddle's syndrome.

with an ensuing hyperactivity of the channel (due to an increased number of channels because of a reduced clearance from the cell membrane).

Patients with GRA, AME, or LS are all retaining excessive sodium and water in the renal distal tubule, where mineralocorticoid receptors are located. This is associated with a loss of potassium in urine and a suppression of renin secretion due to the plasma volume expansion.

Several other rare mendelian forms of hypertension exist, such as pseudohypoaldosteronism type II (associated with hyperkalemia), hypertension with brachydactyly, and a syndrome of insulin resistance, diabetes mellitus, and high blood pressure linked with missense mutations in the peroxisome proliferator-activated receptor γ (PPARγ).

Essential Hypertension

Cardiovascular homeostasis is normally maintained by a close interplay between various mechanisms. In patients with essential hypertension, one or more of these mechanisms may be dysregulated, the imbalance manifesting by an increase in blood pressure (Fig. 86.1).

Familial Predisposition

There exists a clear familial aggregation of blood pressure. Newborns of hypertensive parents have higher blood pressures than those of normotensive parents, the difference becoming prominent in adolescents. Also, blood pressure correlates better between monozygotic than dizygotic twins. Finally, subjects with a positive family history of hypertension are particularly prone to develop hypertension. In most patients, hypertension seems to be polygenic. Most likely, specific genes interact with environmental factors to determine the expression of hypertension, with degrees of contribution depending possibly on sex, race, and age.[3,4] This view is compatible with the heterogeneous character of hypertension. The expression of some genes can be detected with the aid of specific biochemical markers. For instance, several membrane cation flux abnormalities are present in a fraction of prehypertensives and hypertensives as well as of their first-degree relatives (see Membrane Abnormalities). Another example is a low urinary kallikrein excretion in hypertension-prone families (see Decreased Activity of Vasodilating Systems, below). Also well established is a genetic influence on salt sensitivity of blood pressure (see Environmental Influences, below). Recently, an inherited character of hypertension has been recognized in patients presenting with high blood pressure, obesity, insulin resistance, and dyslipidemia (see Hyperinsulinemia, below).

Several tests may be clinically useful to identify normotensive persons genetically prone to develop future hypertension. They include an excessive blood pressure increase in response to physical exercise or mental arithmetic.[5,6] Searching for the expression of candidate genes of hypertension may help to detect persons susceptible to become hypertensive and to initiate early preventive treatment.[4] Conceivably, it may also provide better insight into the mechanisms responsible for the blood pressure elevation and allow for more rational therapeutics.

Specific mutations of several candidate genes seem to be positively related with essential hypertension. This is the case for variants in genes encoding angiotensinogen,[7,8] aldosterone synthase,[9] endothelial nitric oxide synthase,[10] and α-adductin, a cytoskeleton protein involved in cell membrane ion transport.[11]

Noteworthy, there exists in humans a polymorphism of angiotensin-converting enzyme (ACE) consisting of either

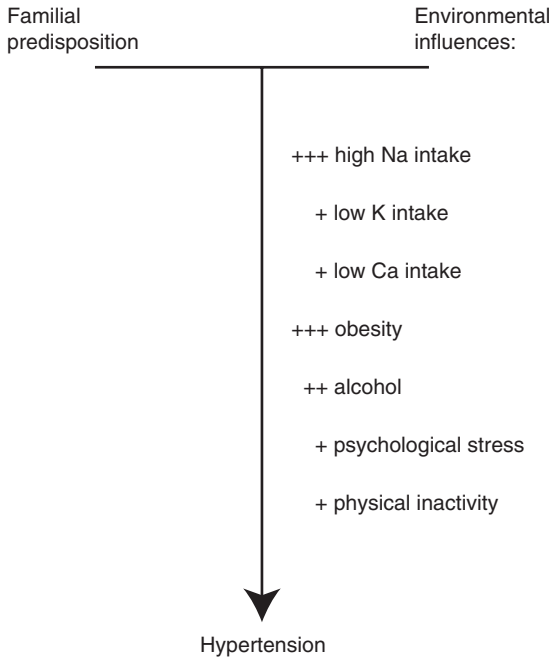


FIGURE 86.1. Schematic representation of the interaction between genetic and environmental factors in the pathogenesis of hypertension. The clinical relevance of the different environmental factors is rated from minor (+) to major (+++).

the absence (deletion, D) or the presence (insertion, I) of a 287-base-pair DNA fragment inside intron 16.[12] The DD and DI genotypes have been claimed to be associated with a higher risk of hypertension.[13,14]

A polymorphism in the gene encoding the angiotensin II type 1 receptor has also been described, but it is still unclear whether mutations in this gene are linked with high blood pressure.[15,16]

Finally, the ENaC gene was also studied in patients with essential hypertension. Co-segregation between mutations of this channel and high blood pressure was found in some, but not all, studies.[17,18]

Most studies performed so far have looked at the association of a variant of a candidate gene and hypertension. As discussed above, they failed to detect a mutation accounting for the abnormal blood pressure in a substantial fraction of the general population. It is hoped that genome scan studies will help to identify genes predisposing to essential hypertension.[19]

Environmental Influences

Sodium Intake

Among environmental factors known to influence blood pressure, salt intake holds a predominant position. Salt consumption can be assessed at best by measuring 24-hour urinary sodium excretion. Numerous epidemiologic studies have pointed to a positive association between dietary sodium chloride overload and the prevalence of hypertension.[20] This is particularly apparent in between-population studies, when comparing low-salt– with high-salt–consuming ethnic groups. A striking feature is the lack of blood pressure elevation with aging in nonindustrialized civilizations accustomed to eating less than 30 mmol sodium per day. Migration studies have also suggested a blood pressure raising effect of the sodium ion. Such studies are of great interest since migrant and nonmigrant communities have a similar genetic background. In contrast to between-population and migration studies, most within-population studies have not found any close relationship between blood pressure and sodium intake. Only a 2.2 mm Hg difference in systolic blood pressure can be expected for a difference of 100 mmol sodium per day.[21] The susceptibility to increased blood pressure in response to sodium loading is highly variable. The salt sensitivity of blood pressure has a familial character and can be evidenced already in the prehypertensive state.[22] Low birth weight has been associated with elevated blood pressure in children and with hypertension in adult.[23] This association may be due to an inborn deficit in nephron number and an ensuing increased renal retention of sodium.[24]

In Western societies, sodium intake is generally between 150 and 250 mmol per day. Individuals becoming hypertensive on such a diet represent presumably salt-sensitive persons. Notably, black individuals exhibit increased propensity to sodium and water conservation, possibly as a consequence of an augmented activity of Na-K-2Cl cotransport in the thick ascending limb of Henle's loop.[25]

Recently a systematic review of genetic polymorphisms in salt sensitivity of blood pressure has been performed.[26] Only a variant of the α-adductin gene was found consistently associated with a sodium-sensitive form of hypertension.

Potassium Intake

The day-to-day variation in potassium intake is larger than that in sodium. Potassium consumption can be evaluated by performing either a 24-hour dietary recall or by measuring 24-hour urinary electrolyte excretion. Migration as well as between- and within-population studies have shown an inverse relationship between potassium intake and the prevalence of hypertension.[27] Black subjects ingest less potassium than white subjects. This may partly explain the tendency for more severe hypertension observed in the former. Actually, low potassium intake may contribute to salt sensitivity.[25,28]

The potassium ion is located fundamentally in the intracellular compartment. Relevantly, erythrocyte potassium content is decreased in patients with essential hypertension.[29]

Calcium Intake

The prevalence of hypertension is higher in geographic areas supplied with "soft" water (i.e., water containing only a limited amount of calcium). Population data indicate that the lower the dietary calcium intake, the greater the likelihood of becoming hypertensive.[30]

Obesity

There is a strong positive correlation between body fat and blood pressure levels, and human obesity and hypertension frequently coexist.[31] Excess weight gain is a consistent predictor for subsequent development of hypertension.[32] The prevalence of hypertension is greater in persons with central, abdominal obesity, as reflected by a high waist-to-hip ratio, than in those with peripheral, gluteal fat and a low waist-to-hip ratio. Hypertension in the obese with fat accumulation in the upper body segments is often associated with insulin resistance, diabetes, and dyslipidemia (see Hyperinsulinemia, below).

Obesity may cause hypertension by various mechanisms.[33–36] An activation of sympathetic nerve activity leading to renal sodium retention seems to play a pivotal role. Hyperleptinemia and hyperinsulinemia represent two mechanisms by which obesity might increase sympathetic nerve activity. Other factors possibly contributing to renal sodium retention in obesity are increased angiotensin II and aldosterone production and raised intrarenal pressures caused by fat surrounding the kidneys.

Alcohol

Regular consumption of more than 30 g/day ethanol is linked with an increased prevalence of hypertension.[37] It is, however, still unclear whether smaller amounts exert a pressor effect. The risk of developing hypertension is predominant when alcohol is taken separately from food, but no consistent association with hypertension risk exists between the beverage types.[38]

Psychological Stress

Behavioral factors are often believed to play a pathogenic role in the development of hypertension.[39] Mental stress can undoubtedly elicit pressor responses. General life event stress, and especially occupational stress, may contribute to sustained hypertension.[40] The blood pressure reactivity to

environmental stimuli seems to be related to personality traits, being exaggerated, for instance, in type A individuals, that is, patients who display a high degree of competitiveness, aggressiveness, impatience, and a striving for achievement.[41] Violence exposure, defined as experiencing, witnessing, or hearing about violence in the home, school, or neighborhood, represents also a risk for developing high blood pressure.[42]

Physical Inactivity

A number of epidemiologic studies have demonstrated an inverse relationship between estimates of physical activity and blood pressure levels.[43] In many studies, however, this association between physical activity and blood pressure disappeared after adjustment for body mass index, probably because physically fit people are usually less obese than persons not exposed to a regular physical activity. There is, however, convincing evidence indicating that high levels of leisure-time physical activity reduces the risk of hypertension independently of most confounding factors, including body weight.[44]

Increased Activity of Vasoconstrictor Systems

Sympathetic Nervous System

The sympathetic nervous system plays a pivotal role in the regulation of vascular tone. It modulates the cardiac output and peripheral vascular resistance, the two determinants of blood pressure. Norepinephrine released by adrenergic nerve endings causes an arterial and venous constriction via activation of postsynaptic α_1- and α_2-receptors (Fig. 86.2). The resulting increase in arteriolar tone is responsible for a blood pressure elevation. β_2-adrenergic receptors are also found postsynaptically. Activation of these receptors leads to vasorelaxation. Cardiac output may be augmented in response to sympathetic stimulation because of an increased venous return and β_1-adrenergic receptor-mediated direct inotropic and chronotropic effects. Sympathetic effects are mediated by epinephrine, predominantly released from the adrenal medulla, and norepinephrine, released into the synaptic cleft from sympathetic nerve endings. Epinephrine, therefore, largely circulates as a hormone, whereas circulating norepinephrine represents the overflow of a local hormone whose site of action is largely on receptors exposed to the synaptic cleft. Presynaptic activation of β_2-receptors facilitates the neurotransmitter release, whereas this process is inhibited by activation of prejunctional α_2-adrenergic receptors. The activity of the sympathetic nervous system is under the control of brain areas involved in cardiovascular homeostasis, for example, brainstem centers governing reflex responses. These cardiovascular centers receive afferent neurons from peripheral cardiopulmonary and arterial baroreceptors and adjust actively the sympathoadrenal outflow.

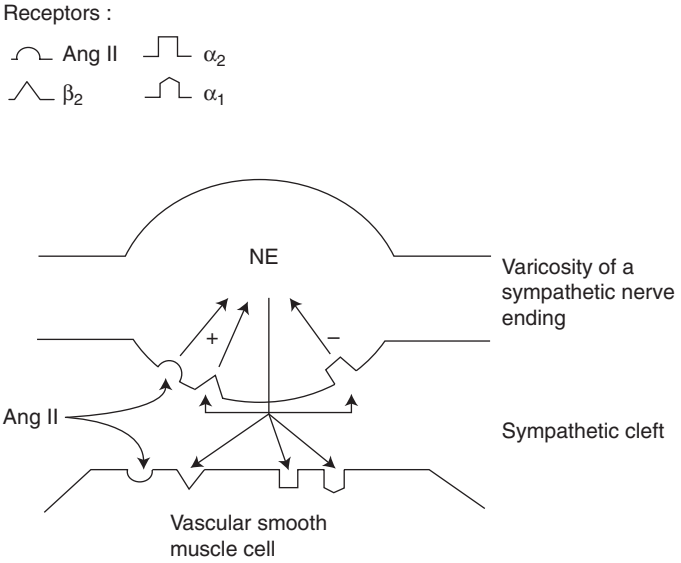


FIGURE 86.2. Presynaptic regulation of norepinephrine release. A positive feedback is exerted by the stimulation of β_2-adrenergic receptors and angiotensin II (Ang II) receptors, and a negative feedback by activation of α_2-adrenoceptors. Postsynaptically, the stimulation of α_1- and α_2-adrenoceptors, as well as that of Ang II receptors causes a vasoconstriction, whereas the stimulation of β_2-adrenoceptors induces a vasodilation.

Clinical evaluation of the neurogenic component of hypertension is difficult.[45] Plasma norepinephrine concentrations are elevated in only a fraction of patients with high blood pressure.[46] Increased levels are observed mainly in younger patients with borderline hypertension, a "hyperkinetic" form of hypertension associated with a high cardiac output.[47] In older patients with established hypertension, cardiac output is no longer elevated, and there is generally no evidence for a causal sympathetic component, at least as assessed by plasma norepinephrine determination. The norepinephrine concentration in the circulation, however, does not necessarily reflect the actual concentration prevailing in the vicinity of pre- and postjunctional adrenergic receptors.[48]

Direct evidence for a neurogenic hyperactivity in hypertensives has been provided by recording peripheral sympathetic drive.[49] Also, spectral analysis of the heart rate variability has suggested enhanced sympathetic and reduced vagal activities in hypertensive patients.[50]

Several dysfunctions of the sympathetic nervous system have been described in hypertensive patients.[45,51–53] Neurogenic factors may contribute to the enhanced peripheral vascular resistance in patients with sustained hypertension because of an increased arteriolar responsiveness to α-adrenergic receptor stimulation. As already pointed out (see Environmental Influences, above), some patients have a genetically linked hyperresponsiveness to ordinary daily psychosocial stimuli or to exaggerated salt intake. Centrally mediated reinforcement of sympathetic nerve activity may contribute to the elevation of blood pressure seen in these patients. Another abnormality involving the central nervous system seems to be an impaired baroreceptor reflex sensitivity, which might be accompanied in hypertensive patients by an enhanced blood pressure variability. Hypertension might also be associated with alterations of β-adrenergic receptors. Young patients with borderline or mild hypertension frequently present with increased heart rate, cardiac output, and forearm blood flow, which points to an enhanced involvement of β-adrenergic receptors. This could be attributed to a heightened density of β-adrenergic receptors or to a hyperresponsiveness of these receptors. Speculatively, as hypertension becomes established, a functional uncoupling of the

β-adrenergic receptor activation from the cellular response could occur, which might be manifest by a greater α-adrenergic receptor-mediated vasoconstriction.

Epinephrine is also a vasoconstrictor potentially contributing to the genesis of hypertension.[54] Plasma levels of this catecholamine are often elevated in patients with borderline or mild hypertension. Epinephrine may act principally by stimulating presynaptic β_2-adrenergic receptors and thereby augmenting the discharge of norepinephrine. Genetic factors might be involved in neurogenic hypertension, as suggested by the finding of variants of the β_2-adrenoceptor.[55]

Renin-Angiotensin-Aldosterone System

Activation of the renin-angiotensin system starts with renin secretion from the kidney and culminates in the formation of angiotensin II (Fig. 86.3). Renin is a proteolytic enzyme, initially synthesized as prorenin, cleaving off the decapeptide angiotensin I from angiotensinogen, a protein substrate produced by the liver and circulating in the blood. Angiotensin I is devoid of any vasoactive effect; a converting enzyme splits it into two fragments of which the larger, an octapeptide, represents the final hormone angiotensin II.[56] The angiotensin-converting enzyme (ACE) is also called kininase II, because it is one of the enzymes physiologically involved in breaking down bradykinin, a vasodilating peptide. Most of the angiotensin I is converted to angiotensin II during its passage through the pulmonary circulation, but ACE is ubiquitously present at the surface of endothelial cells.[57] Moreover, the enzyme is found in the circulation. Non–ACE-dependent pathways can also transform angiotensin I into angiotensin II. This can be done, for example, in humans by chymase,[58] a chymotrypsin-like proteinase present not only in mast cells, but also in the heart and blood vessels.[59,60] Notably, there seems to exist in the vasculature all the components required for the generation of angiotensin II, including renin and angiotensinogen. Tissue angiotensin II generation appears, however, to depend mainly on renin and angiotensinogen originating from the circulation and to occur outside rather than inside the cells.[61]

Two subtypes of angiotensin II receptors have been characterized in humans: AT_1- and AT_2. Stimulation of the AT_1-receptor is responsible for all main effects of angiotensin II (Fig. 86.4).[62–66] The AT_1-receptor has been cloned and sequenced. It is G-protein coupled and contains 359 amino acids. Angiotensin II can increase blood pressure by several mechanisms. It is a potent vasoconstrictor, stimulates aldosterone release from the adrenal glomerulosa, has a direct salt-retaining effect on the renal proximal tubule (see Renal Sodium Retention, below) and reinforces the neurogenic-controlled vascular tone (see Sympathetic Nervous System, above). Angiotensin II interacts with the peripheral sympathetic nervous system by activating receptors located on sympathetic nerve endings to facilitate norepinephrine release. Postsynaptically, it may enhance the contractile response to α-adrenergic receptor stimulation. Circulating angiotensin II may also reach brainstem cardiovascular centers through areas devoid of tight blood–brain barrier, thereby increasing sympathetic efferent activity. Other effects of AT_1-receptor stimulation are an activation of vascular and cardiac growth, an enhanced collagen synthesis, and a suppression of renin release. An important effect mediated by the AT_1-receptor is the activation of membrane reduced nicotinamide adenine dinucleotide (phosphate) [NAD(P)H] oxidase, increasing thereby the generation of reactive oxygen species in the vasculature and facilitating by this mechanism the atherosclerotic process.[67] Activation of AT_1-receptor also induces a procoagulant state by stimulating the formation of plasminogen-activator (PAI-1) by endothelial cells. Regarding the vascular and cardiac effects of AT_2-receptor stimulation, they seem to counterbalance those exerted by the AT_1-receptor.[62,66,68,69] The vasodilation induced by the stimulation of the AT_2-receptor may involve bradykinin and nitric oxide (NO) (see Kallikrein-Kinin System, below).[70]

In a majority of patients with essential hypertension, renin secretion ranges, for a given state of sodium balance, within the same limits as those established in normotensive subjects. In approximately 15% of the patients, however, plasma renin activity is higher than normal, whereas in roughly 25% renin release is reduced.[71] Renin secretion is increased by sodium depletion and suppressed by sodium loading. In a given hypertensive patient, the contribution of angiotensin II to the maintenance of high blood pressure is

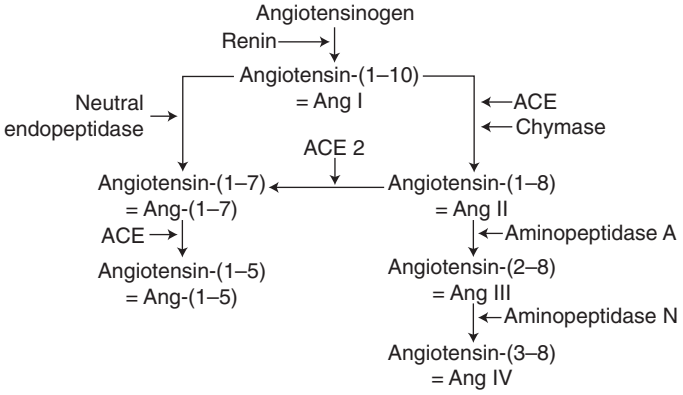


FIGURE 86.3. Components of the renin-angiotensin system. ACE, angiotensin converting enzyme.

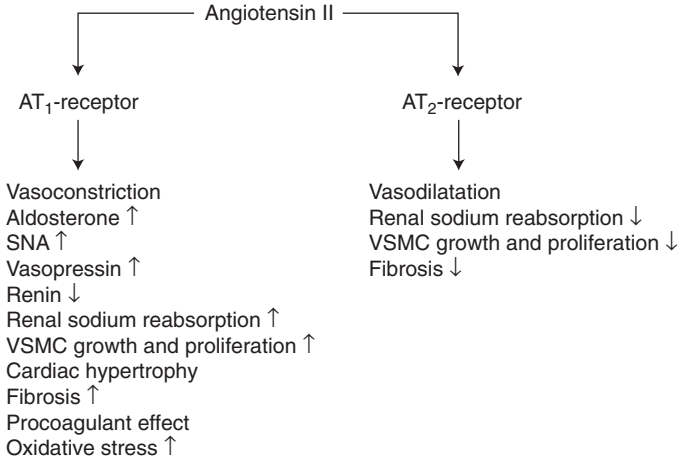


FIGURE 86.4. Main effects of angiotensin II mediated by stimulation of the AT_1– and AT_2–receptors. SNA, sympathetic nerve activity; VSMC, vascular smooth muscle cell.

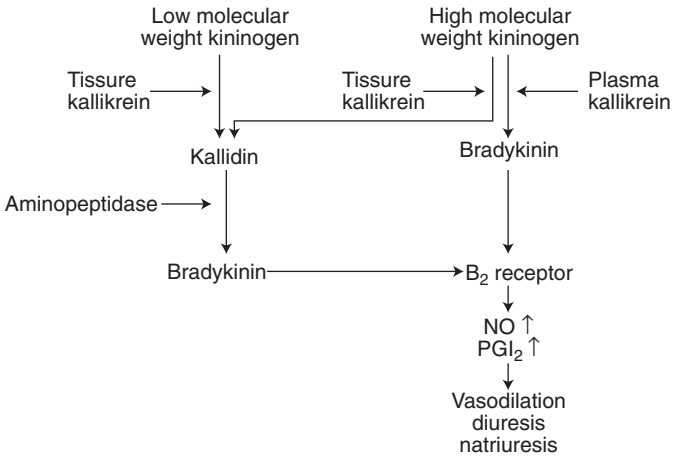


FIGURE 86.5. Components and actions of the kallikrein-kinin system. NO, nitric oxide; PGI_2, prostacyclin.

thus augmented by shifting from a high- to a low-sodium diet.[72] Activation of β-adrenergic receptors triggers the release of renin from juxtaglomerular cells. In the early phase of hypertension, the high renin levels may be secondary to an increased autonomic activity.[73] Renin secretion decreases with age, both in normotensive and hypertensive people, reflecting presumably a sodium retention associated with a progressive decline in functional nephrons.[74] Racial differences exist with regard to renin secretion. Thus, plasma renin activity is generally lower in blacks than in whites.[75]

Until recently the octapeptide angiotensin II [angiotensin-(1–8)] was thought to be the only active component of the renin-angiotensin system. It now appears that an angiotensin II–derived peptide [angiotensin-(1–7)] binds to a specific receptor to cause a vasorelaxation.[76–78] Angiotensin-(1–7) can be directly generated from angiotensin I under the action of neutral endopeptidase and from angiotensin-(1–8) under the action of different peptidases, including a membrane-bound ACE-related carboxypeptidase (ACE2) expressed mainly in the heart and the kidney, an enzyme whose activity is not blocked by ACE inhibitors.[79,80]

Aldosterone is classically considered to play a pivotal role in modulating circulatory volume by retaining sodium in the kidney. Activation of mineralocorticoid receptors by this hormone may also contribute to the development of cardiac hypertrophy and fibrosis.[81]

Decreased Activity of Vasodilating Systems

Kallikrein-Kinin System

The basic elements of the kallikrein-kinin system consist of proteases (kallikreins) that release kinins from precursor proteins (kininogen).[82,83] There are two kinds of kallikrein, namely, plasma and tissue kallikrein (kininogenases) (Fig. 86.5). Plasma kallikrein produces the nonapeptide bradykinin from a high molecular weight kininogen, whereas tissue kallikrein cleaves both low and high molecular weight kininogen to generate the decapeptide kallidin, the latter being then processed to bradykinin. The stimulation of the bradykinin B2-receptor causes the release from the endothelium of NO (see Endothelial Dysfunction, below) and prostacyclin (PGI_2) (see Prostaglandins, below). In the kidney, kinins have a natriuretic effect, which is presumably NO- and prostaglandin-mediated. Mineralocorticoids, prostaglandins, and a high sodium intake increase urinary kallikrein excretion.

The plasma kallikrein-kinin system is involved mainly in the local regulation of vascular tone and blood flow. During infusion of bradykinin in hypertensive patients, extremely high concentrations of the peptide have to be reached to reduce systemic blood pressure.[84] An abnormality in the activity of the renal kallikrein-kinin system is plausible in hypertension. Urinary kallikrein excretion is often lessened in hypertensive patients, but a causal relationship between a decreased intrarenal formation of kinins and the abnormal elevation of blood pressure has still not been proven. As already mentioned in this chapter (see Familial Predisposition, above) a deficiency in urinary kallikrein has been recognized as a strong marker of a genetic component of essential hypertension.

Interestingly, a close interplay exists between the renin-angiotensin and the kallikrein-kinin systems.[80,85] AT_2-receptor stimulation may activate kininogenase activity, leading to the generation of kinins.[86,87] Moreover plasma kallikrein has been implicated in the activation of prorenin.[88]

Atrial Natriuretic and Brain Natriuretic Peptides

Atrial natriuretic peptide (ANP) is a 28-amino-acid residue that is released into the circulation by cardiac atria.[89–91] It possesses diuretic, natriuretic, and vasodilatory properties (Fig. 86.6). It also exerts an inhibitory action on aldosterone, renin, and vasopressin release. Moreover, this peptide decreases sympathetic nerve activity, produces a shift of fluid from the vascular space to the extravascular compartment, and has an antigrowth activity. Atrial natriuretic peptide is secreted mainly as a result of atrial stretching. Raised ANP plasma levels have been described in a fraction of patients with essential hypertension, but a role for atrial distention in the genesis of the elevated levels has not been established. Blood volume is generally not expanded in such patients, but it is possible that, due to a greater venous return, a shift of blood to the thorax occurs, with an ensuing increase in central blood volume. Evidence for an enhanced venous tone in essential hypertensive patients has been presented.[92] Furthermore, enlarged atria have been demonstrated by echocardiography in hypertensive persons with elevated plasma ANP levels, which can be taken as an argu-

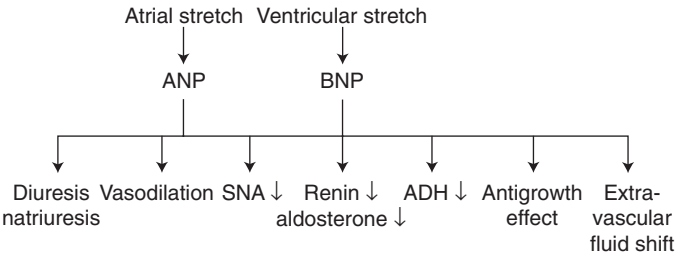


FIGURE 86.6. The atrial natriuretic peptide (ANP) and the brain natriuretic peptide (BNP) are secreted in the circulation in response to atrial and ventricular stretch, respectively. These hormones then act on target organs to lower blood pressure and decrease total body sodium. ADH, antidiuretic hormone; SNA, sympathetic nerve activity.

ment in favor of atrial distention as a major stimulus for ANP release.[93] This finding is also compatible with the increased central venous pressures measured in some hypertensive patients.[94] Plasma ANP levels have been repeatedly shown to increase in response to sodium loading, in both normotensive and hypertensive persons. The propensity of ANP to increase during exposure to a high dietary intake appears to be blunted in normotensive individuals with a family history of hypertension, suggesting a link between this hereditary disturbance and the predisposition to future hypertension.[95]

Brain natriuretic peptide (BNP) is a 32-amino-acid peptide structurally related to ANP that is synthesized mainly by myocytes of the left ventricle subjected to an increased wall tension.[96] The actions of BNP are similar to those of ANP. Plasma concentrations of BNP are raised in a variety of conditions, particularly where cardiac chamber stress is increased, for instance in patients with diastolic or systolic diastolic dysfunction, as well as in patients with primary aldosteronism or renal failure.[97]

Prostaglandins

Arachidonic acid is the precursor of prostaglandins. It is released from phospholipids contained in cell membranes under the action of phospholipase A_2 (Fig. 86.7). Activation of this enzyme may result from a variety of stimuli, including angiotensin II, norepinephrine, and bradykinin. Arachidonic acid is then converted to prostaglandins by the cyclooxygenases COX-1 and COX-2.[98] Both enzymes are involved in physiologic and pathophysiologic processes. The main prostaglandins involved in cardiovascular regulation are prostaglandin E_2 (PGE_2, a vasodilator), thromboxane A_2 (TxA_2, a proaggregatory vasoconstrictor), and prostacyclin (PGI_2, an antiaggregatory vasodilator). Prostaglandins are rapidly destroyed by local metabolism. It is unlikely that these substances play a major role away from the site of their synthesis. Vasodilatory prostaglandins not only possess direct relaxant properties, but also attenuate the vasoconstrictor effect of angiotensin II and norepinephrine. PGI_2 and PGE_2, via a presynaptic effect, diminish the release of norepinephrine induced by sympathetic nerve stimulation. Both prostaglandins have a stimulatory effect on renin release. The renin response to salt restriction is regulated mainly by COX-2.[99] In the kidneys, prostaglandin-related mechanisms seem to participate also in the regulation of renal perfusion and blood flow distribution. PGE_2 is believed to be the main prostaglandin synthesized in the kidney. It can promote water and sodium excretion and might mediate, at least in part, the renal effects of kinins. In the endothelium the production of PGI_2 depends primarily on COX-2. In platelets the only isoform present is COX-1, which leads to the synthesis of TXA_2.

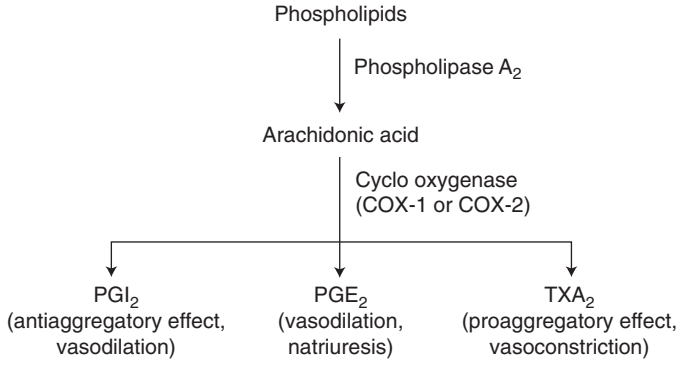


FIGURE 86.7. Steps in prostaglandin synthesis. COX-1 and COX-2, cyclooxygenase-1 and -2; PGI_2, prostacyclin; TXA_2, thromboxane A_2; PGE_2 prostaglandin E_2.

A deficiency in vasodilatory prostaglandins seems to exist in patients with essential hypertension.[100] This is suggested by the finding of a reduced urinary excretion of PGE_2 and 6-keto-PGF_1 (the stable metabolite of PGI_2) in some hypertensive patients. On the other hand, there is evidence for an increased production of TxA_2 in essential hypertension.[101] These observations, therefore, point to an imbalance between anti- and prohypertensive prostaglandins as a possible pathogenic factor of hypertension.

Renal Sodium Retention

Salt accumulation in the body is one of the principal mechanisms contributing to the development of essential hypertension. As already discussed, all major determinants of blood pressure control can influence, in one way or another, renal sodium handling, serving mainly for short-term adjustments of sodium balance. This is the case, for instance, with the sympathetic nervous system and the renin-angiotensin-aldosterone system, which both induce sodium retention. The kidneys also have a key role in controlling the long-term arterial pressure level because of their intrinsic ability to respond to an elevation in blood pressure by an increase in fluid excretion.[102] The so-called pressure diuresis-natriuresis encourages the return of high blood pressure to normal. Any dysfunction in this renal-volume mechanism for blood pressure homeostasis could lead to hypertension. In fact, this mechanism is still operating in hypertensive patients, but at higher blood pressure values and in the presence of a volume overload. During the initial phase of hypertension cardiac output is usually high, maybe as a consequence of a subtle increase in blood volume and venous return (Fig. 86.8). With time, high cardiac output hypertension might be converted to high peripheral resistance hypertension. This phenomenon could be accounted for by a whole-body autoregulation. This means that blood vessels in the tissues would be able to progressively adapt to protect against a high cardiac output–associated local hyperperfusion. This can be done not only by increasing the vascular tone, but also by inducing structural changes, which is translated by a reduction in the lumen diameter or by decreasing the tissue vascularity.[103,104] At this late stage, the high blood pressure is due primarily to an increase in total peripheral resistance, the cardiac output being generally normal again because of nervous reflex responses. The pressure diuresis-natriuresis mechanism is still operating, but with a higher blood pressure for a given urinary sodium and water excretion. About one half of patients with essential hypertension increase their blood pressure during the shift from a low- to a high-sodium intake.[105] These salt-sensitive patients with a difficulty in handling sodium often have a positive family history for hypertension.

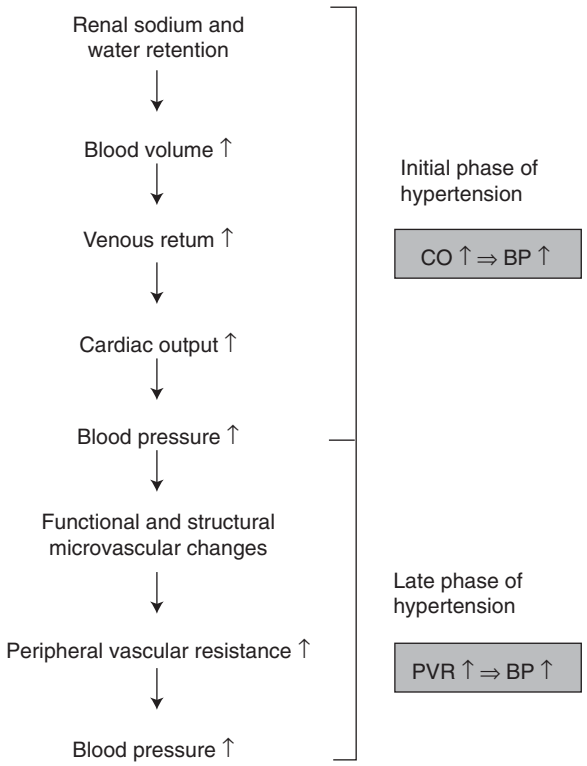


FIGURE 86.8. Sequence of events leading from a high cardiac output to a high vascular resistance hypertension. CO, cardiac output; BP, blood pressure; PVR, peripheral vascular resistance.

Hyperinsulinemia

Hypertension, visceral obesity (increased waist-to-hip ratio or increased abdominal circumference), dyslipidemia [low high-density lipoprotein (HDL) cholesterol], and glucose intolerance represent a cluster of cardiovascular risk factors that are often associated (known as metabolic syndrome) and are known to augment considerably the incidence of cardiovascular complications.[33,106–108] The criteria proposed by a panel of experts to diagnose the metabolic syndrome are summarized in Table 86.2.[109] As many as 25% of adults living in the United States fulfill such simple criteria.[110] The different disorders encountered in the metabolic syndrome not only might coexist incidentally, but also could be the direct consequence of a common disturbance. In this respect, resistance of peripheral tissues to the action of insulin may play a pivotal role. Hypertensive patients often exhibit some degree of hyperinsulinemia. The excessive production of insulin may by itself lead to an increase in blood pressure; insulin causes a renal sodium reabsorption, has a stimulatory effect on the sympathetic nervous system, and constitutes a growth factor (see Vascular Structural Changes, below). The hyperinsulinemia-associated hypertension has a strong genetic component.

Several factors might be implicated in the pathogenesis of insulin resistance. Plasma free fatty acid concentrations are frequently increased in patients with metabolic syndrome.[111] Elevated free fatty acids have an inhibitory effect on insulin signaling, resulting in a reduction in insulin-stimulated glucose muscle transport. Also, the adipose tissue produces a number of proteins, called adipocytokines, that might either improve (adiponectin) or impair [tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6)] insulin sensitivity.[112,113] Notably, adiponectin secretion is reduced in subjects with visceral obesity, while that of TNF-α and IL-6 is increased. Insulin-resistance may also be linked to endothelial dysfunction.[114]

TABLE 86.2. Clinical identification of the metabolic syndrome according to the Adult Treatment Panel (ATP III) criteria

Abdominal obesity	
Men	>102 cm
Women	>88 cm
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥6.1 mmol/L (≥110 mg/dL)
Fasting triglycerides	≥1.7 mmol/L (≥150 mg/dL)
HDL-cholesterol	
Men	<1.04 mmol/L (<40 mg/dL)
Women	<1.3 mmol/L (<50 mg/dL)

Diagnosis of the metabolic syndrome is made when three or more of the risk determinants are present.

Endothelial Dysfunction

The endothelium has a strategic position in the cardiovascular system, being located between the blood and the vasculature, and produces a variety of vasoactive factors.[115,116] One of the most important of them is nitric oxide (NO), known also as endothelium-derived relaxing factor (EDRF), which possesses potent vasorelaxant properties. It is released from the endothelial cell in response to physical stimuli (shear stress, hypoxia), as well as to the activation of endothelial receptors. It is synthesized from l-arginine by a nitric oxide synthase, an enzyme present constitutively in endothelial cells (Fig. 86.9). Thus, the acetylcholine- and bradykinin-mediated vasodilation is endothelium-dependent. The crucial role of NO is illustrated by the fact that acetylcholine, in the absence of endothelium, is a vasoconstrictor rather than a vasodilator. Nitric oxide release is also stimulated by activa-

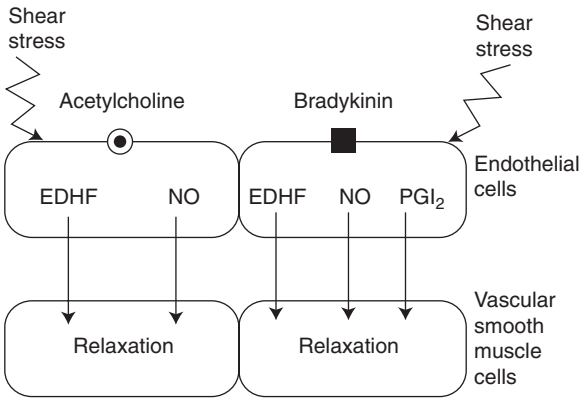


FIGURE 86.9. Schematic representation of the vasorelaxing factors released by the endothelium. EDHF, endothelium-derived hypopolarizing factor; NO, nitric oxide, PGI_2, prostacyclin.

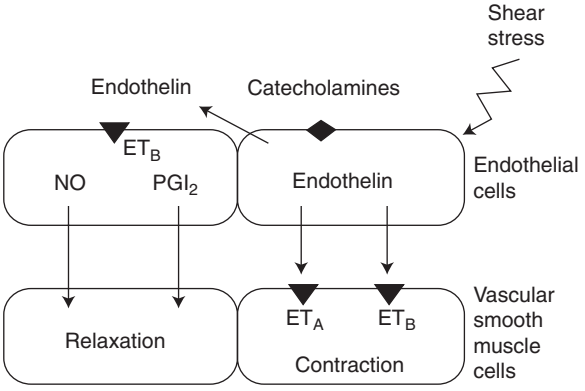


FIGURE 86.10. Schematic representation of the effects of endothelin. NO, nitric oxide; PGI_2, prostacyclin; ET_A and ET_B, subtypes of endothelin receptors.

tion of endothelial α-adrenergic and endothelin receptors, allowing the attenuation the contractile response of vascular smooth muscle cells. Nitric oxide also inhibits platelet aggregation, leukocyte adhesion, and vascular smooth muscle cell proliferation.[117] Vasorelaxant factors other than NO can be formed by the endothelium, in particular PGI_2 (see Prostaglandins, above), which is co-released with NO in response to bradykinin, and the endothelium-derived hyperpolarizing factor (EDHF).[116] The EDHF activity may be either contact-mediated (transfer of electrical current from endothelial to vascular smooth muscle cells via myoendothelial gap junctions) or related to the diffusion of factors from the endothelium, the potassium ion notably.[118,119]

The endothelium also produces the most potent endogenous vasoconstrictor known so far, a 21-amino-acid peptide called endothelin (Fig. 86.10).[120] This peptide comes from a precursor (big endothelin) upon the action of an endothelin-converting enzyme. Stimuli of endothelin release include the shear stress, thrombin, angiotensin II, vasopressin, and catecholamines. Stimulation of endothelin (ET) receptors located on the endothelium (ETB receptors) causes the release of NO and PGI_2. The vasoconstrictor effect of endothelin is due to the activation of ETA and ETB receptors present in the vasculature. The contractile response to endothelin is markedly blunted by NO, but is considerably enhanced by other vasoconstrictors.

Endothelium dysfunction, defined as a deranged vasodilatory capacity, is present in many hypertensive patients, as indicated by an impaired vasodilatory response to acetylcholine in different vascular beds.[121,122] Part of the endothelial dysfunction may be due to an increased oxidative stress leading to loss of NO bioactivity because of the generation of peroxynitrite.[123] An endothelium dysfunction seems to be frequently associated in hypertensive patients with the DD polymorphism of ACE gene.[124] Regarding circulating levels of endothelin, consistent augmentations have been reported only in patients with severe hypertension, but plasma endothelin levels do not necessarily reflect the local concentrations achieved at the surface of vascular smooth muscle cells.[125] In addition there might be an enhanced contractile effect of endothelin along with the diminished availability of NO.[126]

Abnormalities in Signal Transduction

The tone of vascular smooth muscle cells increases in response to a rise in cytosolic free calcium.[127] The calcium ion can enter into the cell through either voltage-operated or receptor-regulated calcium channels. The former respond to the depolarization of the cell membrane and the latter to the ligand-receptor interaction. The principal agonists thought to play a role in the pathogenesis of hypertension are coupled to G-protein receptors (α-adrenergic receptor stimulants, angiotensin II, endothelin, vasopressin, and TxA_2).[128,129] The cytosolic part of these receptors is connected through a G-protein to phospholipase C (PLC). Upon stimulation with the ligand—for instance, the AT_1 receptor with angiotensin II—PLC becomes activated, leading to the hydrolysis of phosphatidylinositol-4,5-biphosphate into diacylglycerol (DAG) and inositol triphosphate (Ins-1,4,5-P_3) (Fig. 86.11). Diacylglycerol activates protein kinase C (PKC) within the membrane, thereby facilitating a number of cellular functions. Ins-1,4,5-P_3 diffuses into the cytosol and activates specific receptors from endoplasmic reticulum, causing the release of calcium necessary for the mediation of the angiotensin II effects. The rapid calcium mobilization by this pathway then stimulates a sustained entry of calcium into the cell. In the vascular smooth muscle cell, the calcium ion bonds to calcium-binding proteins. The resulting complex activates a myosin light chain kinase (MLCK); the myosin filaments are phosphorylated and interact with actin filaments to generate a contraction. Whether alterations in this second messenger system contribute to the pathogenesis of hypertension remains to be elucidated. This is conceivable considering the fact that the basal and agonist-stimulated intracellular free calcium concentration is increased in platelets from hypertensive patients.[130]

The vasorelaxation resulting from β-adrenergic receptor stimulation is mediated by the intracellular formation of cyclic adenosine monophosphate (cAMP) (Fig. 86.12). The

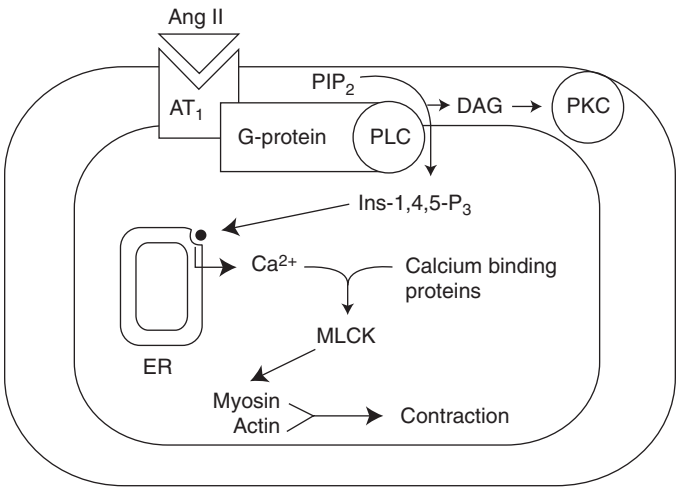


FIGURE 86.11. Schematic representation of the mode of action of angiotensin II (Ang II) in vascular smooth muscle cells. AT_1, AT_1–subtype of angiotensin II receptor; PLC, phospholipase C; PKC, protein kinase C; PIP_2, phosphatidylinositol-4,5–biphosphate; DAG, 1,2–diacylglycerol; Ins-1,4,5–P_3, inositol-1,4,5–triphosphate; ER, endoplasmic reticulum; MLCK, myosin light chain kinase.

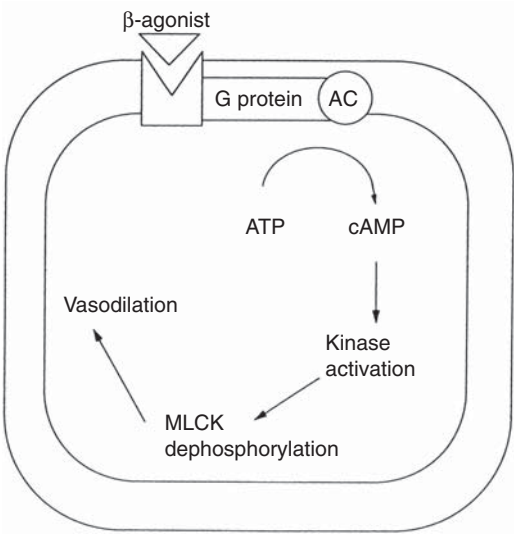


FIGURE 86.12. Schematic representation of the mode of the cellular mechanisms involved in the β-adrenergic receptor-induced vasodilation. AC, adenylate cyclase; MLCK, myosin light chain kinase.

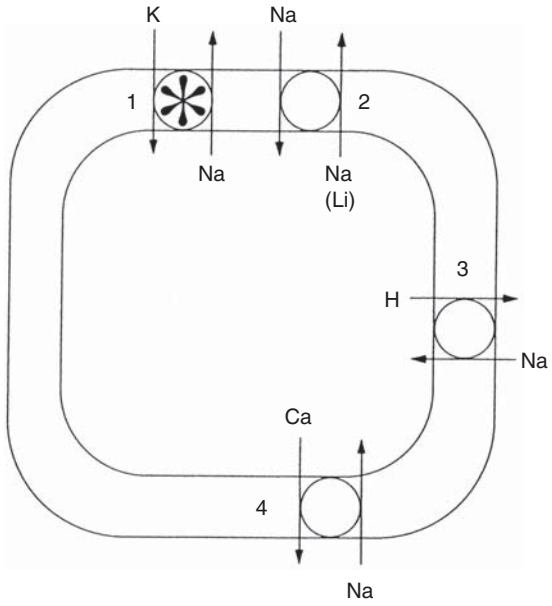
ligand-receptor interaction activates a stimulatory G protein. During this process, the guanosine triphosphatase (GTPase) activity of a G-protein subunit is modified, permitting the replacement of the bound guanosine diphosphate (GDP) by guanosine triphosphate (GTP). This leads to the activation of adenylate cyclase and thereby to the generation of cAMP from adenosine triphosphate (ATP). This second messenger activates specific protein kinase, with subsequent dephosphorylation of MLCK and reduction of myosin phosphorylation, which in turn causes vasodilatation. The β-receptor–stimulated adenylate cyclase activity is reduced in lymphocytes of hypertensive patients.[131] Interestingly, this abnormality can be corrected by a low sodium diet. A cAMP hyperresponsiveness, however, has been found in platelets of hypertensive patients.[132] It remains, therefore, uncertain whether alterations in the cAMP signaling pathway modulate in essential hypertensive patients the vascular response to β-adrenergic receptor activation.

Atrial natriuretic peptide, BNP, and NO exert their vasodilatory action by increasing the generation of cyclic guanosine monophosphate (cGMP). The natriuretic peptides activate a particulate, membrane-bound guanylate cyclase, leading to the transformation of GTP to cGMP. This latter nucleotide activates specific kinases, with a reduction in intracellular free calcium as the ultimate consequence. Cyclic guanosine monophosphate can eventually egress through the cellular membrane. Nitric oxide acts on a soluble, cytosolic guanylate cyclase. Notably, both the circulating concentration and the urinary excretion of cGMP are on the average similar in patients with essential hypertension and in normotensive subjects.[133,134]

Membrane Abnormalities

Sodium metabolism has been extensively examined in erythrocytes, leukocytes, and platelets of hypertensive patients, the assumption being that the ionic membrane transport of these blood cells is identical to that of vascular smooth muscle cells. Only the main abnormalities will be described here.[135] The ouabain-sensitive, sodium-potassium ATPase is inhibited in many patients with essential hypertension (Fig. 86.13). This defect may be due to the presence in the circulation of a factor able to block this pump and appears to have an inherited character. In contrast, the activity of the erythrocyte sodium-lithium countertransport is abnormally increased in some patients with primary hypertension. In the absence of lithium, this system allows the exchange of sodium between the extra- and the intracellular compartment. The physiologic role of this transport system is not yet understood. Intriguingly, essential hypertensive patients with insulin resistance often exhibit an increased activity of this countertransport.[136] A third ionic perturbation present in essential hypertension is linked to the sodium-hydrogen antiport.[137] This system allows the extrusion of intracellular protons in exchange for extracellular sodium and plays a role in the regulation of cytosolic pH. The activity of this sodium-hydrogen antiport is increased in platelets of essential hypertensives.

The pathogenesis of essential hypertension has been hypothetically linked to the inhibition of the sodium pump and the ensuing increase in intracellular sodium, which reduces the concentration gradient between extra- and intracellular sodium. As a consequence, the activity of the sodium-calcium exchanger might be increased and result in an accumulation of intracellular calcium and vasoconstriction.[127]



1 Sodium-potassium ATPase
2 Sodium-lithium countertransport
3 Sodium-hydrogen antiport
4 Sodium-calcium exchanger

FIGURE 86.13. Electrolyte transport systems that function abnormally in essential hypertension.

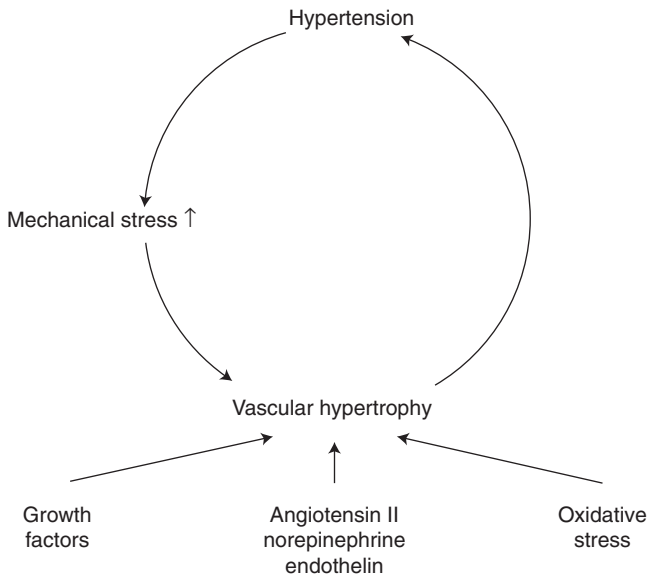


FIGURE 86.14. Schematic representation of factors promoting the development of vascular hypertrophy.

Hypertensive patients often exhibit an altered membrane microviscosity due to changes in lipid composition.[138] This membrane abnormality might influence the activity of proteins involved in ion transport, signal transduction, cell calcium handling, and intracellular pH regulation, and therefore contribute to the pathogenesis of essential hypertension.

Vascular Structural Changes

When exposed to high blood pressure, resistance blood vessels undergo an adaptive hypertrophy that makes it possible to keep the wall stress constant but that amplifies considerably the vascular responsiveness to all constrictors (Fig. 86.14).[139] Vascular hypertrophy may be promoted by growth factors. In addition, the raised intracellular free calcium and activation of protein kinase C (PKC) mediated by vasoconstrictors such as norepinephrine, angiotensin II, and endothelin induces the expression of proto-oncogenes, which in turn stimulate cell growth.[140] The increased oxidative stress observed in human hypertension is thought to play a critical role in the vascular wall remodeling.[141] This is also true for matrix metalloproteinases, that is, enzymes that are essential for the degradation and the reorganization of extracellular matrix. These enzymes are upregulated in conditions associated with elevations in reactive oxygen species.[142] The enhanced sodium-proton exchange activity observed in patients with essential hypertension seems to be associated with vascular hypertrophy, but it is still unknown whether this abnormal activity represents a causal factor for structural changes.[137]

Hypertensive patients tend to have an increased stiffness of large arteries as compared with normotensive individuals.[143–145] This change in the viscoelastic properties of the arterial wall is accompanied by an inflammatory process leading to an increased collagen content and an acceleration of pulse wave velocity.[146] As a consequence the reflected pressure wave returns early backward toward the heart, resulting in an amplification of aortic systolic pressure.[147] This accounts for the fact that pulse pressure, defined as the difference between systolic and diastolic pressure, is widened in elderly hypertensive patients, which may be reflected by an isolated elevation of systolic blood pressure.

Secondary Forms of Hypertension

The main causes of secondary forms of hypertension are shown in Table 86.3.

Renal Diseases

Renal diseases are observed in 3% to 4% of hypertensive adults.[148] The kidney has a pivotal position in hypertensive disorders. On the one hand, it may cause or accelerate hypertension.[149] On the other hand, the kidney is a target, high blood pressure being a major determinant of renal function deterioration. All forms of renal parenchymal disease may be associated with hypertension, including glomerulonephritis, interstitial nephritis, diabetic nephropathy, polycystic kidney disease, and reflux nephropathy. The prevalence of hypertension in these disorders ranges, depending on the series, from 25% to 80%. At the stage of terminal renal failure, 80% to 90% of patients have hypertension. Unilateral renal diseases can also be involved in the pathogenesis of hypertension. To be mentioned are hydronephrosis, radiation nephritis, and renal tumors or cysts. A hallmark of chronic renal failure is salt and water retention, resulting in increased plasma and extracellular fluid volumes. The activity of the renin-angiotensin systems may be not adequately suppressed in the face of the volume overload. Increased intraglomerular pressure and hyperfiltration are thought to play critical roles in the deterioration of renal function, especially in patients with diabetic nephropathy. The deleterious effect of angiotensin II on intraglomerular hemodynamics is mainly due to its preferential action at the efferent arteriole. The renin-angiotensin system contributes to the maintenance of high blood pressure in many patients with polycystic kidney disease. In patients with hydronephrosis, large tumors, or cysts, localized renal ischemia with stimulation

TABLE 86.3. Causes of secondary forms of hypertension

Renal diseases
Renovascular hypertension
Coarctation of the aorta
Pheochromocytoma
Primary aldosteronism
Cushing syndrome
Congenital adrenal hyperplasia
Thyroid disease
Hyperparathyroidism
Acromegaly
Pregnancy
Brainstem compression
Obstructive sleep apnea
Oral contraceptives
Iatrogenic hypertension

of renin release may occur. Furthermore, some tumors can secrete renin. This is typically the case for benign juxtaglomerular cell tumors, but some nephroblastomas and renal cell carcinomas may also be a source of renin.

Over the last few years increasing attention has been paid to the significance of microalbuminuria. In patients with hypertension or diabetes the presence of an increased urinary albumin excretion represents a marker not only of an altered permeability of glomerular capillaries and an incipient renal damage, but also of endothelial dysfunction and increased cardiovascular risk.[150] Relevantly, patients with chronic kidney disease are considered today at high risk of developing cardiovascular complications.[151]

Renovascular Hypertension

Renovascular hypertension is the prototype of renin-dependent hypertension. Any obstructing lesion located on the renal arterial tree may cause, beyond a critical degree of stenosis, a pressure gradient and a blood flow reduction, thereby triggering the release of renin from the ischemic kidney.[152] Not every stenotic lesion is functionally significant so that the diagnosis of renovascular hypertension should not be based exclusively on the documentation of an anatomic obstruction. In the population of hypertensive patients, the prevalence of this form of hypertension has been estimated at about 5%, but it may be much higher at around 30% among severely hypertensive patients.[153] The main causes of renovascular hypertension are atherosclerosis, fibromuscular dysplasia, renal artery stenosis on a transplant kidney, and dissection of the aorta involving renal arteries. Atherosclerotic lesions (stenosis, occlusion, or aneurysm) are most frequent in middle-aged and older patients, especially in men having a generalized vascular disease. In patients with longstanding hypertension, the presence of a renal artery stenosis may aggravate the severity of hypertension. Most patients exhibit other risk factors for cardiovascular disease. The kidney function is often impaired due to concurrent nephroangiosclerosis, and bilateral lesions are frequent.

Fibromuscular dysplasia involves primarily medium-sized arteries in the renal and cerebral vascular bed.[154] The cause of this disease is unknown, but genetic factors, female sex hormones, and ischemia of the arterial wall may play a role. Patients with fibromuscular dysplasia are often young women. Progression of stenotic lesions is slower in patients with fibromuscular dysplasia than in those with atherosclerotic lesions. Rare causes of renovascular hypertension are Takayasu's arteritis, and hereditary connective tissue disorders (Ehlers-Danlos syndrome, Marfan syndrome, and neurofibromatosis). Cholesterol crystal embolism represents a still-underdiagnosed cause of renal dysfunction that may be precipitated by invasive vascular procedures.[155] The renal atheroembolization may be associated with a renin-dependent form of hypertension.

Coarctation of the Aorta

Hypertension developing during childhood or early adulthood might be due to a narrowing (coarctation) of the aorta just below the origin of the left subclavian artery. Typically, blood pressure is much higher in the upper than in the lower part of the body. The renin-angiotensin system may be activated in some patients with coarctation, contributing to the elevation of blood pressure, which, however, seems to result primarily from the mechanical obstruction.[156]

Pheochromocytoma

Pheochromocytomas are potentially lethal, catecholamine-secreting tumors.[157,158] They consist of chromaffin cells (i.e., cells of neuroectodermal origin that become black when exposed to chromium salts). These tumors are localized predominantly in the adrenal medulla, either unilaterally or bilaterally. They can also occur in extraadrenal sites, the chromaffin cells being associated with sympathetic ganglia (paraaortic, urinary bladder, chest, neck, rectum). About 10% of patients with pheochromocytoma harbor multicentric lesions (Table 86.4). A familial character is found in approximately 10% of pheochromocytomas, and some of them may be associated with other endocrine tumors [multiple endocrine neoplasia (MEN) syndrome]. The prevalence of pheochromocytoma among hypertensive patients is estimated at less than 0.1%. In about one half of the patients the discharge of catecholamines from the tumor causes only paroxysmal hypertension. Malignant pheochromocytomas are rare. Pheochromocytoma cells may secrete norepinephrine, epinephrine, and dopamine, with usually a prominence of norepinephrine over the other catecholamines. Some pheochromocytomas may also release vasoactive peptides, for instance the vasoconstrictor neuropeptide Y. Catecholamines are metabolized more or less rapidly within the tumor so that the amount of catecholamines reaching the circulation can greatly vary.

Primary Aldosteronism

Primary aldosteronism is a syndrome characterized by hypertension with excessive production of aldosterone, potassium loss, sodium retention, and suppressed renin secretion.[159,160] The prevalence rate of this disorder has long be regarded as very low, about 0.1% among unselected hypertensives. The increased aldosterone secretion may be due to the presence of a unilateral adrenocortical adenoma (known as Conn syndrome). Very seldom is the tumor an aldosterone-secreting carcinoma. Ectopic aldosterone-producing tumors have been described in the ovaries. In about one third

TABLE 86.4. Characteristics of pheochromocytomas and of the multiple endocrine neoplasia syndrome (MEN)

Pheochromocytoma: "rough rule of 10"
10% are extraadrenal
10% are malignant
10% are familial
10% occur in children
10% are bilateral
10% are multiple (other than bilateral adrenal)
MEN syndromes
MEN II (Sipple syndrome or MEN IIa)
Pheochromocytoma associated with medullary thyroid carcinoma and hyperparathyroidism
MEN III (multiple mucosal neuroma syndrome or MEN IIb)
Pheochromocytoma associated with medullary thyroid carcinoma, multiple mucosal neuromas, and possibly intestinal ganglioneuromatosis and marfanoid habitus

of patients with primary aldosteronism, no tumor can be evidenced. In this subset of patients, the increased production of aldosterone is associated with a diffuse or focal hyperplasia of the adrenal zona glomerulosa. These changes are bilateral, and the glands often bear multiple nodules (idiopathic hyperaldosteronism). A nonnegligible fraction of patients with low renin hypertension might actually have an idiopathic hyperaldosteronism.[161]

Cushing's Syndrome

Hypertension may be due to an overproduction of cortisol from the adrenal, a condition known as Cushing's syndrome. The excessive secretion of cortisol may be due to an increased release of ACTH (pituitary Cushing's syndrome) caused by the corticotrophin-releasing factor originating from the hypothalamus.[162] This idiopathic form of glucocorticoid excess is associated with bilateral adrenal hyperplasia and accounts for about 70% of all cases of Cushing's syndrome. In some patients, ACTH or ACTH-like peptides are produced by nonendocrine malignant tumors. Hypersecretion of cortisol, and sometimes also of other steroids, may arise from adrenal neoplasms, either benign or malignant (adrenal Cushing's syndrome). Cortisol has normally a weak mineralocorticoid activity because it is rapidly inactivated to cortisone by the 11β-hydroxysteroid dehydrogenase that is located in aldosterone-sensitive cells. At high plasma concentrations, however, cortisol might exert a mineralocorticoid activity, as the neutralizing capacity of the 11β-hydroxysteroid dehydrogenase may be overpassed. Notably, glucocorticoids increase the hepatic synthesis of angiotensinogen, enhancing perhaps by this way the generation of angiotensin II. The major mechanism involved in the pathogenesis of hypertension in Cushing's syndrome seems to be a hypercontractile response to vasoconstrictors.

Congenital Adrenal Hyperplasia

Inborn errors of corticosteroid biosynthesis are rare causes of hypertension.[163] Figure 86.15 illustrates the steps of aldosterone and cortisol synthesis, with the position of two key enzymes, the 17- and the 11-hydroxylases. The deficiency of these enzymes may be more or less complete. In both cases, the production of cortisol is impaired, preventing the feedback inhibition of ACTH release. Consequently, steroids proximal to the biosynthetic impediment accumulate. Subjects with 17-hydroxylase deficiency have a marked elevation in plasma 11-deoxycorticosterone (DOC), a steroid with potent mineralocorticoid properties, while androgens and estrogens cannot be formed normally (primary amenorrhea and sexual infantilism in females and pseudohermaphroditism in males). Reduced 11-hydroxylation leads to an increase in DOC, 11-deoxycortisol, and androgen levels (virilization and pseudohermaphroditism).

Thyroid Disease

Thyroid hormone is implicated in cardiovascular regulation.[164] It decreases peripheral vascular resistance and mediates an increase in blood volume, cardiac contractility and chronotropy, as well as cardiac output. It also activates the renin-angiotensin system and triggers the release of natriuretic peptides. In hyperthyroidism, the pulse pressure is usually widened, and high systolic pressure can be seen together with normal or even low diastolic pressures. This form of hypertension is mainly due to an increased cardiac output. In patients with hypothyroidism, the prevalence of hypertension is high, at around 20%, and the elevation of blood pressure is mainly diastolic, reflecting an increased systemic vascular resistance.

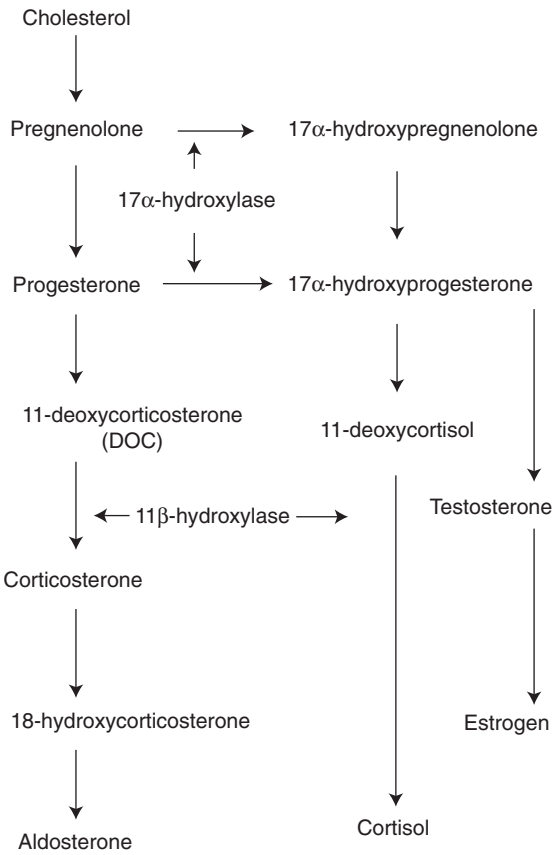


FIGURE 86.15. Steps in aldosterone and cortisol synthesis.

Hyperparathyroidism

The incidence of hypertension is increased among patients with primary hyperparathyroidism.[165] Several factors might contribute to this association, such as hypercalcemia, an activation of the renin-angiotensin system, or a vascular hyperresponsiveness to vasoconstrictors. Evidence has been provided for the release of a hypertensive factor in the circulation of hypertensive patients with primary hyperparathyroidism.[166] This parathyroid hypertensive factor might increase calcium uptake in vascular smooth muscle and potentiate the contractile response to norepinephrine and angiotensin II.[167]

Acromegaly

Patients with acromegaly produce an excess of growth hormone in the anterior lobe of the pituitary and commonly exhibit an elevated blood pressure. Vascular hypertrophy may have a role in the pathogenesis of acromegalic hypertension.

Another potential mechanism is an increase in intracellular calcium due to the presence in the circulation of a substance with an inhibitory activity on the sodium-potassium ATPase.[168]

Pregnancy

Preeclampsia is a form of hypertension developing most often in nulliparous women, usually during the third trimester of gestation, and accompanied by proteinuria, edema, and possibly also by microangiopathic hemolytic anemia and liver function disturbances.[169] Preeclampsia may progress to eclampsia, a condition characterized by life-threatening convulsions. Preeclampsia can be seen early during the course of pregnancy in women with chronic, preexisting hypertension. Pregnant women are normally highly resistant to the action of pressor agonists, for instance, to that of angiotensin II. In contrast, the sensitivity to vasoconstrictors is markedly increased in women with preeclampsia, accounting at least in part for the raised vascular peripheral resistance. The abnormal reactivity of the vasculature may be caused by an imbalance in the production of vasodilating and vasoconstrictor prostaglandins. It may also reflect endothelial dysfunction, with a deficiency in NO synthesis and an increased endothelin release.[170,171] Blood pressure typically normalizes within a few days during the postpartum period. Women with insulin resistance or gestational diabetes are at increased risk to develop preeclampsia.[172]

Brainstem Compression

A neurogenic form of hypertension may result from the compression of the rostral ventrolateral region of the medulla oblongata by arteries or veins.[173]

Obstructive Sleep Apnea

Patients with obstructive sleep apnea (OSA) experience repetitive apneic periods during sleep.[174] These patients have a high prevalence of hypertension. Obstructive sleep apnea is especially common in obese middle-aged men. Snoring and alcohol abuse may contribute to the pathogenesis of this disease. During cessation of air flow, arterial oxygen content decreases and arterial carbon dioxide levels increase. Hypoxia and hypercapnia, acting via the chemoreflexes, activate the sympathetic nervous system, and thereby increase blood pressure during sleep.[175] Hypoxia is a potent stimulus of endothelin release. Significant increases in blood pressure and plasma endothelin levels have been reported in sleep apneics.[176] The nighttime elevation of blood pressure may carry over to daytime and cause sustained hypertension. Obstructive sleep apnea is often associated with obesity, insulin resistance, an excessive daytime sleepiness, and impaired cognitive and sexual functions.

Oral Contraceptives

Oral contraceptives tend to increase blood pressure in the majority of women, but true hypertension develops in less than 5% of pill users.[177,178] Between users and nonusers a significant difference in daytime ambulatory blood pressures has been found throughout the menstrual cycle.[179] The estrogenic component of oral contraceptives is the main determinant of the blood pressure elevation.[180] Progestagens alone generally have no or little effect on blood pressure.[181,182] Estrogen-containing contraceptive pills stimulate the hepatic synthesis of angiotensinogen, but this, however, does not result in consistent raised plasma angiotensin II levels, even if increased angiotensin II concentrations have been measured.[183] Estrogens and synthetic gestagens may induce some sodium retention in susceptible persons, while natural progesterone has an antimineralocorticoid activity.[184] The precise mechanisms responsible for this type of hypertension, therefore, remain unclear. The blood pressure effect of oral contraceptives is dose dependent, thus encouraging prescription of preparations with low estrogen-progesterone content. After withdrawal of oral contraceptives, several months are sometimes needed for recovery of normal blood pressure values.

Iatrogenic Hypertension

A number of medications can be responsible for a sustained elevation of blood pressure (Table 86.5).[185] They include substances with gluco- or mineralocorticoid activities. Chronic excessive ingestion of licorice may cause a form of hypertension mimicking primary aldosteronism. This is because the licorice extract contains a substance, glycyrhizinic acid, that inhibits 11β-hydroxysteroid dehydrogenase activity, thus leading to increased plasma cortisol levels, a steroid possessing mineralocorticoid activities. Some drugs may increase blood pressure by enhancing α-adrenoceptor stimulation. Phenylephrine as well as other α-adrenergic receptor agonists, including alkaloids related to ergotamine, produce vasoconstriction by activating postsynaptic adrenergic receptors. Amphetamines augment the discharge of norepinephrine from terminal nerve endings while cocaine prevents the catecholamine neuronal reuptake. This may lead to severe hypertension, tachycardia, and seizures.[186] Cyclosporine has a hypertensive effect depending on dosage and duration of treatment.[187] Renal sodium retention together with enhanced thromboxane A_2 and endothelin release might contribute to the cyclosporine-induced vasoconstriction, which is reversible after discontinuation of the drug. There is now available a recombinant human erythropoietin that can be used to correct anemia in patients on chronic hemodialysis. Striking increments in blood pressure can be seen in patients receiving erythropoietin, the overall prevalence of erythropoietin-induced hypertension being about 30%.[188] The hormone may increase blood pressure via a direct effect or indirectly by heightening the vascular responsiveness to angiotensin II.

TABLE 86.5. Drugs that can lead to hypertension

Gluco- and mineralocorticoids
Licorice
Sympathomimetics (decongestants, anoretics)
Amphetamines
Cocaine
Cyclosporine
Erythropoietin
Nonsteroidal antiinflammatory drugs

The erythropoietin-induced rise in hematocrit and blood viscosity is also a potential cause of increased peripheral resistance. Nonsteroidal antiinflammatory drugs raise blood pressure only modestly in individuals not on antihypertensive treatment, although this may lead occasionally to hypertensive levels.[189,190] These drugs, by inhibiting cyclooxygenase, may attenuate the blood pressure–lowering effect of practically all antihypertensive agents.[191]

Clinical Recognition

History

Each patient should be questioned regarding a family history of hypertension, diabetes, hyperlipidemia, ischemic heart disease, and stroke.[192–196] Information should also be obtained about the personal history of cardiovascular, cerebrovascular, and renal symptoms or diseases, as well as about the existence of associated risk factors or any clinically relevant disorder. Attention must be paid to the dietary habits, with special reference to sodium intake, to alcohol consumption and smoking, to weight gain, and to physical activities. Psychosocial and environmental factors (e.g., lifestyle, family situation, working conditions, educational level) should be detailed. It is essential to get a history of the patient's hypertension, including the known duration of the blood pressure elevation, the efficacy and tolerability of previous antihypertensive therapy, as well as the presence of symptoms suggesting a secondary form of hypertension such as symptomatic hypertensive attacks (hypertension is paroxysmal in 25% of patients with pheochromocytoma, and headache, sweating, and tachycardia are encountered in 95% of them). Palpitations, anxiety, and tremulousness are suggestive of pheochromocytoma producing predominantly epinephrine.[157,158] Symptoms are unusual in patients with uncomplicated essential hypertension, the most common consisting of early morning, usually occipital, headache, tinnitus, blurred vision, and dizziness. All prescribed and over-the-counter medications taken by the patient should be noted.

Physical Examination

A complete physical examination, including weight and height measurements, is mandatory for each patient.[192–196] Particularly pertinent for the evaluation of hypertension is auscultation of the abdomen (a bruit is present in about 40% of patients with renal artery stenosis) and of the main large arteries. The diminution or the absence of peripheral arterial pulsation may point to a generalized arteriopathy. Reduced and delayed femoral pulses with preserved pulses in the upper extremities may be a clue for the diagnosis of the coarctation of the aorta, especially if a systolic murmur is audible in the back. An abnormal aortic pulsation may reveal the presence of an aneurysm. Funduscopic examination should be performed, with pupil dilation if necessary, at least in patients with severe hypertension. Hypertensive retinopathy can be classified in four grades according to the severity of the retinal changes: grade I, arteriolar narrowing; grade II, narrowing and arteriovenous nicking; grade III, narrowing, nicking, and retinal hemorrhages or exudates; grade IV, papilledema. Inspection of the skin may reveal café-au-lait spots and widespread subcutaneous neuromas characteristic of neurofibromatosis, a condition frequently associated with pheochromocytoma. Patients with pheochromocytoma are often pale during catecholamine surge. Truncal striae and central obesity along with atrophy of the skin may be due to hypercortisolism. Patients with advanced renal failure exhibit a urochrome pigmentation. The presence of tophi points to the diagnosis of gout. Hyperlipidemic patients may have xanthelamas, xanthomas, or a corneal arcus. The acromegalic patient has typical appearance, with enlarged hands and feet and coarsening of the facial features (broad nose, prominent lips, thickened skin). Patients with hypothyroidism may present with thin, brittle nails, thinning of hair, hard pitting edema, and delayed return of deep tendon reflexes, whereas those with hyperthyroidism often show a goiter, a tremor, and an exophthalmos that is at times associated with a pretibial, hard, and nonpitting swelling. Cardiac examination may be a sensitive means of identifying left ventricular hypertrophy. The apical impulse felt with the patient lying in the left lateral decubitus position exhibits a sustained outward thrust often occupying an area larger than 2 cm in diameter in patients with hypertrophy. A diffuse apical heave is indicative of left ventricular dilation. An early diastolic murmur of aortic regurgitation along the left sternal border may be observed in severe hypertension and often disappears when the blood pressure is lowered.

Measurement of Blood Pressure

Obtaining correct blood pressure readings is critical for the diagnosis of hypertension.[197,198] This implies the use of accurate equipment and of an appropriate technique of measurement. The cuff bladder should transmit the pressure evenly to the underlying brachial artery. A standard sized bladder (12–16 by 26–30 cm) is suitable for most adults. For those with large obese or muscular arms, a special bladder (12–16 by 36–40 cm) is required. A bladder adapted to the arm circumference is also necessary for children. The manometer (mercury, aneroid, or electronic device) should be checked regularly. The patient should rest for at least 5 minutes, preferably in the seated posture for routine measurements, with the arm fully relaxed at the level of the heart. When pressure is taken for the first time using the auscultatory method, the cuff should be inflated and deflated rapidly and the systolic blood pressure approximated by disappearance and reappearance of the radial pulse. Subsequent readings can then be made by inflating the cuff to 20 to 30 mm Hg above this value. In this way it is possible to avoid errors in the determination of systolic blood pressure due to an auscultatory gap. Deflation of the cuff should be performed at a rate of about 2 mm/s. The systolic pressure is defined as the first appearance of a Korotkoff sound and the diastolic by the disappearance of the Korotkoff sound (phase 5). In some subjects (mainly in young subjects and in pregnant women), sounds can be detected until nearly zero. In this case, the diastolic pressure represents the level at which a muffling of the Korotkoff sounds becomes apparent (phase 4). Blood pressure should be measured to the nearest 2 mm Hg in order not to give preference to 0 and 5 as terminal digits. At least two measurements should be taken at intervals of at least 1

minute, and those two readings should be averaged to represent the patient's blood pressure. It is advisable to measure blood pressure also with the patient standing, especially if he is aged or complains of symptoms potentially related to orthostatic hypotension. Normally the systolic pressure falls slightly in the standing position and the diastolic pressure rises. Blood pressure differences may exist between arms. Bilateral measurement therefore should be done at the initial visit. Interarm differences up to 20 mm Hg systolic and 10 mm Hg diastolic are acceptable.

Automated devices measuring brachial artery blood pressure according to the oscillometric technique are increasingly used, as the trend is to ban mercury because of its potential toxicity on environment. A large number of validated, easy to use automated devices are now available (see www.dableducational.com for an updated listing). Wrist blood pressure monitors are popular among patients, but the reliability of most of them remains to be proven.

Workup of the Hypertensive Patient

The goal of the initial workup of the hypertensive patient is to assess whether there is damage of target organs, to look for coexisting risk factors, and to judge whether additional investigations are needed for the diagnosis of a potentially curable form of secondary hypertension.[192–196] Table 86.6 summarizes the proposed laboratory tests and complementary investigations. Urinalysis should be performed on a fresh, if possible first-morning, specimen. Dipstick tests can be used in everyday practice for the detection of glucose and protein in the urine. The measurement of microalbuminuria (defined as a urinary albumin excretion of 30 to 300 mg/24 hours; an albuminuria of 20 to 200 μg/min in an overnight urine collection; an albumin/creatinine ratio between 2.5 and 25 mg/mmol or an albumin concentration between 20–30 and 200–3000 mg/L in an early urine spot) is increasingly advocated.[150] Getting an electrocardiogram is a necessity. Although not very sensitive as an indicator of cardiac hypertrophy, this test gives useful information on conduction disturbances and ischemic heart disease. Echocardiography is not recommended for every patient, but it is superior to the electrocardiogram in assessing left ventricular mass.[199] It also allows a reliable evaluation of the systolic function of the myocardium. The chest x-ray may identify cardiomegaly, pulmonary congestion, and unfolding of the thoracic aorta, suggestive of aortic aneurysm. Moreover, erosion of the ribs secondary to the dilatation of intercostal arteries can be seen in patients with coarctation of the aorta. A number of prospective epidemiologic studies have demonstrated that a single measurement of high-sensitivity C-reactive protein (CRP) has a strong predictive value with regard to the cardiovascular outcome.[200] Increased CRP concentrations may reflect a chronic low-grade inflammation as it occurs during the atherosclerotic process. The measurement of high-sensitivity CRP therefore might be useful to detect high-risk patients.

More extensive routine evaluation of the vasculature and heart is advocated by some in order to more precisely define the need for lowering blood pressure and treating other risk contributors in individual patients.[201] Possible vascular studies include ultrasound of the carotid artery and left ventricle for wall thickness, pulse waveform analysis to identify artery wall stiffness, digital photography of the optic fundus for more precise retinal vascular assessment, and blood levels of B-type natriuretic peptide for detecting early left ventricular dysfunction. Measurement of the blood pressure response to a standardized exercise stress may also provide insight into vascular stiffness and cardiac and vascular load during daily activity.

TABLE 86.6. Workup of the hypertensive patient

- Routine tests
  - Blood
    - Hemoglobinemia
    - Hematocrit
    - Serum concentration of :
      - Creatinine
      - Sodium
      - Potassium
      - Calcium
      - Uric acid
      - Glucose (fasting or postprandial)
      - Low-density lipoprotein (LDL) cholesterol
      - High-density lipoprotein (HDL) cholesterol
      - Triglycerides
  - Urine
    - Examination for the presence of cells and casts
    - Dipstick test for the presence of glucose and albumin
  - Electrocardiogram
- Optional tests
  - Posteroanterior chest x-ray
  - Echocardiography
  - Carotid (and femoral) ultrasound
  - C-reactive protein
  - Microalbuminuria (essential in patients with diabetes or nephropathy)
  - Quantitative albuminuria (if dipstick test positive)
  - Self-measurement of blood pressure at home
  - Noninvasive ambulatory blood pressure monitoring

The Search for Secondary Hypertension

Renovascular Hypertension

Identification of patients with renovascular hypertension is an important task, since this form of hypertension is potentially curable. Special examinations for detecting renal artery stenosis, however, cannot be performed in every individual with hypertension.[202] The diagnostic tests should be limited to patients with increased likelihood of disease. Such patients are those presenting with an abrupt onset of hypertension, a severe or malignant hypertension, a treatment-resistant hypertension, a known occlusive arterial disease, an unexplained elevation of serum creatinine, or a deterioration of renal function reversibly induced by an ACE inhibitor. A history of smoking heightens the suspicion of renovascular disease. Table 86.7 lists the most common procedures used to detect and confirm the presence of a renal artery stenosis. Measurement of plasma renin activity is of no help in the screening for renovascular hypertension, as renin secretion is not necessarily elevated in this condition and can be high even in patients with essential hypertension. Measurement of plasma renin activity at peak ACE inhibition, for instance, 90 minutes following oral administration of 25 mg captopril (captopril test), helps to discriminate between patients with renovascular stenosis and those with essential hypertension, the reactive hyperreninemia (due to the lack of angiotensin II to exert a feedback inhibitory action on renin secretion)

TABLE 86.7. Diagnostic procedures for renovascular hypertension, primary aldosteronism, and pheochromocytoma

Renovascular hypertension
Plasma renin activity
Captopril test
Renal vein renins
Renal scintigram during angiotensin-converting enzyme (ACE) inhibition
Intravenous pyelogram
Intravenous or intraarterial digital substraction angiography
Gadolinium-enhanced three-dimensional magnetic resonance angiography
Duplex ultrasound
Primary aldosteronism
Plasma renin activity
Plasma or urinary aldosterone
Aldosterone/renin ratio
Computed tomographic scan
Magnetic resonance imaging
Adrenal scintillation scanning with radioiodinated cholesterol
Adrenal vein sampling and adrenal venography
Pheochromocytoma
Urinary catecholamine, metanephrine, or vanillylmandelic acid
Plasma catecholamines or metanephrines
Clonidine test
Computed tomographic scan
Magnetic resonance imaging
Scintigraphy with radioiodinated metaiodobenzylguanidine (MIBG)
Vena cava blood sampling

being clearly more pronounced in the former than in the latter. This test must be performed after discontinuation of all antihypertensive medications, which is impossible for safety reasons in most patients. Demonstration that renal arterial stenosis is sufficient to have functional consequences requires determination of renin levels bilaterally in the renal veins to confirm lateralization of renin secretion. In this case, the afflicted kidney constitutes the source of circulating renin levels while renin release is suppressed in the contralateral kidney. The difference in renal vein renins can be amplified by prior stimulation of renin secretion using either a diuretic or an ACE inhibitor. A convenient, noninvasive screening test is the renal scintigram. The value of this test is considerably increased by comparing renograms obtained before and after a single dose of captopril. It may be adequate to perform only one scintigraphy, but at peak ACE inhibition. In the affected kidney, the inhibition of angiotensin II synthesis produces a dilatation of the efferent arteriole, with a consequent fall in glomerular filtration and delay in renal excretion of the radioactive tracer. An asymmetry of uptake (suggestive of a severe lesion), excretion, or both can be seen. A major advantage of renal scintigraphy coupled with captopril challenge is its predictive value in terms of detecting patients who are most likely to benefit from revascularization of renal artery stenosis. The use of intravenous pyelography in diagnosing renovascular hypertension is declining, since bilateral or branch stenoses are regularly missed by this examination. Intravenous digital subtraction angiography is a much better alternative, but its resolution is not as good as that obtained by intraarterial injection of the dye. The invasive route therefore may be preferable, except in patients with severe atherosclerotic disease who are at higher risk to develop complications such as hemorrhage, thrombosis, and cholesterol embolization. Three-dimensional magnetic resonance angiography combined with gadolinium contrast is very appealing. A major concern regarding the usefulness of Doppler flow studies in the screening of renovascular hypertension is the skill of the sonographer, which influences greatly the value of the ultrasound investigation. Assessment of the renal resistance index by Doppler ultrasonography may help to predict the response of blood pressure and renal function to revascularization.[203] A meta-analysis of diagnostic tests for renovascular hypertension has shown better results using computed tomography angiography and gadolinium-enhanced magnetic resonance angiography than ultrasonography and captopril renal scintigraphy.[204]

Primary Aldosteronism

Classically, patients with primary aldosteronism present with hypokalemia.[205] Serum potassium concentration may occasionally be normal. This is mostly the case when dietary sodium intake is low, so that only a small amount of sodium is available at the distal tubule to be exchanged with potassium. An underlying primary aldosteronism should also be suspected when patients develop marked hypokalemia in response to diuretic therapy. The diagnosis of primary aldosteronism is based on the demonstration of a suppressed plasma renin activity together with elevated plasma aldosterone concentrations or increased urinary aldosterone excretion (Table 86.7). The aldosterone/renin ratio is increasingly used as a screening test for primary aldosteronism.[206] There is no functional test to differentiate with certainty adenoma and hyperplasia. The highly efficient imaging techniques [computed tomography (CT) scan and magnetic resonance imaging (MRI)] may be unable to detect small adrenal tumors. In some cases, adrenal scintillation scanning using radioiodinated cholesterol may be useful. Other investigations like adrenal vein sampling, for exploring separately aldosterone secretion from each gland, and adrenal venography are no longer recommended.

Pheochromocytoma

Pheochromocytoma should be suspected in all patients with suggestive history, with or without associated hypertension (approximately 15% of patients are normotensive).[207] Patients with a family history of pheochromocytoma should also be systematically screened for the presence of a catecholamine-secreting tumor. The first diagnostic step is the demonstration of an excessive release of catecholamines. This can be done by measuring 24-hour urinary excretion of either free (i.e., unconjugated) catecholamines or their metabolites (metanephrines, vanillylmandelic acid) or by determining plasma catecholamine concentrations (Table 86.7). In most patients, the urinary determinations are adequate for establishing the diagnosis. The assays of catecholamines and metanephrines should be performed preferentially by high-performance liquid chromatography and electrochemical detection or radioenzymatic techniques to avoid interference with a number of medications. The false-negative rate for urinary vanillylmandelic acid is very high (around 30%), which strongly limits its diagnostic value. In principle, large tumors tend to release mainly metabolized catecholamines into the circulation, giving high concentrations of metabolites relative to free catcholamines in the urine, the converse being true for small pheochromocytomas. In some patients

with only slightly elevated plasma catecholamines, a clonidine suppression test may be helpful. Clonidine is an α_2-adrenergic receptor stimulant lowering blood pressure via a centrally mediated decrease in sympathetic activity and, in the periphery, by a presynaptic inhibition of norepinephrine release. This agent, therefore, is expected to decrease the plasma concentration of norepinephrine in patients with essential hypertension, but not that of patients with pheochromocytoma, in whom the regulation of catecholamine release is autonomous. Computed tomographic scan is a convenient and efficient way to localize pheochromocytomas anywhere in the body. Magnetic resonance imaging is excellent in visualizing tumors located in the adrenal and can be used safely in pregnant women.

Another way to locate adrenal and extraadrenal pheochromocytomas is scintigraphy with radioiodinated metaiodobenzylguanidine (MIBG). This substance is taken up by chromaffin tissues by the catecholamine pump. The MIBG scintigraphy can be very useful in locating metastatic tumors. The uptake of MIBG may be inhibited by some drugs, including labetalol, an agent possessing at the same time α- and β-adrenoceptor properties. This agent is frequently prescribed when considering the presence of a pheochromocytoma, but should be discontinued if possible several days before scintigraphy. Selective blood sampling along the vena cava for catecholamine determination is rarely required for the localization of the tumor.

Others

Renal ultrasound examination, intravenous pyelogram, and biopsy are the principal methods used for diagnosing kidney diseases. In patients with primary hyperparathyroidism, serum calcium levels (corrected for serum albumin) and serum ionized calcium levels are raised, whereas serum inorganic phosphorus concentration is low. The diagnosis is confirmed by the measurement of elevated levels of parathyroid hormone-like protein in the plasma. Hypothyroidism is characterized by low free serum thyroxine (T_4) values in the face of increased serum concentrations of thyroid-stimulating hormone (TSH), the opposite being true for hyperthyroidism. The diagnosis of Cushing syndrome is highly suspected based on the measurement of an increase in plasma cortisol concentration or 24-hour urinary free cortisol excretion, but should be confirmed by a dexamethasone suppression test. Elevated fasting serum growth hormone (GH) levels or nonsuppression of GH secretion after an oral glucose tolerance test are typical diagnostic features in patients with acromegaly. Polysomnography is helpful to assess whether patients have obstructive sleep apnea. Brainstem vascular compression can be demonstrated by MRI.

Natural History

Pathologic Consequences of Hypertension

Hypertension is a strong and independent risk factor for cardiovascular diseases.[208–210] There is a consistent and graded relation between both systolic and diastolic blood pressure and various cardiovascular complications, including stroke, coronary heart disease, cardiac hypertrophy, and congestive heart failure. The likelihood of developing renal disease,[211] peripheral arterial disease, and aneurysm of the aorta is also augmented by hypertension. A continuum exists between the level of both systolic and diastolic pressure and mortality due to stroke or ischemic heart disease, without any evidence of a threshold down to at least 115/75 mm Hg, as shown in a large meta-analysis of 61 prospective studies involving one million adults throughout middle and old age.[212] To be pointed out is the fact that increased pulse pressure (which corresponds to the difference between systolic and diastolic blood pressure) is also an independent predictor of cardiovascular risk.[213] It is important to recognize, however, that the linear relationship between measured pressure and morbid events and between pulse pressure and morbid events does not necessarily mean that the pressure is the cause of such events. Since some people with normal pressures suffer cardiovascular morbid events and others with elevated pressures do not, the pressure may in part be a guide to the likelihood of vascular disease not being the contributor. Thus, individuals with pressures below 120/80 mm Hg are far less likely to harbor vascular disease than those with pressures above 140/90 mm Hg. In addition a widened pulse pressure is likely a manifestation of stiffened arteries, a sign of advancing vascular disease, not necessarily a contributor to vascular disease.

Factors other than the blood pressure level per se can influence adversely the prognosis of hypertensive patients. Traditional risk factors for cardiovascular events include, in addition to age, sex (the risk is greater in men than in women), and family history of premature coronary artery disease or stroke (at age <55 years in men and <65 years in women), dyslipidemia (increased LDL cholesterol and/or decreased HDL cholesterol levels), smoking, diabetes, and sedentary lifestyle.[192–196] Novel risk factors have been identified, in particular left ventricular hypertrophy, hypertriglyceridemia, microalbuminuria, abdominal obesity (abdominal circumference ≥102 cm in men or ≥88 cm in women), insulin resistance (syndrome X), hyperhomocystinemia, and increased plasma levels of high-sensitivity CRP, lipoprotein (a), and fibrinogen.[214] It is noteworthy that left ventricular hypertrophy is a major cause of cardiac systolic and diastolic dysfunction, reduces coronary blood flow, and increases the incidence of life-threatening cardiac arrhythmia.[199] A key point is that the coexistence of several risk factors amplifies drastically the likelihood of developing cardiovascular events, the final risk being much greater than the sum of the individual risks. It is therefore necessary to take into account all risk factors in caring for hypertensive patients. This approach provides an estimate of absolute risk in an individual patient with a goal for intervention targeted to reduce that risk.[215]

Prevention of Cardiovascular Diseases by Antihypertensive Treatment

There is now ample evidence that cardiovascular morbidity and mortality can be effectively reduced by antihypertensive therapy.[216–218] Beneficial effects have been observed not only in patients with severe hypertension but also in those with modestly elevated blood pressures. In a meta-analysis of 14 randomized intervention studies of antihypertensive treat-

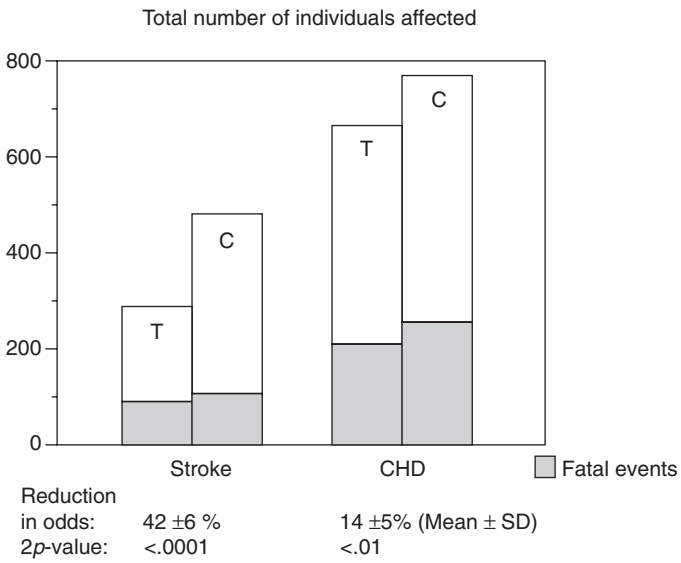


FIGURE 86.16. Effects of blood pressure reduction on stroke and coronary heart disease (CHD). The results represent a complication of 14 randomized intervention trials. T, treatment group; C, control group.

ment,[219] the morbidity and mortality from stroke and coronary heart disease were both significantly reduced, the protecting effect being manifestly more pronounced for the cerebrovascular than the coronary heart diseases (Fig. 86.16). For a drug-induced 6 mm Hg decrease in diastolic pressure, a 42% reduction in the incidence of stroke can be anticipated over a 2- to 3-year period as compared with 12% for the incidence of heart attacks. When considering elderly hypertensives almost the same figures are true. The combined results of five randomized trials of antihypertensive treatment in patients older than 60 years have shown a 34% and 19% reduction in the incidence of stroke and coronary heart disease, respectively.[220] This protecting effect was observed over an average follow-up of nearly 5 years and for a mean blood pressure reduction of 15 mm Hg for systolic and 6 mm Hg for diastolic. Even elderly patients with isolated systolic hypertension, as defined by a systolic pressure of 160 mm Hg or higher and a diastolic pressure of 90 mm Hg or less, derive benefit from antihypertensive therapy. Over a 5-year treatment period, a 36% reduction in stroke incidence and 27% reduction in coronary heart disease has been observed. Overall, the cardiovascular protection afforded by antihypertensive therapy seems to depend more on the magnitude of blood pressure reduction than the drug regimen.[217,221]

An area of uncertainty remains regarding the limited effectiveness of antihypertensive drugs in preventing myocardial infarction relative to the marked beneficial impact on stroke incidence. Several reasons have been advanced in an attempt to explain this phenomenon. The development of coronary heart disease depends (probably more than that of stroke) on risk factors commonly associated with hypertension. Unfortunately, prospective trials aimed to evaluate antihypertensive therapy were not directed to correct simultaneously in each patient the whole constellation of risk factors. Possibly a treatment-induced slowing of the progression of coronary lesions may have passed unnoticed because of a too short follow-up. Furthermore, some antihypertensive agents may have a deleterious effect on lipid or glucose metabolism. This might conceptually attenuate the coronary protection otherwise provided by the blood pressure reduction. Finally, the suboptimal results of antihypertensive therapy, with regard to coronary heart disease, could result from a too aggressive treatment, especially in patients with preexisting ischemic heart disease. In these patients, lowering diastolic blood pressure below a critical level might conceivably impair myocardial perfusion and precipitate myocardial infarction.[222] A large trial aimed at assessing the optimum diastolic blood pressure to reach during antihypertensive treatment has been performed.[223] Almost 19,000 patients aged 50 to 80 years were randomly allocated to a target diastolic blood pressure of ≤90 mm Hg, ≤85 mm Hg, or ≤80 mm Hg. The treatment was initiated in all patients with the calcium antagonist felodipine, with the possibility of adding other drugs (beta-blocker, ACE inhibitor) or to increase the doses according to a predetermined schedule when needed. The average follow-up was 3.8 years. No difference was found between the three target groups with regard to the cardiovascular morbidity and mortality. Considering all patients together, the lowest incidence of major cardiovascular events occurred at a mean achieved diastolic blood pressure of 82.6 mm Hg and the lowest risk of cardiovascular mortality at a mean diastolic blood pressure of 86.5 mm Hg. Further reductions of diastolic blood pressures below these values were safe, arguing against the warning that an intensive lowering of diastolic blood pressure in hypertensive patients should be avoided.

Notably, interventions directed to control optimally all risk factors in hypertensive patients on antihypertensive therapy allow a further reduction of cardiovascular mortality.[224]

Definition of Hypertension

Casual Office Blood Pressure

Blood pressure is normally distributed within the population, with no natural cutoff point allowing discrimination between normotensive and hypertensive individuals. Moreover, the tendency for blood pressure to rise with age makes it difficult to apply uniformly any criteria of normal blood pressure. In women the blood pressure rise is steeper after menopause.[225] The definition of hypertension is in some way arbitrary. By choosing specific blood pressure levels as upper limits of normal it is meant that the cardiovascular risk becomes high enough to warrant an intervention. Most so-called hypertensive individuals have only slightly elevated blood pressures. Even small blood pressure reductions in these hypertensives are associated, in terms of public health, with a substantial reduction in cardiovascular morbidity and mortality. The proposed definitions of normo- and hypertension proposed by major guidelines are very similar.[192–196] Table 86.8 gives as an example the definitions proposed by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in the U.S.A. (JNC 7 Report).[193] The key point is that a blood pressure ≥140 mm Hg for systolic and/or ≥90 mm Hg for diastolic has

TABLE 86.8. Definitions and classification of blood pressure (BP) levels according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) report

	Systolic BP (mm Hg)		*Diastolic BP (mm Hg)*
Normal	<120	and	<80
Prehypertension	120–139	and/or	80–89
Stage 1 hypertension	140–159	and/or	90–99
Stage 2 hypertension	≥160	and/or	≥100

When a patient's systolic and diastolic BPs fall into different categories, the higher category should apply.

to be considered as abnormally elevated. Isolated systolic hypertension is defined as a systolic blood pressure ≥140 mm Hg together with a diastolic blood pressure <90 mm Hg. Individuals with blood pressures at the upper range of normalcy should be followed regularly and be advised to initiate lifestyle modifications. The definitive diagnosis of hypertension should be based on repeated blood pressure measurements on different occasions. The goal of treatment is to bring blood pressure below 140/90 mm Hg using lifestyle measures together with pharmacologic treatment when needed. Strict blood pressure control (<130/80 mm Hg) is required in patients with diabetes or chronic renal disease. Lower targets are even desirable if proteinuria is >1 g/day.

Noninvasive Ambulatory Blood Pressure Monitoring

Blood pressures recorded during everyday activities away from the medical setting are usually lower than casual office blood pressures.[198] Target-organ damage is more closely associated with ambulatory blood pressures than conventional casual blood pressures, as a consequence mainly of the large number of blood pressure readings made available by ambulatory recordings.[226] Nighttime blood pressure is normally lower than daytime blood pressure. The lack of a normal nocturnal decline in blood pressure may be seen in patients with essential hypertension, but is observed particularly in patients with secondary forms of hypertension, in preeclampsic women, in patients with sleep apnea syndrome, and in diabetics with peripheral neuropathy. A blunted day–night fall in blood pressure seems to be harmful. An extreme nocturnal dipping, however, may represent an increased risk of stroke. Table 86.9 shows the normal ranges that are currently proposed.[192,193,198] There is still no firm consensus on the use of noninvasive blood pressure monitoring. This technique allows the detection of patients with white-coat hypertension, that is, patients whose blood pressures are high only in a medical setting.[227] White-coat hypertension is encountered commonly, in approximately 20% of mild hypertensives. In general, target-organ damage in white-coat hypertension is less prevalent than that in sustained hypertension. Patients with white-coat hypertension, however, seem to have a higher cardiovascular risk than do normotensives. They should be advised to initiate lifestyle changes and followed regularly as they are prone to develop sustained hypertension. The main indications for ambulatory blood pressure monitoring are considerable variability of office blood pressure, high office blood pressure in patients with low global cardiovascular risk, treatment-resistant hypertension, and the presence of symptoms possibly attributable to hypo- or hypertension.

TABLE 86.9. Recommended levels of normality for ambulatory and home blood pressures (BP) measurements in adults according to the JNC 7 report and the guidelines of the European Society of Hypertension

	JNC 7 report	*European recommendations*
Ambulatory BPs		
Awake	<135/85	<135/85
Asleep	<120/75	<120/70
24-hour average		<125/80
Home BPs	<135/85	<135/85

Self-Measurement of Blood Pressure

Self-monitoring of blood pressure by patients at home has become increasingly popular in recent years, in parallel with the exploding availability of electronic, easy to use, and affordable blood pressure measuring devices.[228] Home blood pressures are usually lower than office blood pressures and have a better prognostic significance than blood pressures obtained in a clinical setting. The value of 135/85 mm Hg may be considered as the upper limit of normality (Table 86.9).[192,193,198,228] Training of patients is essential to obtain reliable blood pressure readings. Patients should measure their blood pressure at home twice in the morning and twice in the evening for at 3 working days if a therapeutic decision has to be taken. Self–blood pressure monitoring is particularly helpful to detect white-coat hypertension, to guide antihypertensive therapy, and to improve the patient's compliance with antihypertensive therapy.

Hypertension as a Vascular Disease

There is growing interest in refining the definition of hypertension to focus on the vasculature and heart in addition to the blood pressure. Such definitions suggest that an abnormal vasculature (thick or stiff arteries, plaque formation, endothelial dysfunction, increased left ventricular mass) represents the disease that mandates blood pressure reduction and hypolipidemic therapy. Since many so-called normotensive individuals have demonstrable disease and many so-called hypertensive patients do not, the goal of this new definition is to bring greater precision to identifying individuals at risk who can benefit from treatment.

Hypertension in Childhood and Adolescence

The prevalence of hypertension in the young is much lower than in adults. The blood pressure elevation is generally mild when it is an early expression of essential hypertension, and severe hypertension mandates a screen for secondary forms of hypertension.[229] Guidelines for upper limits of blood pressure normalcy in children and adolescents are given in Table 86.10.[230]

TABLE 86.10. Classification of hypertension in the young by age group

		High normal	*Significant hypertension*	*Severe hypertension*
Percentile		≥90th	≥95th	≥99th
Infants (≥2 yr)	SBP	≥104	≥112	≥118
	DBP	≥70	≥74	≥82
Children (3–5 yr)	SBP	≥108	≥116	≥124
	DBP	≥70	≥76	≥84
Children (6–9 yr)	SBP	≥114	≥122	≥130
	DBP	≥74	≥78	≥86
Children (10–12 yr)	SBP	≥122	≥126	≥134
	DBP	≥78	≥82	≥90
Adolescents (13–15 yr)	SBP	≥130	≥136	≥144
	DBP	≥80	≥86	≥92
Adolescents (16–18 yr)	SBP	≥136	≥142	≥150
	DBP	≥84	≥92	≥98

DBP, diastolic blood pressure (mm Hg); SBP, systolic blood pressure (mm Hg).

Hypertension in Pregnancy

Blood pressure during pregnancy should not exceed 140/90 mm Hg, and lower values are desirable.[231] Hypertension during pregnancy comprises preexisting hypertension, gestational hypertension (known as preeclampsia when associated with proteinuria), and preexisting hypertension with worsening of blood pressure and development of proteinuria during pregnancy.[232] Hypertension during pregnancy, especially gestational hypertension with proteinuria, might have an adverse impact on neonatal and maternal outcomes.

Malignant Hypertension

Malignant hypertension is a form of hypertension progressing rapidly to terminal renal failure if untreated.[233] This condition is characterized by a severe hypertension, grade IV retinopathy, and impaired renal function due to thrombotic microangiopathy. All types of hypertension may progress to this fulminating disease, but the risk is particularly prominent in patients with underlying renal disease. The incidence of malignant hypertension has declined, probably because of early diagnosis and improved management of hypertension in recent years.

Assessment of Risk

Hypertension guidelines prevailing today stress the importance of correcting all modifiable risk factors when treating patients with high blood pressure.[192–196] Most of them propose a risk stratification strategy based on blood pressure levels as well as on the presence or absence of concomitant cardiovascular risk factors, target organ damage, and associated clinical conditions. Table 86.11 illustrates the factors influencing prognosis to be taken into account according to the World Health Organization/International Society of Hypertension guidelines.[194] The risk stratification approach allows the classification of patients in three categories with increasing likelihood of developing a major cardiovascular event within the next 10 years: low risk, <10%; medium risk, 15% to 20%; and high risk, >20%. The option proposed by the JNC 7 report is different as the decision to treat hypertension should be taken primarily on blood pressure levels, with no need of a risk stratification.[193]

Treatment

Nonpharmacologic Control of Hypertension

Environmental factors may contribute importantly to the blood pressure elevation observed in hypertensive patients. By changing the patent's lifestyle, it is possible to lower blood pressure in a large portion of patients with established hypertension as well as to prevent the development of hypertension in many persons at risk of developing high blood pressure. Various nonpharmacologic therapies are now advocated as first-line intervention in patients diagnosed as hypertensive. This approach is safe and may be enough to normalize blood pressure, mainly in patients with slightly increased blood pressure. Moreover, nondrug therapy may enhance the efficacy of antihypertensive therapy, allowing a reduction of medication requirements.[192–196]

Sodium Restriction

Long-term adherence to rigid sodium restriction, especially for asymptomatic hypertensive patients, is difficult. It is therefore reasonable to restrict only modestly the dietary sodium intake, to about 100 mmol/day. That the dietary manipulation is really effective in lowering blood pressure is exemplified in Figure 86.17, which relates the changes in

TABLE 86.11. Stratification of risk to quantify prognosis

	Blood pressure (mm Hg)		
Other risk factors and or disease history	*Grade 1 (SBP 140–159 or DBP 100–109)*	*Grade 2 (SBP 160–179 or DBP 100–109)*	*Grade 3 (SBP ≥ 189 DBP ≥ 110)*
I No other risk factors	Low risk	Medium risk	High risk
II 1 to 2 risk factors	Medium risk	Medium risk	High risk
III 3 or more risk factors, or TOD, or ACC	High risk	High risk	High risk

SBP, systolic blood pressure, mm Hg; DBP, diastolic blood pressure, mm Hg; TOD, target-organ damage; ACC, associated clinical conditions.

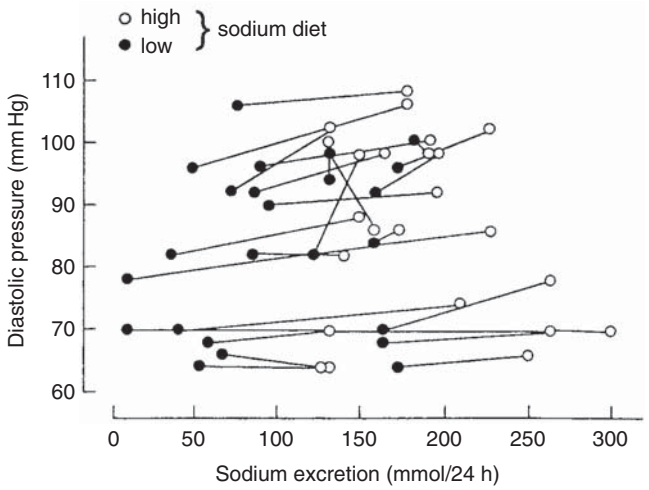


FIGURE 86.17. Systolic and diastolic blood pressures on a high- and a low-sodium intake in 16 studies published from 1973 to 1987.

diastolic pressure to those in 24-hour urinary sodium excretion observed in 16 studies.[234] For a 100 mmol/day reduction in sodium intake, systolic pressure may be expected to decrease by 5.4 mm Hg and diastolic pressure by 6.5 mm Hg. Not every patient responds, however, to the change in sodium balance with a blood pressure fall. Moderate salt restriction also has a demonstrable blood pressure lowering effect as an adjuvant to antihypertensive therapy.

An effective way to reduce sodium intake is to adopt the healthy DASH (Dietary Approaches to Stop Hypertension) eating plan consisting of a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat.[235]

Weight Reduction

Weight reduction in obese patients is associated with a well-documented reduction of blood pressure. This is illustrated in Figure 86.18, which is taken from an analysis of 11 published trials.[234] For each 1-kg fall in body weight, systolic and diastolic pressures are anticipated to decrease by 1.6 and 1.3 mm Hg, respectively. Part of the blood pressure lowering effect of low calorie diets may be due to a concomitant reduction in sodium intake.

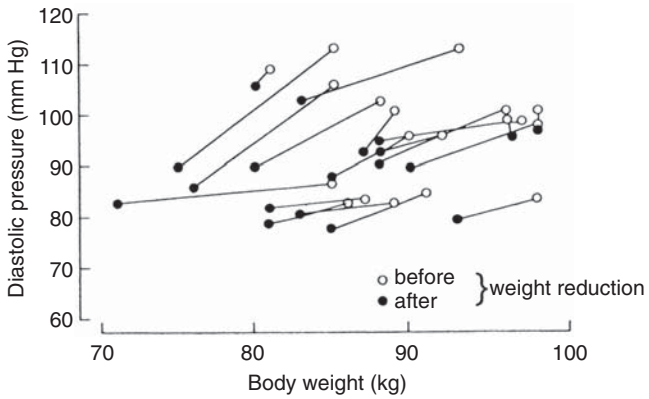


FIGURE 86.18. Systolic and diastolic blood pressures before and after body weight reduction in 11 studies published from 1954 to 1985.

Alcohol Restriction

Reduction of alcohol consumption has a significant blood pressure lowering effect. Moderating alcohol intake to no more than two standard drinks a day (20 g equivalent absolute ethanol) seems to be wise advice, particularly since alcohol consumption in this range may have a protective effect against cardiovascular disease.[236]

Physical Exercise

Regular physical exercise not only has a lowering effect on blood pressure but also influences favorably other risk factors by increasing HDL cholesterol and by helping to maintain normal body weight and to discourage smoking.[237] The physical training need not be strenuous to be efficacious. Dynamic, predominantly isotonic exercise (walking, jogging, running, bicycling, swimming) should be preferred to static, isotonic exercise (weight lifting), the latter inducing considerable elevations of blood pressure during the effort. In a meta-analysis of 44 randomized trials, regular physical exercise has been shown to lower blood pressure in hypertensive patients by an average of 7.4/5.8 mm Hg.[238] The frequency, duration, and intensity of exercise have to be tailored to the individual patient (for instance, brisk walking for at least 30 minutes, most days of the week, or jogging for 20 to 30 minutes, two to three times a week). The intensity of exercise can be expressed by the level of perceived exertion (patients should be able to talk during exercise; if they cannot, they should decrease the exercise), or based on the heart rate (HR) achieved during exercise [HR to be achieved during exercise = resting HR × x% of maximal HR (maximal HR = 220 − age; x = 50% for light exercise, 50% to 75% for moderate exercise, and >75% for heavy exercise)].

Pharmacologic Treatment

Over the last two decades, the treatment of hypertension has improved considerably. Several new well-tolerated antihypertensive drugs have become available that have enhanced the therapeutic possibilities. The major classes of antihypertensive agents are diuretics, beta-blockers, ACE inhibitors, angiotensin II antagonists (AT_1-receptor blockers), calcium antagonists, and α_1-blockers (Fig. 86.19). All these drugs have the advantage of lowering blood pressure by different mechanisms. This is very important since hypertension is a highly heterogeneous disease. Additionally, these drugs can be combined when required. Table 86.12 gives a list of specific antihypertensive agents and their recommended doses.

Diuretics

Diuretics are still a cornerstone in the management of hypertension.[192–196] These medications inhibit renal sodium reabsorption in the early distal convoluted tubule (thiazides, metolazone, indapamide), in the thick ascending limb of the loop of Henle (furosemide, bumetanide, ethacrynic acid, toresemide), or in the late distal convoluted tubule and the

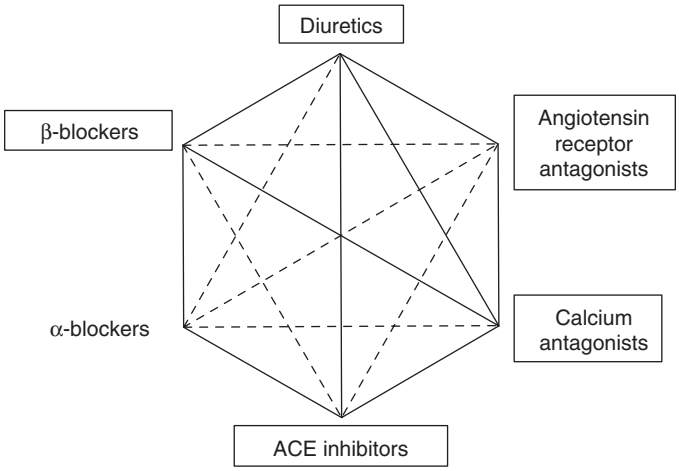


FIGURE 86.19. The main classes of antihypertensive agents. The frames indicate classes proven to be beneficial in controlled interventional trials and widely considered as a first-line option to initiate antihypertensive therapy. When required, the different classes of agents can be combined. The most rational combinations are represented by thick lines.

TABLE 86.12. Antihypertensive drugs and dosage recommendations

Class	*Drug*	*Usual dose Range, mg/d*	*Usual daily frequency**
Thiazide diuretics			
	Chlorothiazide	125–500	1–2
	Chlorthalidone	12.5–25	1
	Hydrochlorothiazide	12.5–50	1
	Polythiazide	2–4	1
	Indapamide	1.25–2.5	1
	Metolazone	0.5–5	1
Loop diuretics			
	Bumetanide	0.5–2	2
	Furosemide	20–80	2
	Toresemide	2.5–10	1
Potassium-sparing diuretics			
	Amiloride	5–10	1–2
	Triamterene	50–100	1–2
Aldosterone receptor blockers			
	Eplerenone	50–100	1
	Spironolactone	25–50	1
Beta-blockers			
	Atenolol	25–100	1
	Betaxolol	5–20	1
	Bisoprolol	2.5–10	1
	Metoprolol	50–100	1–2
	Metoprolol extended release	50–100	1
	Nadolol	40–120	1
	Nebivolol**	2.5–5	1
	Propranolol	40–160	2
	Propranolol long–acting	60–180	1
	Timolol	20–40	2
Beta-blockers with intrinsic sympathomimetic activity			
	Acebutolol	200–800	2
	Penbutolol	10–40	1
	Pindolol	10–40	2
Combined α-blockers and β-blockers			
	Carvedilol	12.5–50	2
	Labetalol	200–800	2
ACEIs			
	Benazepril	10–40	1
	Captopril	25–100	2
	Enalapril	5–40	1–2
	Fosinopril	10–40	1
ACEIs			
	Lisinopril	10–40	1
	Moexipril	7.5–30	1
	Perindopril	4–8	1
	Quinapril	10–80	1
	Ramipril	2.5–20	1
	Trandolapril	1–4	1
Angiotensin II antagonists			
	Candesartan	8–32	1
	Eprosartan	400–800	1–2
	Irbesartan	150–300	1
	Losartan	25–100	1–2
	Olmesartan	20–40	1
	Telmisartan	20–80	1
	Valsartan	80–320	1–2

Class	*Drug (Trade Name)*	*Usual Dose Range, mg/d*	*Usual Daily Frequency**
CCBs—Nondihydropyridines			
	Diltiazem extended release	180–420	1
	Diltiazem extended release	120–540	1
	Verapamil immediate release	80–320	2
	Verapamil long acting	120–480	1–2
	Verapamil	120–360	1
CCBs—Dihydropyridines			
	Amlodipine	2.5–10	1
	Felodipine	2.5–20	1
	Isradipine	2.5–10	2
	Nicardipine sustained release	60–120	2
	Nifedipine long-acting	30–60	1
	Nisoldipine	10–40	1
α_1-blockers			
	Doxazosin	1–16	1
	Prazosin	2–20	2–3
	Terazosin	1–20	1–2
Central α_2-agonists and other centrally acting drugs			
	Clonidine	0.1–0.8	2
	Clonidine patch	0.1–0.3	1 weekly
	Methyldopa	250–1000	2
	Moxonidine**	0.2–0.6	1–2
	Reserpine	0.1–0.25	1

*In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval (trough effect). BP should be measured just prior to dosing to determine if satisfactory BP control is obtained. Accordingly, an increase in dosage or frequency may need to be considered. These dosages may vary from those listed in the *Physicians' Desk Reference,* 57th ed.

**Not included in the JNC7 report.

collecting duct (spironolactone, triamterene, amiloride). Thiazides (hydrochlorothiazide, chlorothiazide, chlorthalidone, bendrofluazide) become ineffective when glomerular filtration rate is below 30 to 40 mL/min. In patients with impaired renal function, the natriuretic action of metolazone, and even more that of loop diuretics, is preserved. Thiazides, metolazone, and loop diuretics increase urinary potassium excretion and tend to decrease body potassium stores, which may result in hypokalemia. In contrast, spironolactone and eplerenone (which compete with aldosterone for receptor sites), amiloride, and triamterene are potassium sparing. The dose-response curve of thiazides, in terms of natriuresis, is quite flat. The occurrence of side effects such as hypokalemia, hyponatremia, hyperuricemia, hyperglycemia, and hypercholesterolemia has a clear-cut dose-dependent character, so that there is an advantage to using only low doses of thiazides. With regard to loop diuretics, increments in doses, even if considerable, are still associated with an enhanced natriuretic response. A disadvantage of the latter diuretics is a rapid onset and a short duration of action, whereas the other types of diuretics have a smoother and more prolonged action, allowing once a day administration. Diuretics with potassium-retaining properties should not be used in patients with renal failure, as the risk of developing a life-threatening hyperkalemia exists. Combinations of thiazide with potassium-sparing diuretics are very popular. Triamterene and amiloride have only a limited natriuretic activity, but their antikaliuretic effect is sufficient to prevent the thiazide-induced hypokalemia in most patients.

The mechanisms involved in the blood pressure lowering action of diuretics are not yet fully understood. At initiation of therapy, the plasma volume is reduced, but this effect does not persist after a few weeks of treatment, despite a persistent decrease in total body sodium, as manifested by a weight gain after drug withdrawal. The long-term antihypertensive effect of diuretics may be due to an attenuation of the vascular responsiveness to pressor stimuli, perhaps as a consequence of a decreased vascular wall content in sodium, the latter being expected to reduce free intracellular calcium.[127] A key limiting determinant of the blood pressure lowering effect of diuretics is the hyperreninemia triggered by the salt depletion. Sources of concern for the use of thiazides are mainly the development of hypokalemia (and hypomagnesemia), which may be linked to an enhanced risk of ventricular arrhythmia, and the existence of unfavorable effects on carbohydrate and lipid metabolism. Diuretics can increase insulin resistance, precipitate overt diabetes in susceptible patients, and increase cholesterol and triglyceride levels. Indapamide and spironolactone seem to be more neutral with regard to the glucose and lipid profiles. As already stressed, potassium depletion is rarely a problem when thiazides are prescribed at a low dosage. Moreover, with the doses currently recommended (e.g., 12.5 to 25 mg/day for hydrochlorothiazide), there is generally no sustained metabolic alteration. Diuretics have proven beneficial effects in the prevention of cardiovascular diseases and still belong, if used at appropriate doses, IN the first-choice medications for the treatment of hypertension. Nonsteroidal antiinflammatory drugs blunt importantly the natriuretic potency of diuretics and may lead to deterioration of renal function. Of note are that spironolactone, mainly at doses exceeding 50 mg/day, can occasionally cause a gynecomastia and that rapid intravenous administration of loop diuretics at high doses is potentially ototoxic.

Beta-Blockers

A large number of beta-blockers are now registered worldwide. All of them compete with catecholamines for β-adrenergic receptors. Some agents bind selectively to β_1-adrenergic receptors that are confined, in the cardiovascular system, to cardiac muscle and conductive system (atenolol, betaxolol, bisoprolol, metoprolol), while others (nadolol, propranolol, sotalol, timolol) block at the same time β_1- and β_2-adrenergic receptors, the latter being located pre- and postsynaptically at the level of sympathetic endings innervating blood vessels as well as on the bronchial smooth muscle. Several agents have an intrinsic sympathomimetic activity (acebutolol, bopindolol, carteolol, oxprenolol, pindolol). Labetalol is a mixture of stereoisomers, one being beta-blocker and another α_1-blocker. Carvedilol has also at the same time β- and α-blocking properties. Some beta-blockers are hydrophilic (acebutolol, atenolol, sotalol) and do not easily pass the blood–brain barrier. Sotalol possesses a class III, amiodarone-like antiarrhythmic activity. Celiprolol has some β_2-agonistic activity. Nebivolol, a β_1-selective blocker, might induce some vasodilation by triggering the release of NO from the endothelium. The various ancillary properties of beta-blockers are not really relevant for long-term antihypertensive efficacy,[239] but they may be more important for the safety profile. Cardioselective agents may be preferred in diabetics on insulin-therapy, since β_2-stimulation helps to restore normal glucose in patients with hypoglycemia. It appears also rational to use a β_1-selective agent in patients with peripheral artery disease as well as in those at risk of pulmonary decompensation, since bronchial spasm could be more easily reversed by a β_2-agonist. The intrinsic sympathomimetic activity can influence the hemodynamic response. Agents with such an activity decrease heart rate and cardiac output only slightly at rest. Beta-blockers tend to reduce HDL cholesterol. This is, however, probably less the case for compounds with intrinsic sympathomimetic or β_1-selective effects. Beta-blockers having poor access to the brain may have fewer central side effects. During chronic administration, all beta-blockers can be given once a day or at most twice daily.

The mechanisms of action of beta-blockers are still not fully elucidated. The contribution of a centrally mediated decrease in sympathetic nerve activity cannot be ruled out. Acutely, the fall in blood pressure induced by β_1- and β_2-adrenergic receptor blockade is associated with an increase in peripheral vascular resistance, but a progressive decline in peripheral resistance is observed with prolonged treatment. One possible explanation is a presynaptic inhibition by the beta-blocker of the positive feedback normally exerted by catecholamines on the release of norepinephrine (Fig. 86.2). Also to be considered is an autoregulatory dilatation of resistance vessels in response to the beta-blocker–induced reduction in cardiac output and tissue perfusion. Still another factor is an inhibition of renin release, mainly with agents lacking any sympathomimetic activity. A disadvantage of beta-blockers is the diminution of exercise capacity. The occurrence of side effects is dose related (asthenia, vivid

dreams, sexual dysfunction, cold extremities). Beta-blockers have negative inotropic and chronotropic effects and may precipitate heart block or congestive heart failure, especially in older patients remaining severely hypertensive during treatment. Asthma may develop in predisposed patients. There is a large body of evidence to suggest a cardioprotective effect of beta-blockers.[240] Such an effect is well documented in postinfarction patients using agents with no intrinsic sympathomimetic activity. Beta-blockers were also part of the treatment of the major interventional trials that have demonstrated a beneficial effect of antihypertensive therapy in the primary prevention of cardiovascular complications. There is, however, a growing concern about the possible adverse impact of antihypertensive drugs on new-onset diabetes.[241,242] It seems that beta-blockers, especially when combined with a thiazide diuretic, increase the risk of developing new diabetes. Carvedilol might improve rather than deteriorate insulin resistance, possibly because this compound has both α- and β-adrenoceptor blocking properties.[243] Today beta-blockers represent still a valuable first-line modality for treating hypertensive patients.

Calcium Antagonists

There exist three major classes of calcium antagonists: the phenylalkylamines (verapamil), the dihydropyridines (amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine), and the benzothiazepines (diltiazem).[244–246] These agents cause vasodilatation by blocking the entry of calcium ions from the extracellular space into the cytoplasm of the cell through voltage-dependent calcium channels. The various types of calcium antagonists can be more or less selective for the heart and the vasculature. Verapamil has the greatest chronotropic and inotropic depressant actions, while the dihydropyridines exert more effect on vascular smooth muscle cells. Diltiazem has an intermediate position, being less potent than verapamil in the heart and less potent than dihydropyridines in blood vessels. The blood pressure lowering effect of calcium antagonists is clearly dose dependent, and the duration of action is related both to the drug and to the administration form. Slow-release preparations have now been developed for most calcium antagonists, making it possible often to administer the medication in a single daily dose. Calcium antagonists are highly metabolized by the liver. The vasodilatation induced by dihydropyridines is frequently accompanied by a reflex increase in sympathetic nerve activity. This counterregulatory mechanism may oppose the fall in blood pressure and tends to be most pronounced at initiation of treatment and to resolve thereafter, perhaps by resetting of the baroreceptor reflex at a lower blood pressure. The most common side effects of calcium antagonists, mainly of the dihydropyridines, are due to the vasodilatation (headache, palpitations, flushing, edema). They are dose dependent, and their incidence can be reduced by using controlled-release forms that tend to prevent large fluctuations in the concentration of the active drug in the blood. The edema is not due to sodium retention, since calcium antagonists possess a natriuretic action, but likely reflects an increased capillary pressure due to arteriolar dilatation. For verapamil, constipation may become a problem when high doses are used. With this medication, atrioventricular block may occasionally occur. Diltiazem is usually well tolerated. Calcium antagonists are neutral in terms of carbohydrate and lipid metabolism.

A few years ago there was a controversy about the safety of calcium antagonists.[247–249] The concerns were that these vasodilating agents might increase the risk of coronary heart disease, cancer, and bleeding. The experience accumulated with calcium blockers has been reviewed in detail by experts. The conclusions were that long-acting calcium antagonists have no adverse impact on the cardiovascular outcome of hypertensive patients.[218,250] Preference should be given to long-acting compounds since, unlike short-acting calcium antagonists, they usually do not trigger a reflex activation of the sympathetic nervous system when lowering blood pressure.[246] Calcium antagonists appeared also not harmful with regard to the risk of cancer and bleeding.[250] Today there is no doubt anymore that calcium antagonist–based regimens confer cardiovascular protection to hypertensives.[218] Calcium antagonists represent a first-choice antihypertensive drug class.

ACE Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors have acquired a wide acceptance as first-line antihypertensive drugs.[251] These agents are generally well tolerated when lowering blood pressure, and the patient's well-being and quality of life do not deteriorate during treatment. Captopril and lisinopril are effective without bioactivation after oral ingestion and absorption, whereas all other ACE inhibitors are administered as prodrugs (benazepril, cilazapril, enalapril, fosinopril, perindopril, quinapril, ramipril, and spirapril) and require de-esterification in the liver to form the active metabolite. Captopril has a rapid onset of action and may decrease blood pressure within minutes, whereas the antihypertensive action of the other inhibitors starts with a few (usually 1 to 3) hours delay. The inhibitory effect of captopril on ACE activity is short lasting, and even high doses of this agent are not sufficient to block the angiotensin I processing enzyme around the clock when given once a day. The other compounds have a more or less longer duration of action. Noteworthy, during prolonged therapy, effective control of blood pressure can be maintained even if converting enzyme intermittently recovers enough activity to generate angiotensin II.[252] The discrepancy between the profile of ACE inhibition and that of the blood pressure fall is particularly striking for captopril, as this compound can often be used successfully in one dose per day. The dosage of most ACE inhibitors should be reduced in patients with impaired renal function. This is less a problem for benazepril, fosinopril, quinapril, and spirapril, since these agents have a dual excretion by the kidney and the liver.

Angiotensin-converting enzyme inhibitors cause a dilatation not only of arterioles and large arteries, but also of the capacitive system. This might partly explain the lack of reflex increase in heart rate even in the face of a blood pressure drop. Another potential reason is that angiotensin II may reinforce the contribution of the sympathetic nervous system to blood pressure maintenance. Whether ACE inhibitors act to some extent by blocking the generation of angiotensin II within vascular smooth muscle cells is still debated.

Also to be considered is the local accumulation, in response to ACE inhibition, of bradykinin. This peptide could trigger the release of both NO and prostacyclin from the endothelium. Aldosterone secretion tends to decrease during ACE inhibition, an effect that may help to counteract the antinatriuretic effect of the blood pressure fall. Angiotensin I levels increase during ACE inhibition. This leads to an increased production of angiotensin-(1–7) by the action of neutral endopeptidase that is not blocked by ACE inhibitors. Interestingly, angiotensin-(1–7) might function as a vasodilator hormone.[253]

Angiotensin-converting enzyme inhibitors are effective in lowering blood pressure in all forms of hypertension. Their efficacy is on the average better in patients with high renin levels than in those with normal or low renin levels, but blockade of angiotensin II synthesis normalizes blood pressure even in a substantial number of patients with suppressed renin activity. Renin profiling, therefore, cannot serve as a reliable indicator of the chronic blood pressure response to ACE inhibition in the individual patient. Angiotensin-converting enzyme inhibitors show equivalent efficacy in all age classes of the population.[254] As monotherapy, these agents are more likely to control blood pressure in white than in black individuals.

Angiotensin-converting enzyme inhibitors have few side effects. By far the most common is a dry cough, which may be related to the accumulation of kinins, substance P, or prostaglandins.[255] Angioedema is a rare but potentially serious reaction to this type of drug. Its mechanisms may again involve kinins, together with an activation of the complement system.[256] The risk of a dangerous increase in serum potassium is small during ACE inhibition unless the drug is combined with a potassium-sparing diuretic, the patient takes oral potassium supplementation, or the renal function is impaired.[257] Skin rashes and dysgeusia were seen quite often during the early years of experience with captopril, when very high doses of this agent were commonly administered. Angiotensin-converting enzyme inhibitors may cause a deterioration of renal function in patients with renal impairment and patients with renal artery stenosis, especially if bilateral. This adverse effect of ACE inhibition relates to the dependence in these patients of glomerular filtration pressure on an angiotensin II–mediated contraction of the efferent arteriole (Fig. 86.20).

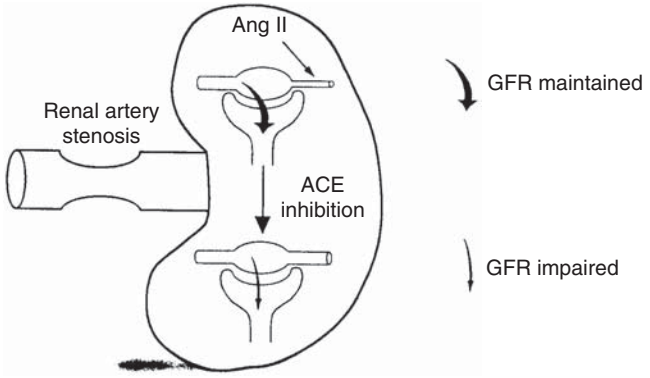


FIGURE 86.20. Effect of ACE inhibition on glomerular filtration rate (GFR) in a kidney irrigated by a stenotic renal artery.

Angiotensin-converting enzyme inhibitors are very attractive in view of the lack of adverse effects on carbohydrate and lipid metabolism. A consistent finding during ACE inhibition is an increased sensitivity to insulin and a reduced incidence of new-onset diabetes compared with conventional therapies such as diuretics and beta-blockers.[241,242]

Angiotensin-converting enzyme inhibitors are increasingly used as first-line medications for the treatment of hypertension as they have been shown to afford cardiovascular protection in interventional, placebo-controlled trials. Drug regimens comprising an ACE inhibitor are equally effective in reducing the risk of major cardiovascular events than regimens based on diuretics, beta-blockers, or calcium antagonists.[218]

Angiotensin II Antagonists

A specific approach to block the renin-angiotensin system is to prevent the binding of angiotensin II at its receptor. This can be done using orally active competitive antagonists of angiotensin II.[258] Those available for clinical use block selectively the AT_1 subtype of angiotensin II, that is, the receptor responsible for all well-established actions of angiotensin II. The first available AT_1-receptor blocker was losartan potassium. After oral administration, this compound is rapidly and extensively transformed to long-acting metabolite, whereas the parent compound, in addition to having a short-lasting blocking effect on the AT_1 receptor, has an uricosuric effect that results in a slight decrease in uricemia. Other angiotensin II antagonists have been developed (candesartan, irbesartan, olmesartan, telmisartan, valsartan). These agents do not need any transformation to block AT_1 receptor. The comparative antihypertensive efficacy of angiotensin II antagonists and ACE inhibitors is a key issue. The two types of blockers of the renin-angiotensin system seem to provide equivalent blood pressure results.

Angiotensin II antagonists have typically a very flat dose-response curve with regard to the incidence of adverse events. Usually, with these drugs, the rate of adverse effects is comparable with that of placebo. Unlike ACE inhibitors, angiotensin II antagonists do not cause cough. During AT_1-receptor blockade, the negative feedback on renin secretion normally exerted by angiotensin II is prevented so that a reactive hyperreninemia develops. AT_1-receptor antagonists leave the AT_2-receptor unopposed. During AT_1 blockade there is therefore an increased stimulation of AT_2 receptors. Whether this is clinically relevant remains unknown. Until now there is no evidence for any problem related to a hyperstimulation of AT_2 receptors. AT_1-receptor blockers have no adverse impact on lipid metabolism, improve insulin sensitivity, and reduce the incidence of new-onset diabetes.[241,242,259] Irbesartan and telmisartan enhance PPARγ activity, a potentially beneficial effect in the prevention of diabetes.[260]

AT_1-receptors blockers represent a valuable option to initiate antihypertensive therapy as they are known to be effective in preventing major cardiovascular events.[218,261]

α_1-Blockers

Selective α_1-adrenergic receptor blockade lowers blood pressure by preventing catecholamine-induced vasoconstriction.[262] Norepinephrine released by sympathetic terminals

can still exert an inhibitory action on catecholamine discharge, as presynaptic receptors belong to the α_2-subtype (Fig. 86.2). This probably explains the greater long-term efficacy of pure α_1-blockers relative to nonselective α_1- and α_2-blockers, as well as the lack of tachycardia. Prazosin was the first α_1-blocker available for clinical use. This drug is short-lasting and has to be given at rather high doses three times a day to be effective. Early experience with this agent has revealed a high incidence of orthostatic hypotension. Moreover, syncopal episodes can occur during initiation of treatment unless a very small dose was used. Slow-release preparations of prazosin now exist in some countries and provide a smoother delivery of the drug. With these formulations, orthostatic hypotension and first-dose collapse have become infrequent. The newer long-acting α_1-blockers have a slow onset of action (terazosin, doxazosin) and are well tolerated. Doxazosin can be administered once daily. α_1-Blockers also have the advantage of no adverse effect on carbohydrate and lipid metabolism. These agents improve insulin sensitivity and HDL cholesterol while reducing modestly total cholesterol, LDL cholesterol, and triglycerides.[263,264] α_1-Blockers are considered today as a second-line therapy, as they seem to increase the risk of cardiac decompensation.[265]

Others

Second-choice antihypertensive agents include a number of inexpensive medications that are still widely used in some areas of the world but that are being increasingly replaced by modern drugs with greater patient acceptability. Reserpine acts by depleting norepinephrine stores in sympathetic nerve endings. Common complaints are drowsiness, sedation, and nasal congestion. A major drawback of this medication is depression, which may develop insidiously. α-Methyldopa is metabolized to α-methylnorepinephrine, which stimulates α_2-adrenergic receptors located at strategic sites in the brainstem, resulting in an inhibition of sympathetic outflow. α-Methyldopa-associated side effects are sedation, dizziness, dry mouth, orthostatic hypotension, and impotence. The direct antiglobin test (Coombs' test) may be positive, and hemolytic anemia is sometimes observed. Rebound hypertension upon withdrawal of treatment might occur. Clonidine is an α_2-adrenergic receptor agonist readily crossing the blood–brain barrier and decreasing sympathetic nerve activity via a central mechanism. This agent frequently causes sedation, dry mouth, constipation, and impotence. Clonidine treatment should not be stopped abruptly to avoid the occurrence of rebound hypertension. A new centrally acting drug (moxonidine) is currently available.[266] This drug reduces sympathetic nerve activity by activating central imidazoline receptors and seems to have a more favorable tolerability profile than older centrally acting agents. Hydralazine, dihydralazine, and minoxidil are pure dilators of the arterial bed. Their long-term antihypertensive efficacy is limited by reflexly mediated counterregulatory mechanisms (increase in heart rate and myocardial contractility, sodium retention). The most common side effects are in conjunction with the vasodilatation (headache, tachycardia, palpitations). Hydralazine and dihydralazine might cause a systemic lupus erythematosus–like syndrome. Minoxidil has the most potent vasodilatory activity. It has to be given with large doses of diuretics to avoid sodium and water retention, and a beta-blocker should be systematically coadministered to prevent heart rate acceleration. The minoxidil-induced vasodilatation is associated with a marked hirsutism, which represents a major problem in children and women.

Sequential Monotherapy

For many years, hypertensive patients have been treated according to the classic stepped-care approach, a second drug being added to the first-line therapy whenever the latter is insufficient to normalize blood pressure.[267] The concept of sequential monotherapy has then emerged.[268] It is derived directly from the inability to predict the blood pressure response to antihypertensive drugs in an individual patient. The purpose of this approach is to establish for each patient the most adequate drug that will control blood pressure when administered as monotherapy (Fig. 86.21). The concept is based on the following observation: most antihypertensive agents of the different therapeutic classes exhibit similar response rates (blood pressure <140/90 mm Hg), of approximately 30% to 40%.[269] However, not every drug normalizes blood pressure in exactly the same fraction of patients. It is therefore possible to normalize blood pressure in more patients by switching one drug to another acting by a different mechanism. This does not mean, however, that every patient should receive consecutively a diuretic, a beta-blocker, a calcium antagonist, a blocker of the renin-angiotensin system, and an α_1-blocker. The presence of associated diseases may preclude the administration of some classes of drug. In some patients, agents may be avoided in order to preserve the patient's lifestyle. For example, beta-blockers might not be chosen for a young patient involved in heavy athletic activities. One important aspect of sequential monotherapy is that drugs must be administered for several weeks in order to evaluate their efficacy appropriately. Thus,

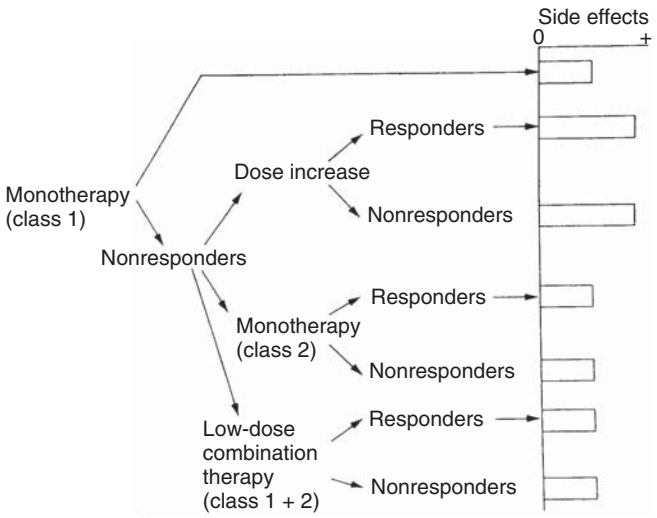


FIGURE 86.21. In nonresponders to a drug acting by a given mechanism, it is preferable, rather than to increase the dose, to switch to another type of antihypertensive agent or to add a small dose of another medication having a different impact on the cardiovascular system.

antihypertensive therapy should ideally not be modified at intervals of less than 4 to 6 weeks. In general, this does not represent a major limitation in patients with moderate uncomplicated hypertension. Although this traditional goal to seek blood pressure control with sequentially selected monotherapy is attractive, the recent therapeutic trend has focused on combination drug therapy for optimal management. Indeed, recent trials have demonstrated that to achieve target blood pressure goals, three or four antihypertensive drugs may be required.

Combination Therapy

Most patients respond to antihypertensive therapy at relatively low doses. Increasing the dosage allows blood pressure to be controlled in more patients, but often at the expense of a higher incidence of side effects. When monotherapy is insufficient to control blood pressure, it is wiser to use a low-dose combination therapy than to increase the dose of a given drug given as monotherapy (Fig. 86.21).[270–272] The six major therapeutic classes act via different mechanisms and can therefore be combined successfully (Fig. 86.19). Diuretics are very useful when associated with any other class of agents. The combination of an ACE inhibitor or an AT_1-receptor blocker with a diuretic is particularly efficacious. Indeed, after blockade of the renin-angiotensin system, blood pressure maintenance depends very much on total body sodium. Commonly, small doses of diuretics are sufficient when combined with a blocker of the renin-angiotensin system. In some cases, however, more potent diuretics such as loop diuretics must be used and titrated to obtain an optimal blood pressure response. In patients already being treated with diuretics, the introduction of a blocker of the renin-angiotensin system should be done cautiously, and it may be wise, in order to avoid hypotension, to interrupt diuretic therapy for 2 or 3 days before adding the blocker. Aldosterone secretion is decreased during ACE inhibition and angiotensin II blockade and may cause serum potassium levels to increase. Nevertheless, potassium-sparing diuretics may be safely combined with blockers of the renin-angiotensin system as long as renal function is normal.[273] Diuretics also potentiate the antihypertensive efficacy of calcium-channel blockers and of beta-blockers. An efficacious and logical combination is the association of a calcium antagonist and a beta-blocker. The vasodilatation induced by dihydropyridine-type calcium antagonists is generally better tolerated after blockade of β-adrenergic receptors. The association of a beta-blocker with verapamil, a calcium-channel blocker with negative inotropic and chronotropic properties, is not recommended because of the increased likelihood of heart block. The ACE inhibitors and angiotensin II antagonists may be combined successfully with a beta-blocker or a calcium antagonist. There is also some evidence for a better blood pressure control when combining an ACE inhibitor and an angiotensin II antagonist. The principal goal of combination therapy is to maximize therapeutic efficacy while minimizing side effects. This is usually possible because low doses of the drugs are often adequate. The treatment can sometimes gain considerably in simplicity and acceptance from the patients by using well-balanced fixed low-dose combinations. Actually, such combinations may be regarded today as valuable options to initiate antihypertensive therapy,[192] especially when blood pressure is higher than 160/100 mm Hg.[193]

Associated Diseases

Hypertensive patients often present with concomitant diseases that must be taken into account when initiating antihypertensive therapy.[192–196] The individualization of treatment is therefore aimed at finding an efficacious and well-tolerated drug that possibly improves or at least does not worsen the course of associated diseases (Table 86.13).

Congestive Heart Failure

For many years, diuretics have played a major role in the treatment of patients with heart failure. More recently, ACE inhibitors, angiotensin receptor blocker (ARBs), and beta-blockers have emerged as important agents to be used in this condition.[274,275] Given alone or in combination with diuretics, blockers of the renin-angiotensin system are effective in treating normotensive patients with moderate or severe congestive heart failure. The situation is somewhat different in hypertensive patients with heart failure. Indeed, in this context, a decrease in blood pressure induced by any hypotensive drug may improve myocardial function. Thus, even drugs with negative inotropic effects may enhance cardiac performance as long as systemic blood pressure is reduced.

TABLE 86.13. Suggested use of antihypertensive drugs in patients with hypertension and associated diseases

Disease	*Diuretics*	*Beta-blockers*	*ACE inhibitors*	*Angiotensin II antagonists*	*Calcium antagonists*	*α-blockers*
Congestive heart failure	+++	++	+++	+++	+	+
Coronary artery disease	+	+++	++	++	+++	+
Left ventricular hypertrophy	++	+++	+++	+++	+++	+++
Renal failure	+++	++	++	++	++	++
Peripheral artery disease	++	+	++	++	+++	+++
Pulmonary obstructive disease or asthma	+++	–	+++	+++	+++	+++
Diabetes mellitus	++	++	+++	+++	++	+++
Hyperlipidemia	+	+	+++	+++	+++	+++
Hypertension during pregnancy	–	+++	–	–	+	+

ACE, angiotensin-converting enzyme; –, contraindicated; +, ++, +++, little to strongly indicated.

The long-term benefit of renin-angiotensin-aldosterone blockers and beta-blockers on the heart appear to be related to their effect to slow or reverse the left ventricular structural remodeling that characterizes heart failure.

Coronary Artery Disease

Beta-blockers and calcium antagonists belong to the first-line therapy of coronary insufficiency in normotensive patients. This is also true in hypertensive patients.[276] Blockers of the renin-angiotensin system may also be beneficial.[277–279]

Left Ventricular Hypertrophy

Cardiac hypertrophy usually regresses if a sustained reduction in blood pressure is achieved. This is indeed the case for patients treated with all classes of hypertensive agents used as first-line therapy.[280] In a meta-analysis involving 80 trials, left ventricular mass index decreased by 13% with AT_1-receptor blockers, by 11% with calcium antagonists, by 10% with ACE inhibitors, by 8% with diuretics and by 6% with beta-blockers.[281] In hypertensive patients with increased cardiac mass, AT_1-receptor blockade is more effective than β-adrenoceptor blockade in inducing left ventricular hypertrophy and provides, for an equivalent blood pressure fall, a superior cardiovascular protection.[282]

Chronic Kidney Disease

Diuretics have an important role in the management of hypertensive patients with renal failure, and their administration is generally necessary to control blood pressure adequately. Blockers of the renin-angiotensin system are particularly effective in reducing proteinuria and slowing the progression of chronic renal failure in hypertensive patients (diabetic or nondiabetic).[283,284]

Peripheral Vascular Diseases

The ACE inhibitors, AT-receptor blockers, and calcium antagonists, and beta-blockers are safe first-line therapies in hypertensive patients suffering from peripheral vascular disease. In contrast, beta-blockers are not usually recommended because they may aggravate claudication. However, a meta-analysis of 11 controlled studies has suggested that the effect of beta-blockers on intermittent claudication is minor.[285]

Bronchial Asthma and Chronic Obstructive Pulmonary Disease

Diuretics, ACE inhibitors, AT-receptor blockers, and calcium-channel blockers can usually be administered safely in patients with bronchial asthma or chronic obstructive pulmonary disease. In contrast, beta-blockers can worsen respiratory function in these patients. An agent with β_2-agonistic activity such as celiprolol might be safer if the administration of a beta-blocker is mandatory.[286]

Diabetes Mellitus

It is now well established that antihypertensive drugs might influence adversely the development of type 2 diabetes. The ACE inhibitors and AT_1-receptor blockers have been shown to improve insulin sensitivity[241,242,259] and delay or prevent the occurrence of new-onset diabetes, which seems to be a major advantage compared with diuretics and beta-blockers.[242,287]

The most important task in treating diabetics with hypertension is to normalize blood pressure, whatever the drugs used to achieve this goal. This is crucial, since lowering blood pressure decreases proteinuria and reduces the rate of decline in renal function. In the Hypertension Optimal Treatment (HOT) study, patients with diabetes mellitus had half of major cardiovascular events in the target group ≤80 mm Hg compared with the target group ≤90 mm Hg.[223] In diabetics, blood pressure should not exceed 130/85 mm Hg. Blockers of the renin-angiotensin system appear particularly beneficial in hypertensive diabetics. These agents can indeed delay the development of microalbuminuria[288] and the progression of the nephropathy to the end stage more effectively than blood pressure control alone.[289–293] Calcium antagonists are also effective antihypertensive drugs in hypertensive diabetics but, in contrast to ACE inhibitors, nifedipine appears to increase rather than decrease proteinuria in patients with diabetic nephropathy.[294] However, this does not appear to be the case for long-acting dihydropyridines.

Hyperlipidemia

As already mentioned, thiazide and beta-blockers may alter adversely lipid metabolism, whereas α-blockers might have a favorable effect.[264,295] During prolonged therapy with the various classes of first-choice antihypertensive agents, however, no significant change in total cholesterol and HDL cholesterol could be evidenced.[280]

Cerebrovascular Diseases

Until recently there was no evidence that some medications are more appropriate than others in the primary prevention of stroke.[296] It now appears that AT_1-blockade may be better in this respect compared with β-adrenoceptor blockade.[282] Elevations in blood pressure are commonly seen in patients with acute stroke, whether they were previously hypertensive or not.[297] In such patients, lowering blood pressure too rapidly and too drastically may reduce cerebral perfusion below the autoregulatory limit, which is generally shifted at a higher level of systemic pressure in ischemic brain areas.[298] Overtreatment following an acute cerebrovascular event, therefore, may aggravate the brain damage. In patients with extreme hypertension, it seems nevertheless justified to lower blood pressure cautiously to about 170/100 mm Hg within a few hours. Blockers of the renin-angiotensin system have well demonstrated protective effects in the secondary prevention of stroke.[299,300]

Hypertension represents a risk factor for cognitive impairment.[301] A significant reduction in the incidence of dementia has been observed in elderly patients with isolated systolic hypertension using a calcium antagonist-based regimen compared with placebo.[302]

Special Considerations

Elderly Patients

Diuretics and calcium antagonists have been claimed to be the most effective in patients with low renin levels, as it is

often the case in older people, the converse being true for beta-blockers and ACE inhibitors.[303] This view has received little support from most trials.[304] Indeed, any drug may normalize blood pressure in a given patient whatever his age. Actually, starting antihypertensive treatment in the elderly with a blocker of the renin-angiotensin system appears to provide a better cardiovascular outcome in comparison with a diuretic-based therapy, despite similar reductions of blood pressure.[305]

Pregnant Women

Nonpharmacologic therapy is particularly attractive for women with pregnancy-induced hypertension.[306] It may be particularly tempting to restrict salt intake, as the elevation of blood pressure is often accompanied by an excessive gain in body weight and edema. On the other hand, preeclampsic women generally have a decreased intravascular volume and salt depletion may worsen this condition, leading to an additional reduction in placental and renal function. Severe salt restriction is not currently recommended during pregnancy. The best nonpharmacologic measure is bed rest, which helps to shift interstitial fluid to the intravascular compartment and improves uterine and renal blood flow. Hospitalization is unfortunately most often required. Practically, it is more convenient to prescribe antihypertensive drugs and to propose bed rest if blood pressure cannot be satisfactorily controlled. Hydralazine and methyldopa have long been used as first-choice medications in pregnancy.[307] Beta-blockers and calcium antagonists (dihydropyridines) are preferable.[192,308] Diuretics should not be used, since they may cause an inappropriate contraction of blood volume. The ACE inhibitors are contraindicated, as they increase the risk of oligohydramnios, fetal anuria, and stillbirth when administered late during pregnancy. α_1-Blockers might also be useful, particularly when combined with a beta-blocker.

Resistant Hypertension

Resistant hypertension can be defined as the persistence of a blood pressure above 140/90 mm Hg despite a drug regimen comprising three or more antihypertensive agents in a rational combination (including a diuretic) at full doses.[309] Table 86.14 summarizes the main causes of resistant hypertension. In patients with refractory hypertension, it is imperative to search for secondary forms of hypertension and to eliminate a problem of noncompliance with the prescribed drug regimen. It may also be wise to make sure that the patient is really hypertensive outside the medical setting.[310] Furthermore, blood pressure measured noninvasively may overestimate the true intraarterial pressure of patients with rigid arteries.[311] There is unfortunately no easy, reliable test to recognize patients with such a pseudohypertension component. Frequently, blood pressure control can be improved by intensifying diuretic therapy, mainly when given on top of a blocker of the renin-angiotensin system. The use of aldosterone antagonists may be of great help to normalize blood pressure.[312] If needed, the dosage of calcium antagonist (preferably of the dihydropyridine class) or α_1-blockers can be increased. The potent vasodilator minoxidil may be useful, but it should be coadministered with a loop diuretic and a beta-blocker to prevent the occurrence of sodium retention and reflex tachycardia. Noteworthy, poor compliance with treatment represents still a leading cause of unsatisfactory blood pressure control.

TABLE 86.14. Causes of resistant hypertension

Misdiagnosis
"White-coat" hypertension
Pseudohypertension
Inappropriate cuff size
Failure to modify lifestyle
Excessive sodium intake
Weight gain
Heavy alcohol intake
Poor compliance
Inadequate treatment
Doses too low
Sodium retention
Activation of the renin-angiotensin system
Activation of the sympathetic nervous system
Secondary forms of hypertension (see Table 86.3)
Associated disorders
Sleep apnea
Chronic pain
Drug interactions (see Table 86.5)

Hypertensive Crisis

Alarming conditions necessitating a normalization of blood pressure within a few minutes are exceptional.[313] They consist mainly of hypertensive encephalopathy, a severe form of hypertension accompanied by neurologic manifestations (headache, alterations of mental status, seizures), of hypertension associated with pulmonary edema, acute myocardial infarction, dissecting aortic aneurysm, eclampsia, and sudden blood pressure elevations due to a surge of catecholamines [pheochromocytoma, rebound hypertension after clonidine withdrawal, acute blood pressure increase during treatment with an monoamine oxidase (MAO) inhibitor]. The most appropriate drug for the treatment of true hypertensive emergency is sodium nitroprusside, an arterial and venous vasodilator acting as a donor of NO inside the vascular smooth muscle cell. This parenterally active drug can be titrated very precisely according to the blood pressure response and usually does not cause a troublesome reflex heart rate acceleration. Accumulation of thiocyanate may occur if treatment is prolonged for several days. Thiocyanate toxicity may be manifested by blurred vision, tinnitus, confusion, and seizures. An option for intravenous infusion is the vasodilator dopamine-1 agonist fenoldopam.[314] Labetalol can be used if needed as small bolus or by continuous infusion even outside an intensive care unit (unlike sodium nitroprusside). This compound possesses at the same time α- and β-blocking properties and is particularly appropriate for the treatment of hyperadrenergic states. In patients with pheochromocytoma, intravenous administration of the α_1- and α_2-adrenergic receptor blocker phentolamine is effective, but a beta-blocker has generally to be added to prevent tachycardia. Nitrates may be helpful to lower blood pressure in patients with pulmonary edema or acute myocardial infarction. Except in the situations described above, it is safer to try to lower blood pressure progressively within a few hours

(hypertensive crisis). This is even true in patients with poststroke hypertension (see Cerebrovascular Diseases, above). Abrupt and marked drops in blood pressure may be hazardous for both the cerebral and the coronary circulation.[315,316] Nifedipine has become very popular in the past few years for nonparenteral treatment of hypertensive crisis. When given sublingually or after chewing, this agent can bring blood pressure down too quickly so that a slow-release formulation is by far preferable.[317] Oral captopril may also be useful, but hypotension may occur in salt-depleted subjects.[318]

Renovascular Hypertension

As expected, blockers of the renin-angiotensin system are often very effective in patients with renovascular hypertension, especially if the renal artery stenosis is unilateral. With other types of medications, multiple combinations are often needed to achieve a satisfactory blood pressure control. As pointed out earlier (in the discussion of ACE inhibitors), blockade of the renin-angiotensin system might be detrimental for the renal function. Glomerular filtration may indeed be strikingly reduced because of the dependence on angiotensin II for the maintenance of an adequate filtration pressure. Cessation of glomerular filtration rate may pass unnoticed in cases of unilateral renal artery stenosis, as the contralateral kidney can still function normally. The experience available to date suggests that the impairment of renal function induced by blockade of the renin-angiotensin system is reversible after withdrawal of the drug. Blockers of the renin-angiotensin system are not strictly contraindicated in patients with renovascular hypertension. They may represent the only way to normalize blood pressure in some patients in whom a correction of the stenosis cannot be performed. Low doses of a short-acting ACE inhibitor or AT_1-receptor blocker are advocated in such instances, so that angiotensin II can act intermittently and restore glomerular filtration for a few hours during the day. It is relevant in this context that a randomized trial has shown similar effects of antihypertensive treatment and angioplasty on blood pressure control in patients with atherosclerotic renal artery stenosis.[319]

Summary

Hypertension is a heterogeneous disorder associated with an increased cardiovascular risk. The early diagnosis and management of this disease is imperative in order to derive the maximum benefit from blood pressure lowering interventions. A large number of antihypertensive drugs acting by various mechanisms are now available. Administered alone or in association, these medications make it possible to normalize blood pressure in nearly all hypertensive persons. Effects should be directed to find a drug regimen that is efficacious and well tolerated for each patient.

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