

Pathogenesis of Hypertension

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Clinical Principles

A clearer understanding of the pathogenesis of hypertension will probably lead to more highly targeted therapies and to greater reduction in hypertension-related cardiovascular disease morbidity than can be achieved with current empirical treatment.

Physiologic Principles

More than 90% of cases of hypertension do not have a clear cause.

Hypertension clusters in families and results from a complex interaction of genetic and environmental factors.

The hypertension-related genes identified to date regulate renal salt and water handling.

Major pathophysiologic mechanisms of hypertension include activation of the sympathetic nervous system and renin–angiotensin–aldosterone system.

Endothelial dysfunction, increased vascular reactivity, and vascular remodeling may be causes, rather than consequences, of blood pressure elevation; increased vascular stiffness contributes to isolated systolic hypertension in the elderly.

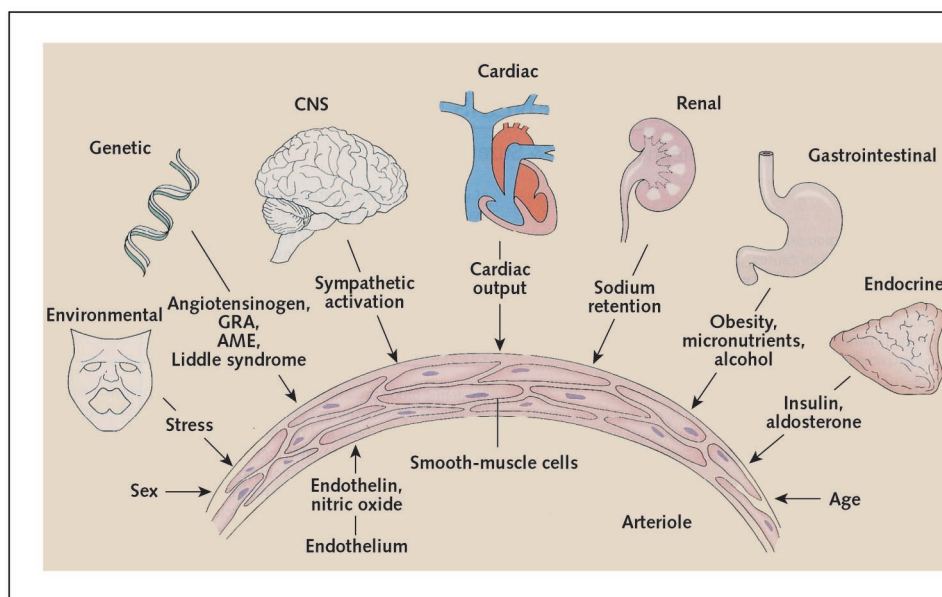
Essential hypertension, or hypertension of unknown cause, accounts for more than 90% of cases of hypertension. It tends to cluster in families and represents a collection of genetically based diseases or syndromes with several resultant inherited biochemical abnormalities (1–4). The resulting phenotypes can be modulated by various environmental factors, thereby altering the severity of blood pressure elevation and the timing of hypertension onset.

Many pathophysiologic factors have been implicated in the genesis of essential hypertension: increased sympathetic nervous system activity, perhaps related to heightened exposure or response to psychosocial stress; overproduction of sodium-retaining hormones and vasoconstrictors; long-term high sodium intake; inadequate dietary intake of potassium and calcium; increased or inappropriate renin secretion with resultant increased production of angiotensin II and aldosterone; deficiencies of vasodilators, such as prostacyclin, nitric oxide (NO), and the natriuretic peptides; alterations in expression of the kallikrein–kinin system that affect vascular tone and renal salt handling; abnormalities of resistance vessels, including selective lesions in the renal microvasculature; diabetes mellitus; insulin resistance; obe-

sity; increased activity of vascular growth factors; alterations in adrenergic receptors that influence heart rate, inotropic properties of the heart, and vascular tone; and altered cellular ion transport (Figure 1) (2). The novel concept that structural and functional abnormalities in the vasculature, including endothelial dysfunction, increased oxidative stress, vascular remodeling, and decreased compliance, may antedate hypertension and contribute to its pathogenesis has gained support in recent years.

Although several factors clearly contribute to the pathogenesis and maintenance of blood pressure elevation, renal mechanisms probably play a primary role, as hypothesized by Guyton (5) and reinforced by extensive experimental and clinical data. As discussed in this paper, other mechanisms amplify (for example, sympathetic nervous system activity and vascular remodeling) or buffer (for example, increased natriuretic peptide or kallikrein–kinin expression) the pressor effects of renal salt and water retention. These interacting pathways play major roles in both increasing blood pressure and mediating related target organ damage. Understanding these complex mechanisms has important implications for the targeting of antihyper-

Figure 1. Pathophysiologic mechanisms of hypertension.



AME = apparent mineralocorticoid excess; CNS = central nervous system; GRA = glucocorticoid-remediable aldosteronism. Reproduced with permission from Crawford and DiMarco (2).

tensive therapy to achieve benefits beyond lowering blood pressure.

GENETICS

Evidence for genetic influence on blood pressure comes from various sources. Twin studies document greater concordance of blood pressures in monozygotic than dizygotic twins (6), and population studies show greater similarity in blood pressure within families than between families (7). The latter observation is not attributable to only a shared environment since adoption studies demonstrate greater concordance of blood pressure among biological siblings than adoptive siblings living in the same household (8). Furthermore, single genes can have major effects on blood pressure, accounting for the rare Mendelian forms of high and low blood pressure (3). Although identifiable single-gene mutations account for only a small percentage of hypertension cases, study of these rare disorders may elucidate pathophysiologic mechanisms that predispose to more common forms of hypertension and may suggest novel therapeutic approaches (3). Mutations in 10 genes that cause Mendelian forms of human hypertension and 9 genes that cause hypotension have been described to date, as reviewed by Lifton and colleagues (3, 9) (Figure 2). These mutations affect blood pressure by altering renal salt handling, reinforcing the hypothesis of Guyton (5) that the development of hypertension depends on genetically determined renal dysfunction with resultant salt and water retention (2).

In most cases, hypertension results from a complex interaction of genetic, environmental, and demographic

factors. Improved techniques of genetic analysis, especially genome-wide linkage analysis, have enabled a search for genes that contribute to the development of primary hypertension in the population. Application of these techniques has found statistically significant linkage of blood pressure to several chromosomal regions, including regions linked to familial combined hyperlipidemia (10–13). These findings suggest that there are many genetic loci, each with small effects on blood pressure in the general population. Overall, however, identifiable single-gene causes of hypertension are uncommon, consistent with a multifactorial cause of primary hypertension (14).

The candidate gene approach typically compares the prevalence of hypertension or the level of blood pressure among individuals of contrasting genotypes at candidate loci in pathways known to be involved in blood pressure regulation. The most promising findings of such studies relate to genes of the renin–angiotensin–aldosterone system, such as the *M235T* variant in the angiotensinogen gene, which has been associated with increased circulating angiotensinogen levels and blood pressure in many distinct populations (15–17), and a common variant in the angiotensin-converting enzyme (ACE) gene that has been associated in some studies with blood pressure variation in men (18, 19). However, these variants seem to only modestly affect blood pressure, and other candidate genes have not shown consistent and reproducible associations with blood pressure or hypertension in larger populations (3); thus, demonstration of common genetic causes of hypertension in the general population remains elusive (16, 20, 21).

The best studied monogenic cause of hypertension is the Liddle syndrome, a rare but clinically important disorder in which constitutive activation of the epithelial sodium channel predisposes to severe, treatment-resistant hypertension (22). Epithelial sodium channel activation has been traced to mutations in the β or γ subunits of the channel, resulting in inappropriate sodium retention at the renal collecting duct level. Patients with the Liddle syndrome typically present with volume-dependent, low-renin, and low-aldosterone hypertension. Screenings of general hypertensive populations indicate that the Liddle syndrome is rare and does not contribute substantially to the development of hypertension in the general population (23). In selected groups, however, evidence suggests that epithelial sodium channel activation might be a more common cause of hypertension. Epithelial sodium channel activation, as evidenced by increased sodium conductance in peripheral lymphocytes, has been noted in 11 of 44 (25%) patients with resistant hypertension (blood pressure uncontrolled while treated with ≥ 3 medications) presenting at our clinic (24). Three of the 11 patients were treated with amiloride, an epithelial sodium channel antagonist, and blood pressure was reduced in all patients. These preliminary results suggest that genetic causes of hypertension, although uncommon in general hypertensive populations, may be more frequent in selected hypertensive populations,

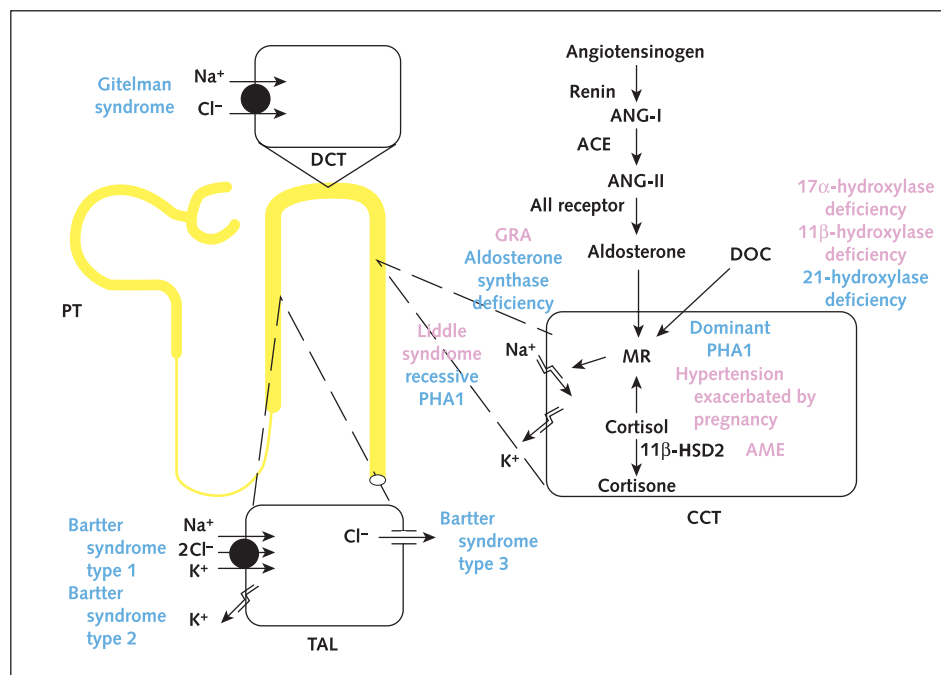
particularly in those resistant to conventional pharmacologic therapies.

INHERITED CARDIOVASCULAR RISK FACTORS

Cardiovascular risk factors, including hypertension, tend to cosegregate more commonly than would be expected by chance. Approximately 40% of persons with essential hypertension also have hypercholesterolemia. Genetic studies have established a clear association between hypertension and dyslipidemia (25). Hypertension and type 2 diabetes mellitus also tend to coexist. Hypertension is approximately twice as common in persons with diabetes as in persons without diabetes, and the association is even stronger in African Americans and Mexican Americans (26). The leading cause of death in patients with type 2 diabetes is coronary heart disease, and diabetes increases the risk for acute myocardial infarction as much as a previous myocardial infarction in a nondiabetic person (26). Since 35% to 75% of the cardiovascular complications of diabetes are attributable to hypertension, diabetic patients need aggressive antihypertensive treatment, as well as treatment of dyslipidemia and glucose control.

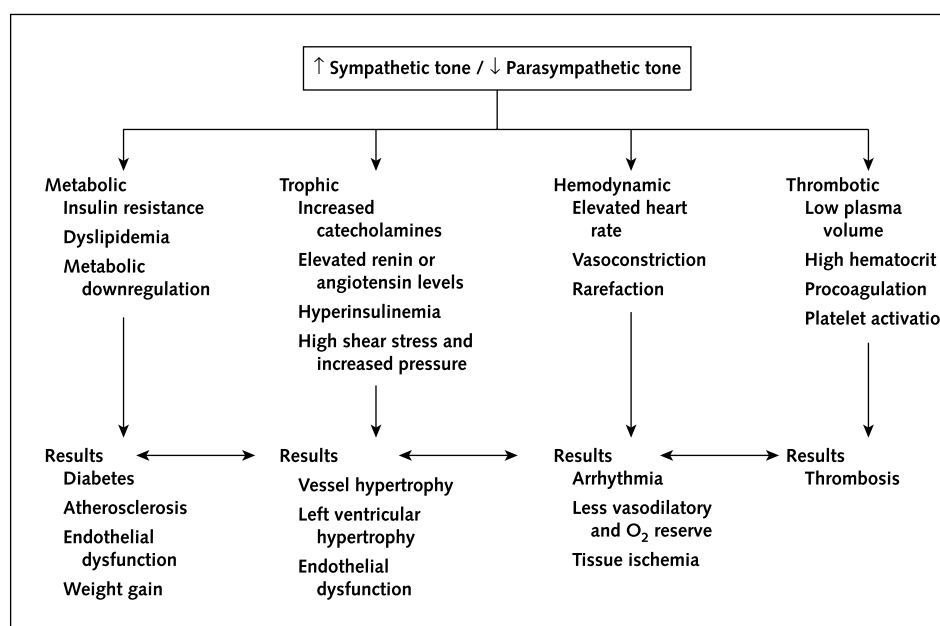
Hypertension, insulin resistance, dyslipidemia, and obesity often occur concomitantly (27). Associated abnormalities include microalbuminuria, high uric acid levels,

Figure 2. Mutations altering blood pressure in humans.



A diagram of a nephron, the filtering unit of the kidney, is shown. The molecular pathways mediating sodium chloride (NaCl) reabsorption in individual renal cells in the thick ascending limb (TAL) of the Henle's loop, distal convoluted tubule (DCT), and the cortical collecting tubule (CCT) are indicated, along with the pathway of the renin-angiotensin system, the major regulator of renal salt reabsorption. Inherited diseases affecting these pathways are indicated (hypertensive disorders [red] and hypotensive disorders [blue]). 11 β -HSD2 = 11 β -hydroxysteroid dehydrogenase-2; ACE = angiotensin-converting enzyme; AME = apparent mineralocorticoid excess; ANG = angiotensin; DOC = deoxycorticosterone; GRA = glucocorticoid-remediable aldosteronism; MR = mineralocorticoid receptor; PHA1 = pseudohypoaldosteronism type 1; PT = proximal tubule. Reproduced from Lifton et al. (3), with permission from Elsevier Science.

Figure 3. Role of the sympathetic nervous system in the pathogenesis of cardiovascular diseases.



Reproduced from Brook and Julius (29), with permission from Elsevier Science.

hypercoagulability, and accelerated atherosclerosis. This cosegregation of abnormalities, referred to as the insulin-resistance syndrome or the metabolic syndrome, increases cardiovascular disease (CVD) risk. Physicians must assess and treat these risk factors individually, recognizing that many hypertensive patients have insulin resistance, dyslipidemia, or both.

SYMPATHETIC NERVOUS SYSTEM

Increased sympathetic nervous system activity increases blood pressure and contributes to the development and maintenance of hypertension through stimulation of the heart, peripheral vasculature, and kidneys, causing increased cardiac output, increased vascular resistance, and fluid retention (28). In addition, autonomic imbalance (increased sympathetic tone accompanied by reduced parasympathetic tone) has been associated with many metabolic, hemodynamic, trophic, and rheologic abnormalities that result in increased cardiovascular morbidity and mortality (Figure 3) (29). Several population-based studies, such as the Coronary Artery Risk Development in Young Adults (CARDIA) study (30), have shown a positive correlation between heart rate and the development of hypertension (elevated diastolic blood pressure). Since most current evidence suggests that, in humans, sustained increases in heart rate are due mainly to decreased parasympathetic tone, these findings support the concept that autonomic imbalance contributes to the pathogenesis of hypertension. Furthermore, since diastolic blood pressure relates more closely to vascular resistance than to cardiac function, these results also suggest that increased sympathetic tone may increase diastolic blood pressure by causing vascular

smooth-muscle cell proliferation and vascular remodeling. Consistent with these population-based observations, norepinephrine spillover studies, which provide an index of norepinephrine release from sympathoeffector nerve terminals, demonstrate that sympathetic cardiac stimulation is greater in young hypertensive patients than in normotensive controls of similar age, supporting the interpretation that increased cardiac sympathetic stimulation may contribute to the development of hypertension (31).

The mechanisms of increased sympathetic nervous system activity in hypertension are complex and involve alterations in baroreflex and chemoreflex pathways at both peripheral and central levels. Arterial baroreceptors are reset to a higher pressure in hypertensive patients, and this peripheral resetting reverts to normal when arterial pressure is normalized (32–34). Resuming normal baroreflex function helps maintain reductions in arterial pressure, a beneficial regulatory mechanism that may have important clinical implications (35). Furthermore, there is central resetting of the aortic baroreflex in hypertensive patients, resulting in suppression of sympathetic inhibition after activation of aortic baroreceptor nerves (36). This baroreflex resetting seems to be mediated, at least partly, by a central action of angiotensin II (37). Angiotensin II also amplifies the response to sympathetic stimulation by a peripheral mechanism, that is, presynaptic facilitatory modulation of norepinephrine release (38). Additional small-molecule mediators that suppress baroreceptor activity and contribute to exaggerated sympathetic drive in hypertension include reactive oxygen species and endothelin (39, 40). Finally, there is evidence of exaggerated chemoreflex function, leading to markedly enhanced sympathetic activation in response to

stimuli such as apnea and hypoxia (41). A clinical correlate of this phenomenon is the exaggerated increase in sympathetic nervous system activity that is sustained in the awake state and seems to contribute to hypertension in patients with obstructive sleep apnea (42).

Chronic sympathetic stimulation induces vascular remodeling and left ventricular hypertrophy, presumably by direct and indirect actions of norepinephrine on its own receptors, as well as on release of various trophic factors, including transforming growth factor- β , insulin-like growth factor 1, and fibroblast growth factors (29). Clinical studies have shown positive correlations between circulating norepinephrine levels, left ventricular mass, and reduced radial artery compliance (an index of vascular hypertrophy) (43, 44). Thus, sympathetic mechanisms contribute to the development of target organ damage, as well as to the pathogenesis of hypertension.

Renal sympathetic stimulation is also increased in hypertensive patients compared with normotensive controls. Infusion of the α -adrenergic antagonist phentolamine into the renal artery increases renal blood flow to a greater extent in hypertensive than normotensive patients, consistent with a functional role for increased sympathetic tone in controlling renal vascular resistance (45, 46). In animal models, direct renal nerve stimulation induces renal tubular sodium and water reabsorption and decreases urinary sodium and water excretion, resulting in intravascular volume expansion and increased blood pressure (47). Furthermore, direct assessments of renal sympathetic nerve activity have consistently demonstrated increased activation in animal models of genetically mediated and experimentally induced hypertension, and renal denervation prevents or reverses hypertension in these models (48), supporting a role for increased sympathetic activation of the kidney in the pathogenesis of hypertension.

Of interest, peripheral sympathetic activity is greatly increased in patients with renal failure compared with age-matched, healthy normotensive individuals with normal renal function (49). This increase is not seen in patients receiving long-term hemodialysis who have undergone bilateral nephrectomy, suggesting that sympathetic overactivity in patients with renal failure is caused by a neurogenic signal originating in the failing kidneys.

VASCULAR REACTIVITY

Hypertensive patients manifest greater vasoconstrictor responses to infused norepinephrine than normotensive controls (50). Although increased circulating norepinephrine levels generally induce downregulation of noradrenergic receptors in normotensive patients, this does not seem to occur in hypertensive patients, resulting in enhanced sensitivity to norepinephrine, increased peripheral vascular resistance, and blood pressure elevations. Vasoconstrictor responsiveness to norepinephrine is also increased in normotensive offspring of hypertensive parents compared with

controls without a family history of hypertension, suggesting that the hypersensitivity may be genetic in origin and not simply a consequence of elevated blood pressure (51).

Centrally acting sympatholytic agents and α - and β -adrenergic antagonists are very effective in reducing blood pressure in patients with essential hypertension, thus providing indirect clinical evidence for the importance of sympathetic mechanisms in the maintenance phase of human hypertension (52). Declining clinical use of the centrally acting agents and of the α -adrenergic antagonists in treating hypertension relates to problems with adverse effects of these agents rather than lack of antihypertensive efficacy.

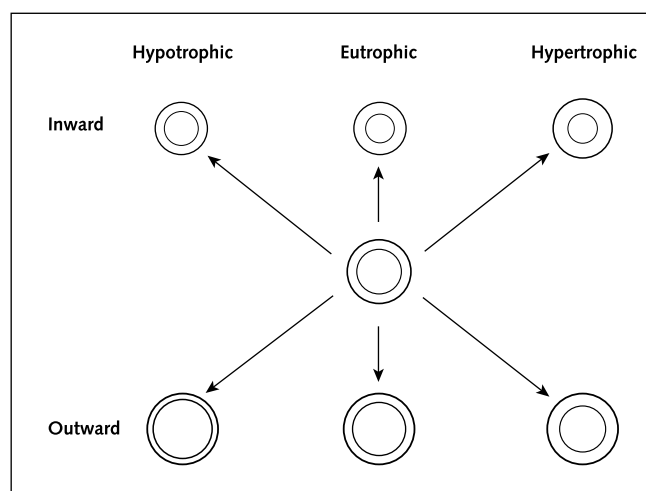
Exposure to stress increases sympathetic outflow, and repeated stress-induced vasoconstriction may result in vascular hypertrophy, leading to progressive increases in peripheral resistance and blood pressure (53). This could partly explain the greater incidence of hypertension in lower socioeconomic groups, since they must endure greater levels of stress associated with daily living. Persons with a family history of hypertension manifest augmented vasoconstrictor and sympathetic responses to laboratory stressors, such as cold pressor testing and mental stress, that may predispose them to hypertension. This is particularly true of young African Americans (54). Exaggerated stress responses may contribute to the increased incidence of hypertension in this group.

VASCULAR REMODELING

Peripheral vascular resistance is characteristically elevated in hypertension because of alterations in structure, mechanical properties, and function of small arteries. Remodeling of these vessels contributes to high blood pressure and its associated target organ damage (55, 56). Peripheral resistance is determined at the level of the precapillary vessels, including the arterioles (arteries containing a single layer of smooth-muscle cells) and the small arteries (lumen diameters $< 300 \mu\text{m}$). The elevated resistance in hypertensive patients is related to rarefaction (decrease in number of parallel-connected vessels) and narrowing of the lumen of resistance vessels. Examination of gluteal skin biopsy specimens obtained from patients with untreated essential hypertension has uniformly revealed reduced lumen areas and increased media-lumen ratios without an increase in medial area in resistance vessels (inward, eutropic remodeling) (Figure 4).

Antihypertensive treatment with several classes of agents, including ACE inhibitors, angiotensin-receptor blockers (ARBs), and calcium-channel blockers, normalizes resistance vessel structure (58). Of interest, β -blocker therapy does not reverse resistance vessel remodeling even when it effectively lowers blood pressure (59). Hypertension can also be reversed rapidly by acute maneuvers (for example, unclipping the 1-kidney, 1-clip Goldblatt model) that do not affect vascular hypertrophy or remodeling. Fur-

Figure 4. How remodeling can modify the cross-sections of blood vessels.



The starting point is the vessel at the center. Remodeling can be hypertrophic (increase of cross-sectional area), eutrophic (for example, no change in cross-sectional area), or hypotrophic (decrease of cross-sectional area). These forms of remodeling can be inward (reduction in lumen diameter) or outward (for example, increase in lumen diameter). Reproduced with permission from Mulvany et al. (57).

Furthermore, various observations, including the dissociation between the blood pressure-lowering and structural effects of antihypertensive drugs and the ability of angiotensin II to induce vascular remodeling when infused at subpressor doses, indicate that the altered resistance vessel structure seen in hypertension is not strictly secondary to the increased blood pressure and is not sufficient to sustain hypertension. To what extent resistance vessel structure plays a direct role in setting the blood pressure and in the pathogenesis of hypertension is a subject of ongoing study and controversy. Furthermore, whether antihypertensive agents that normalize resistance vessel structure are more effective in preventing target organ damage and CVD than agents that lower blood pressure without affecting vascular remodeling remains to be determined.

RENAL MICROVASCULAR DISEASE: A HYPOTHETICAL UNIFYING PATHOPHYSIOLOGIC MECHANISM

The intriguing hypothesis, originally proposed by Henke and Lubarsch (60) and Goldblatt (61), that primary renal microvascular disease may be responsible for the development of hypertension has recently been revived by Johnson and colleagues (4) and tested in various animal models. These authors have suggested a unified pathway for the development of hypertension whereby the kidney undergoes subclinical injury over time, leading to the development of selective afferent arteriopathy and tubulointerstitial disease (Figure 5). They hypothesize that the pathway may be initiated by various factors, such as hyperactivity of the sympathetic nervous system (62) or increased activity of the renin-angiotensin-aldosterone sys-

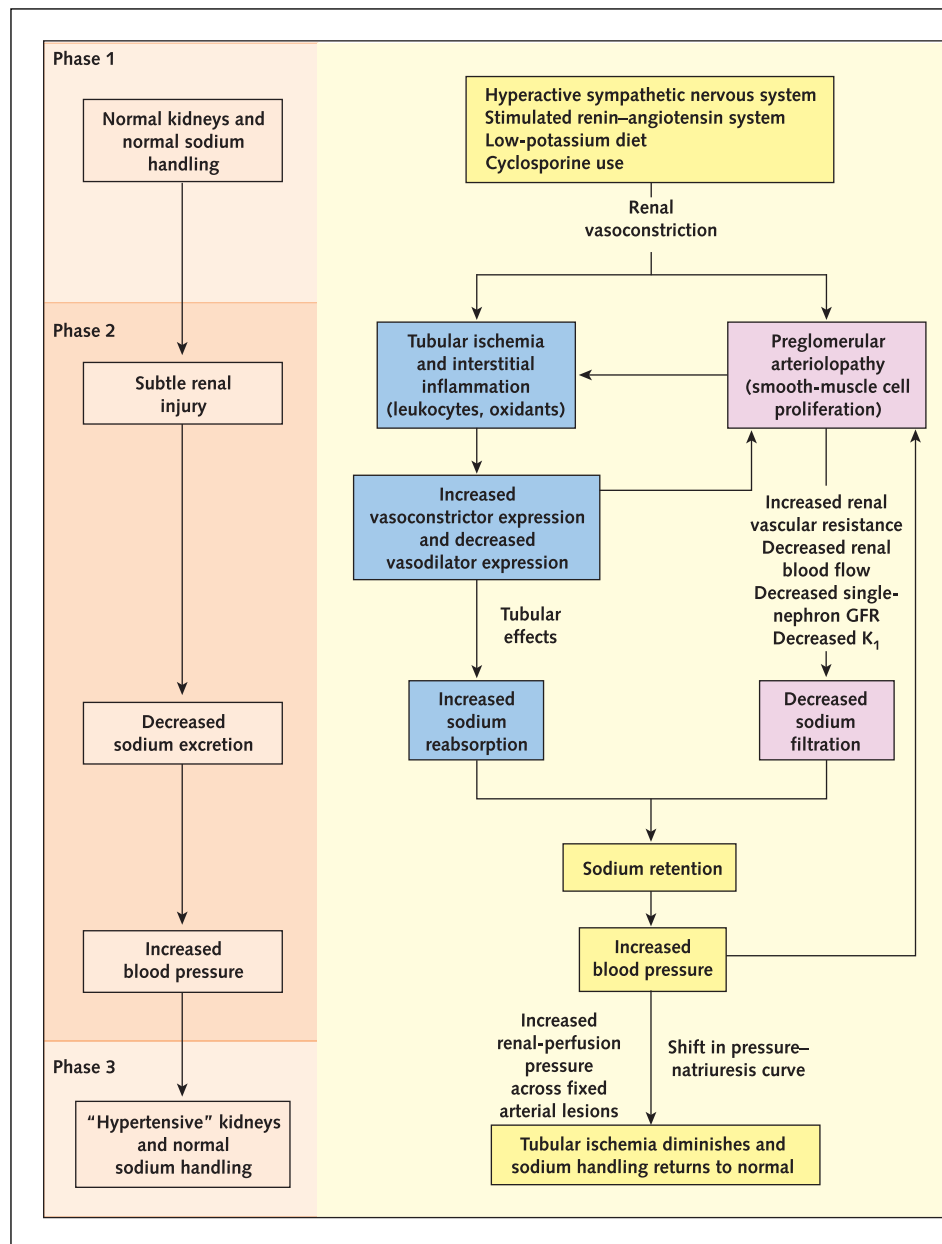
tem (15), and that initiation of the pathway may be facilitated by various genetic factors that stimulate sodium reabsorption or limit sodium filtration, as well as by primary microvascular or tubulointerstitial renal disease. These factors result in renal vasoconstriction, which may lead to renal (particularly outer medullary) ischemia, thus stimulating the influx of leukocytes and local generation of reactive oxygen species (63–65). Local generation of angiotensin II at sites of renal injury has been invoked as a stimulus for structural alterations (renal microvascular disease) and hemodynamic effects (increased vascular resistance, low ultrafiltration coefficient, and decreased sodium filtration), which lead to hypertension (66, 67). While this pathway ties in many of the established theories of the pathogenesis of hypertension, it should be confirmed in human disease (4).

URIC ACID: A PROPOSED PATHOPHYSIOLOGIC FACTOR IN HYPERTENSION

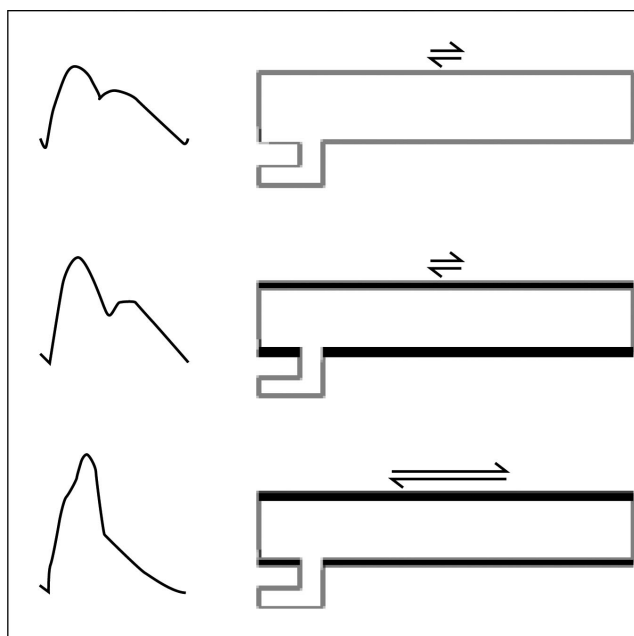
Hyperuricemia is clearly associated with hypertension and CVD in humans, but whether it is an independent risk factor with a pathogenic role in CVD or only a marker for associated CVD risk factors, such as insulin resistance, obesity, diuretic use, hypertension, and renal disease, is unclear (68–71). Mechanistic studies in humans have also linked uric acid to hypertension. Hyperuricemia in humans is associated with renal vasoconstriction (72) and is positively correlated with plasma renin activity in hypertensive patients (73), suggesting that uric acid could have adverse effects that are mediated by an activated renin-angiotensin-aldosterone system. Furthermore, hyperuricemia occurring as a complication of diuretic therapy has been implicated as a risk factor for CVD events. The Systolic Hypertension in the Elderly Program (SHEP) trial (74) found that participants who developed hyperuricemia while receiving chlorthalidone therapy sustained CVD events at a rate similar to participants treated with placebo. Preliminary findings from the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial (Høiegggen A, Kjeldsen SE, Julius S, Devereux RB, Alderman M, Chen C, et al. Relation of serum uric acid to cardiovascular endpoints in hypertension: The LIFE Study. [Manuscript submitted]) have shown that baseline serum uric acid level was associated with increased risk for CVD in women, even after adjustment for concomitant risk factors (Framingham risk score). Treatment with the uricosuric ARB losartan statistically significantly attenuated the time-related increase in serum uric acid in the LIFE trial, and this difference seemed to account for 27% of the total treatment effect on the composite CVD end point. These provocative findings suggest a need for further studies of the role of uric acid in the pathogenesis of hypertension and CVD in humans and its potential as a therapeutic target.

A novel mechanism by which uric acid can stimulate the development of hypertension has recently been identi-

Figure 5. A pathway for the development of salt-sensitive hypertension.



The development of salt-sensitive hypertension is proposed to occur in 3 phases. In the first phase, the kidney is structurally normal and sodium is excreted normally. However, the kidney may be exposed to various stimuli that result in renal vasoconstriction, such as hyperactivity of the sympathetic nervous system or intermittent stimulation of the renin-angiotensin system. During this phase, the patient may have either normal blood pressure or borderline hypertension, which (if present) is salt-resistant. In the second phase, subtle renal injury develops, impairing sodium excretion and increasing blood pressure. This phase is initiated by ischemia of the tubules, which results in interstitial inflammation (involving mononuclear-leukocyte infiltration and oxidant generation), which in turn leads to the local generation of vasoconstrictors, such as angiotensin II, and a reduction in the local expression of vasodilators, especially nitric oxide. In addition, renal vasoconstriction leads to the development of preglomerular arteriopathy, in which the arterioles are both thickened (because of smooth-muscle cell proliferation) and constricted. The resulting increase in renal vascular resistance and decrease in renal blood flow perpetuate the tubular ischemia, and the glomerular vasoconstriction lowers the single-nephron glomerular filtration rate (*GFR*) and the glomerular ultrafiltration coefficient (K_f). These changes result in decreased sodium filtration by the glomerulus. The imbalance in the expression of vasoconstrictors and vasodilators favoring vasoconstriction also leads to increased sodium reabsorption by the tubules; together, these changes lead to sodium retention and an increase in systemic blood pressure. In the third phase, the kidneys equilibrate at a higher blood pressure, allowing them to resume normal sodium handling. Specifically, as the blood pressure increases, there is an increase in renal perfusion pressure across the fixed arterial lesions. This increase helps to restore filtration and relieve the tubular ischemia, thereby correcting the local imbalance in vasoconstrictors and vasodilators and allowing sodium excretion to return toward normal levels. However, this process occurs at the expense of an increase in systemic blood pressure and hence a rightward shift in the pressure-natriuresis curve. In addition, this condition is not stable, since the increase in blood pressure may lead to a progression in the arteriopathy, thereby initiating a vicious circle. During this phase, sodium sensitivity may be observed as a decrease in blood pressure when sodium intake is restricted, whereas increased sodium intake will have a lesser effect on blood pressure because of the intact but shifted balance between blood pressure and natriuresis. The early phase of this pathway may be bypassed in the presence of other mechanisms, such as primary tubulointerstitial disease, genetic alterations in sodium regulation and excretion, or a congenital reduction in nephron number that limits sodium filtration. Adapted with permission from Johnson et al. (4). Copyright © 2002 Massachusetts Medical Society. All rights reserved.

Figure 6. Simple tubular models of the systemic arterial system.

Top. Normal distensibility and normal pulse wave velocity. **Middle.** Decreased distensibility but normal pulse wave velocity. **Bottom.** Decreased distensibility with increased pulse wave velocity. The amplitude and contour of pressure waves that would be generated at the origin of these models by the same ventricular ejection (flow) waves are shown (left). Decreased distensibility as such increases pressure wave amplitude, whereas increased wave velocity causes the reflected wave to return during the ventricular systole. Reproduced from Oparil and Weber (78), with permission from Elsevier Science.

fied (75, 76). Uric acid has been shown in a rodent model to stimulate renal afferent arteriopathy and tubulointerstitial disease, leading to hypertension. In this model, mild hyperuricemia induced by the uricase inhibitor oxonic acid resulted in hypertension associated with increased juxtaglomerular renin and decreased macula densa neuronal NO synthase expression. The renal lesions and hypertension could be prevented or reversed by lowering uric acid levels and by treatment with an ACE inhibitor, the ARB losartan, or arginine, but hydrochlorothiazide did not prevent the arteriopathy despite controlling blood pressure. The observations that uric acid can induce platelet-derived growth factor (PDGF) A-chain expression and proliferation in smooth-muscle cells (76, 77) and that these effects can be partially blocked by losartan provide a cellular or molecular mechanism to account for these findings. Whether uric acid has similar nephrotoxic and hypertension-promoting effects in humans is controversial and deserves further investigation.

ARTERIAL STIFFNESS

Systolic blood pressure and pulse pressure increase with age mainly because of reduced elasticity (increased stiffness) of the large conduit arteries. Arteriosclerosis in these arteries results from collagen deposition and smooth-

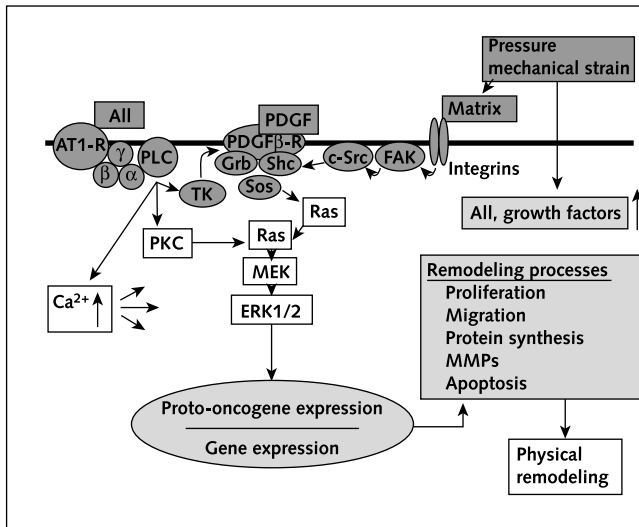
muscle cell hypertrophy, as well as thinning, fragmenting, and fracture of elastin fibers in the media (78). In addition to these structural abnormalities, endothelial dysfunction, which develops over time from both aging and hypertension, contributes functionally to increased arterial rigidity in elderly persons with isolated systolic hypertension (79). Reduced NO synthesis or release in this setting, perhaps related to the loss of endothelial function and reduction in endothelial NO synthase, contributes to increased wall thickness of conduit vessels, such as the common carotid artery. The functional importance of NO deficiency in isolated systolic hypertension is supported by the ability of NO donors, such as nitrates or derivatives, to increase arterial compliance and distensibility and reduce systolic blood pressure without decreasing diastolic blood pressure. Other factors that decrease central arterial compliance include estrogen deficiency, high dietary salt intake, tobacco use, elevated homocysteine levels, and diabetes. These factors may damage the endothelium.

The distending pressure of conduit vessels is a major determinant of stiffness. The 2-phase (elastin and collagen) content of load-bearing elements in the media is responsible for the behavior of these vessels under stress. At low pressures, stress is borne almost entirely by the distensible elastin lamellae, while at higher pressures, less distensible collagenous fibers are recruited and the vessel appears stiffer (78). Conduit vessels are relatively unaffected by neurohumoral vasodilator mechanisms. Instead, vasodilation is caused by increased distending pressure and associated with increased stiffness. Conversely, conduit vessels do respond to vasoconstrictor stimuli, including neurogenic stimulation during simulated diving, electrical nerve stimulation, and norepinephrine infusion (80, 81).

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

In younger persons (Figure 6, top), pulse wave velocity is sufficiently slow (approximately 5 m/s) so that the reflected wave reaches the aortic valve after closure, leading to a higher diastolic blood pressure and enhancing coronary perfusion by providing a “boosting” effect. In older persons, particularly if they are hypertensive, pulse wave velocity is greatly increased (approximately 20 m/s) because of central arterial stiffening. At this speed, the reflective wave reaches the aortic valve before closure, leading to a higher systolic blood pressure, pulse pressure, and afterload and a decreased diastolic blood pressure, in some cases compromising coronary perfusion pressure (Figure 6, bot-

Figure 7. Signal transduction pathways for mechanical stress in rat mesenteric small arteries.



AT₁-R = angiotensin II type 1 receptor; ERK1/2 = extracellular signal-regulated kinases 1 and 2; FAK = focal adhesion kinase; MEK = mitogen-activated protein kinase extracellular signal-regulated kinase; MMP = matrix metalloproteinase; PDGF = platelet-derived growth factor; PDGFβ-R = platelet-derived growth factor-β receptor (receptor tyrosine kinase); PKC = protein kinase C; PLC = phospholipase C; TK = tyrosine kinase. c-Src, Ras, and Raf are specific tyrosine kinases; Grb, Sch, and Sos are domain adaptor proteins; and α, β, and γ are G-protein subunits. Reproduced with permission from Mulvany (86).

tom). This phenomenon explains the increase in systolic blood pressure and pulse pressure and decrease in diastolic blood pressure in the elderly population and is exaggerated in the presence of antecedent hypertension. The increase in systolic blood pressure increases cardiac metabolic requirements and predisposes to left ventricular hypertrophy and heart failure. Pulse pressure is closely related to systolic blood pressure and is clearly linked to advanced atherosclerotic disease and CVD events, such as fatal and nonfatal myocardial infarction and stroke. Pulse pressure is a better predictor of CVD risk than systolic blood pressure or diastolic blood pressure.

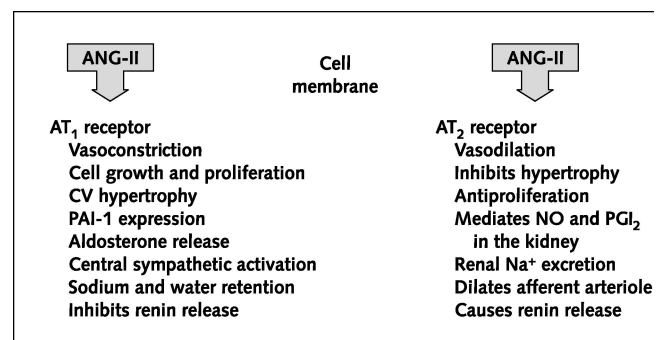
Most antihypertensive drugs act on peripheral muscular arteries rather than central conduit vessels. They reduce pulse pressure through indirect effects on the amplitude and timing of reflected pulse waves. Nitroglycerine causes marked reductions in wave reflection, central systolic blood pressure, and left ventricular load without altering systolic blood pressure or diastolic blood pressure in the periphery. Vasodilator drugs that decrease the stiffness of peripheral arteries, including ACE inhibitors and calcium-channel blockers, also reduce pulse wave reflection and thus augmentation of the central aortic and left ventricular systolic pressure, independent of a corresponding reduction in systolic blood pressure in the periphery (82). Antihypertensive drugs from several classes have been shown to reduce systolic blood pressure and CVD morbidity and mortality in patients with isolated systolic hypertension (83, 84).

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Angiotensin II increases blood pressure by various mechanisms, including constricting resistance vessels, stimulating aldosterone synthesis and release and renal tubular sodium reabsorption (directly and indirectly through aldosterone), stimulating thirst and release of antidiuretic hormone, and enhancing sympathetic outflow from the brain. Of importance, angiotensin II induces cardiac and vascular cell hypertrophy and hyperplasia directly by activating the angiotensin II type 1 (AT₁) receptor and indirectly by stimulating release of several growth factors and cytokines (85). Activation of the AT₁ receptor stimulates various tyrosine kinases, which in turn phosphorylate the tyrosine residues in several proteins, leading to vasoconstriction, cell growth, and cell proliferation (Figure 7) (86). Activation of the AT₂ receptor stimulates a phosphatase that inactivates mitogen-activated protein kinase, a key enzyme involved in transducing signals from the AT₁ receptor. Thus, activation of the AT₂ receptor opposes the biological effects of AT₁ receptor activation, leading to vasodilation, growth inhibition, and cell differentiation (Figure 8) (87, 88). The physiologic role of the AT₂ receptor in adult organisms is unclear, but it is thought to function under stress conditions (such as vascular injury and ischemia reperfusion). When an ARB is administered, renin is released from the kidney because of removal of feedback inhibition by angiotensin II. This increases generation of angiotensin II, which is shunted to the AT₂ receptor, favoring vasodilation and attenuation of unfavorable vascular remodeling.

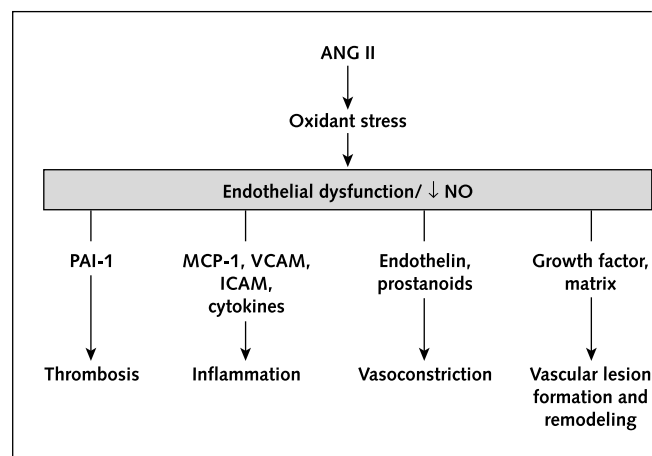
Local production of angiotensin II in various tissues, including the blood vessels, heart, adrenals, and brain, is controlled by ACE and other enzymes, including the serine proteinase chymase. The activity of local renin-angiotensin

Figure 8. The angiotensin II types 1 (AT₁) and 2 (AT₂) receptors have generally opposing effects.



The AT₁ receptor leads to vasoconstriction, cell growth, and cell proliferation; the AT₂ receptor has the opposite effect, leading to vasodilation, antigrowth, and cell differentiation. The AT₁ receptor is antinatriuretic; the AT₂ receptor is natriuretic. The AT₁ receptor stimulation results in free radicals; AT₂ stimulation produces nitric oxide (NO) that can neutralize free radicals. The AT₁ receptor induces plasminogen activator inhibitor-1 (PAI-1) and other growth family pathways; the AT₂ receptor does not. The angiotensin-receptor blockers bind to and block selectively at the AT₁ receptor, promoting stimulation of the receptor by angiotensin II.

Figure 9. Mechanisms of angiotensin II (ANG II)–dependent, oxidant-mediated vascular damage.



ICAM = intercellular adhesion molecule; MCP-1 = monocyte chemoattractant protein-1; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor-1; VCAM = vascular cell adhesion molecule.

systems and alternative pathways of angiotensin II formation may make an important contribution to remodeling of resistance vessels and the development of target organ damage (including left ventricular hypertrophy, congestive heart failure, atherosclerosis, stroke, end-stage renal disease, myocardial infarction, and arterial aneurysm) in hypertensive persons (85).

ANGIOTENSIN II AND OXIDATIVE STRESS

Stimulating oxidant production is another mechanism by which angiotensin II increases cardiovascular risk (Figure 9). Hypertension associated with long-term infusion of angiotensin II is linked to the upregulation of vascular p22phox messenger RNA (mRNA), a component of the oxidative enzyme nicotinamide adenine dinucleotide phosphate [NAD(P)H] oxidase (89). The angiotensin II receptor–dependent activation of NAD(P)H oxidase is associated with enhanced formation of the oxidant superoxide anion ($O_2^{\cdot-}$). Superoxide readily reacts with NO to form the oxidant peroxynitrite ($ONOO^-$). A reduction in NO bioactivity may thus provide another mechanism to explain the enhanced vasoconstrictor response to angiotensin II in hypertension (90). The NAD(P)H oxidase may also play an important role in the hypertrophic response to angiotensin II since stable transfection of vascular smooth-muscle cells with antisense to p22phox inhibits angiotensin II–stimulated protein synthesis (91). Other vasculotoxic responses to angiotensin II that are linked to the activation of NAD(P)H oxidase include the oxidation of low-density lipoprotein cholesterol and increased mRNA expression for monocyte chemoattractant protein-1 and vascular cell adhesion molecule-1 (92, 93).

It has been shown that ACE inhibitors and ARBs limit oxidative reactions in the vasculature by blocking the acti-

vation of NAD(P)H oxidase. These findings have led to the hypothesis that the ACE inhibitors and ARBs may have clinically important vasoprotective effects beyond lowering blood pressure. Important randomized clinical trials have supported this hypothesis.

CLINICAL TRIALS OF ACE INHIBITORS AND ARBs IN PREVENTING CVD OUTCOMES

The Heart Outcomes Prevention Evaluation (HOPE) study (94) tested the hypothesis that ACE inhibitors have beneficial effects on vascular disease complications beyond their effects on blood pressure and heart failure. The study was stopped early because of a 20% reduction in relative risk for the primary outcome (a combination of cardiovascular death, myocardial infarction, and stroke) in the ACE inhibitor group compared with a placebo (usual care) control group. The large reduction in risk was achieved in the face of apparently small reductions in blood pressure. The mean reduction in blood pressure in the ACE inhibitor group reported by the investigators was only 3/2 mm Hg. The HOPE trial was not a blood pressure trial and did not include the frequent and carefully standardized blood pressure measurements that are usually made in such trials. Patients enrolled in the HOPE trial were not required to be hypertensive; the mean blood pressure on admission was 139/79 mm Hg. The results of the HOPE trial point toward possible direct effects of ACE inhibitors on the heart and vasculature in addition to their effects on blood pressure.

The Second Australian National Blood Pressure Study (ANBP 2) (95) has reinforced the concept that ACE inhibitor therapy offers selective advantages for the hypertensive patient. The study compared ACE inhibitor with diuretic-based treatment in elderly hypertensive patients who were at relatively low CVD risk. In men, the ACE inhibitor treatment was more effective than diuretic treatment in preventing cardiovascular events, including myocardial infarction but not stroke, despite similar blood pressure reductions in both treatment groups. The treatment effect was not statistically significant for women. The robustness of the study's findings has been questioned on the basis of its relatively small sample size and design issues.

The LIFE trial was the first randomized, controlled outcome trial to demonstrate that any particular antihypertensive drug class confers benefits beyond blood pressure reduction and is more effective than any other class in preventing CVD events and death (96). The LIFE trial compared the effects of treatment with the ARB losartan and β -blocker–based treatment with atenolol in high-risk patients with left ventricular hypertrophy diagnosed by electrocardiography. Losartan-based treatment resulted in a 13% greater reduction in the primary composite end point (death, myocardial infarction, or stroke) and 25% greater reductions in stroke and new-onset diabetes than β -blocker–based treatment, despite similar decreases in blood pres-

sure. The benefits of losartan-based treatment in LIFE are particularly impressive since β -blocker-based regimens have reduced CVD events by 15% to 45% in previous trials. Of interest, losartan did not have an incremental effect beyond that of the β -blocker in preventing myocardial infarction, probably reflecting robust cardioprotective effects of the β -blocker class.

Randomized, controlled trials have also provided strong evidence that ARBs have renoprotective effects in patients with type 2 diabetes, macro- or microalbuminuria, and varying levels of renal dysfunction that do not seem to depend on blood pressure. The Reduction of Endpoints in NIDDM [non-insulin-dependent diabetes mellitus] with the Angiotensin II Antagonist Losartan trial (RENAAL) (97) showed that, compared with a placebo (usual care) group, losartan treatment slowed the progression of renal disease, reduced proteinuria, and led to other clinical benefits in normotensive or hypertensive patients with type 2 diabetes. Losartan had a minimal effect on blood pressure, and its favorable renal effects seemed to be independent of blood pressure. There was no significant effect on CVD end points. The Irbesartan Type II Diabetic Nephropathy Trial (IDNT) (98) randomly assigned hypertensive patients with type 2 diabetes, nephropathy, and renal dysfunction to treatment with irbesartan, amlodipine, or placebo (usual care). Blood pressure was controlled with medications other than ACE inhibitors or ARBs. Irbesartan treatment slowed the progression of renal disease compared with both placebo and amlodipine despite equivalent blood pressure reductions with amlodipine. Cardiovascular outcomes did not differ between treatment groups. Similar benefits were reported in the Irbesartan in Type 2 Diabetes with Microalbuminuria (IRMA 2) trial (99), which assessed the effects of irbesartan (150 or 300 mg/d) versus placebo on progression of renal disease in patients with type 2 diabetes, microalbuminuria, and hypertension. On the basis of these findings, many experts now recommend ARBs for treating hypertension in patients with type 2 diabetes and albuminuria (100–102).

The LIFE trial is the only study to demonstrate that ARB treatment of hypertensive diabetic patients has survival benefits beyond lowering blood pressure (103). Losartan treatment resulted in a 39% greater reduction in total mortality and a 37% greater reduction in CVD mortality than atenolol. The primary composite end point was reduced by 25% in the losartan group compared with the atenolol group. The reduction in heart failure was 41% greater in the losartan group than in the atenolol group. In contrast, the Antihypertensive and Lipid Lowering to Prevent Heart Attack (ALLHAT) trial (104), the largest outcome trial of antihypertensive treatment (with 42 418 participants), found no difference between diuretic-based treatment and ACE inhibitor-based or calcium-channel blocker-based treatment in preventing fatal and nonfatal

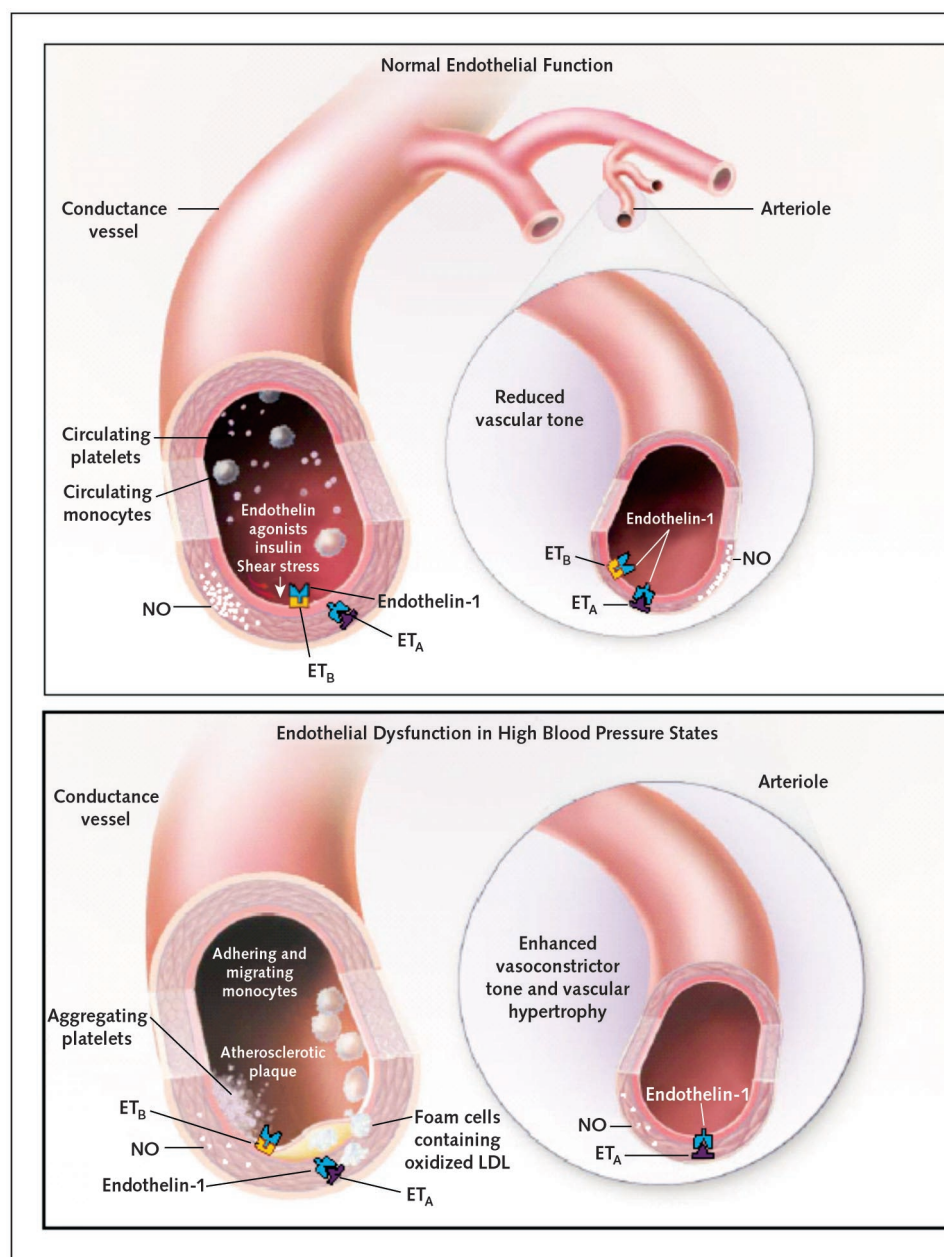
coronary events and mortality. The thiazide-type diuretic used in ALLHAT was more effective in lowering blood pressure and preventing some secondary end points, including heart failure and stroke, than the ACE inhibitor, particularly in African-American patients (a group underrepresented in most large trials). The ALLHAT leadership group recommends thiazide-type diuretics as initial therapy for most hypertensive patients because of their efficacy in preventing CVD outcomes in a wide variety of patient subgroups, as well as their low cost. These findings are consistent with a renal mechanism as the “final common pathway” in the pathogenesis of clinical hypertension.

ALDOSTERONE

Aldosterone is synthesized in a regulated fashion in extra-adrenal sites and has autocrine or paracrine actions on the heart and vasculature (105). The heart and blood vessels also express high-affinity mineralocorticoid receptors that can bind both mineralocorticoids and glucocorticoids and contain the enzyme 11β -hydroxysteroid dehydrogenase II, which inactivates glucocorticoids. Activation of these mineralocorticoid receptors is thought to stimulate intra- and perivascular fibrosis and interstitial fibrosis in the heart. The nonselective aldosterone antagonist spironolactone and the novel selective aldosterone receptor antagonist eplerenone are effective in preventing or reversing vascular and cardiac collagen deposition in experimental animals. Spironolactone treatment for patients with heart failure reduced circulating levels of procollagen type III *N*-terminal aminopeptide, indicating an antifibrotic effect. Spironolactone and the better-tolerated selective aldosterone receptor antagonist eplerenone are being used to treat patients with hypertension, heart failure, and acute myocardial infarction complicated by left ventricular dysfunction or heart failure because of their unique tissue protective effects (106, 107).

Evidence is accumulating that aldosterone excess may be a more common cause of or contributing factor to hypertension than previously thought. Hypokalemia was thought to be a prerequisite of primary hyperaldosteronism, but it is now recognized that many patients with primary hyperaldosteronism may not manifest low serum potassium levels. Accordingly, screening hypertensive patients for hyperaldosteronism has expanded and a higher prevalence of the disorder has been revealed. Prevalence rates between 8% and 32% have been reported on the basis of the patient population being screened (higher in referral practices, where the patient mix tends to be enriched with refractory hypertension and lower in family practices or community databases) (108). In our own referral practice, which includes a high proportion of patients with treatment-resistant hypertension, the prevalence of aldosterone excess is 24% (109).

Figure 10. Endothelial function in the normal vasculature and in the hypertensive vasculature.



Large conductance vessels (*left*), for example, epicardial coronary arteries, and resistance arterioles (*right*), are shown. In normal conductance arteries (*top*), platelets and monocytes circulate freely, and oxidation of low-density lipoprotein is prevented by a preponderance of nitric oxide (NO) formation. At the level of the small arterioles, reduced vascular tone is maintained by constant release of nitric oxide. Endothelin-1 normally induces no vasoconstriction or only minimal vasoconstriction through stimulation of type A endothelin receptors (ET_A) located on smooth-muscle cells and contributes to basal nitric oxide release by stimulating type B endothelin receptors (ET_B) on endothelial cells. In the hypertensive microvasculature (*bottom*), decreased activity of nitric oxide and enhanced ET_A -mediated vasoconstrictor activity of endothelin-1 result in increased vascular tone and medial hypertrophy, with a consequent increase in systemic vascular resistance. At the level of conductance arteries, a similar imbalance in the activity of endothelial factors leads to a proatherosclerotic milieu that is conducive to the oxidation of low-density lipoprotein, the adhesion and migration of monocytes, and the formation of foam cells. These activities ultimately lead to the development of atherosclerotic plaques, the rupture of which, in conjunction with enhanced platelet aggregation and impaired fibrinolysis, results in acute intravascular thrombosis, thus explaining the increased risk for cardiovascular events in patients with hypertension. These mechanisms may be operative in patients with high normal blood pressure and may contribute to their increased cardiovascular risk. Adapted with permission from Panza et al. (111).

ENDOTHELIAL DYSFUNCTION

Nitric oxide is a potent vasodilator, inhibitor of platelet adhesion and aggregation, and suppressor of migration and proliferation of vascular smooth-muscle cells. Nitric

oxide is released by normal endothelial cells in response to various stimuli, including changes in blood pressure, shear stress, and pulsatile stretch, and plays an important role in blood pressure regulation, thrombosis, and atherosclerosis

(110). The cardiovascular system in healthy persons is exposed to continuous NO-dependent vasodilator tone, but NO-related vascular relaxation is diminished in hypertensive persons (Figure 10). The observation that in vivo delivery of superoxide dismutase (an enzyme that reduces superoxide to hydrogen peroxide) reduces blood pressure and restores NO bioactivity provides further evidence that oxidant stress contributes to the inactivation of NO and the development of endothelial dysfunction in hypertensive models (112, 113). It has been suggested that angiotensin II enhances formation of the oxidant superoxide at concentrations that affect blood pressure minimally (89). Increased oxidant stress and endothelial dysfunction may thus predispose to hypertension. This concept is subject to debate and ongoing investigation. It is clear, however, that antihypertensive drugs that interrupt the renin–angiotensin–aldosterone system, including ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists, are effective in reversing endothelial dysfunction. This action may at least partly account for their cardioprotective effects.

ENDOTHELIN

Endothelin is a potent vasoactive peptide produced by endothelial cells that has both vasoconstrictor and vasodilator properties. Circulating endothelin levels are increased in some hypertensive patients, particularly African Americans and persons with transplant hypertension, endothelial tumors, and vasculitis (114). Endothelin is secreted in an abluminal direction by endothelial cells and acts in a paracrine fashion on underlying smooth-muscle cells to cause vasoconstriction and elevate blood pressure without necessarily reaching increased levels in the systemic circulation. Endothelin receptor antagonists reduce blood pressure and peripheral vascular resistance in both normotensive persons and patients with mild to moderate essential hypertension (115), supporting the interpretation that endothelin plays a role in the pathogenesis of hypertension. Development of this drug class for the indication of systemic hypertension has been discontinued because of toxicity (teratogenicity, testicular atrophy, and hepatotoxicity). However, endothelin antagonists are indicated for treating pulmonary hypertension (116) and may prove to be clinically useful in the therapy for other forms of vascular disease.

SUMMARY

The complexity of pathophysiologic mechanisms that lead to blood pressure elevation is such that selective, mechanistically based antihypertensive treatment is rarely possible in any hypertensive patient. Hypertension is highly prevalent among middle-aged and elderly persons in our population (117), and the success rate in controlling blood pressure in these individuals is poor (117, 118). For example, in the ALLHAT trial, 34% of participants did not achieve the goal blood pressure of less than 140/90

mm Hg despite use of combination therapy, including a β -blocker (104). Current treatment guidelines generally recommend a generic approach to treating hypertension, with little emphasis on selecting therapy on the basis of the underlying pathophysiology of the elevated blood pressure (100–102). With increased recognition of specific causes, it may be possible to develop therapies selective for distinct pathophysiologic mechanisms with fewer adverse effects, resulting in more effective blood pressure reduction.

Use of powerful new techniques of genetics, genomics, and proteomics, integrated with systems physiology and population studies, will make possible more selective and effective approaches to treating and even preventing hypertension in the coming decades.

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