Rational drug therapy based on understanding the pathophysiology of hypertension

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■ Increased peripheral vascular resistance is the hemodynamic hallmark of chronic hypertension. Evidence suggests that Ca^{2+} is vital in mediating vasoconstrictive mechanisms. Calcium channel blockers correct the specific arteriolar vasoconstrictive mechanism without unwanted compensatory actions. Human primary hypertension may also be related to volume variations in which renal influences contribute to elevated arterial pressure and diuretics may be necessary to control the hypertension. Patients in whom neurogenic-mediated vasoconstriction predominates show increased catecholamine production and renin release. These patients can be treated with either α- or β-receptor blocking agents or with converting enzyme inhibitors. Recent biochemical and pharmacological advances and a clear understanding of cardiovascular physiology have allowed more rational and individualized therapy for hypertensive patients, using minimal numbers of drugs in their minimal effective doses. Long-term monotherapy is now possible for different subgroups because of the specific and selective actions of newer antihypertensive agents.

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THE THERAPEUTIC approach to the hypertensive individual should be based on an understanding of the factors that initiate and maintain elevated arterial pressure, the consequences of inadequate treatment, and the pharmacology of antihypertensive drugs. All of these factors may then be integrated into an effective treatment program.

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PHYSIOLOGIC DETERMINANTS OF ARTERIAL PRESSURE

Arterial blood pressure depends mainly on two factors: the resistance of the circulating system to the flow of blood through it and the volume of fluid contained within the blood vessels (*Figure 1*). Cardiac output depends primarily on heart rate and stroke volume. Stroke volume depends on the filling pressure of the heart, while the filling pressure results from the blood volume within the venous reservoir and the compliance of the venous system. The capacity and pressure in this venous reservoir are continuously adjusted by contraction and relaxation of the smooth muscle in the venous wall. This permits the filling pressure of the heart to be continuously regulated so that an appropriate stroke volume is maintained. For any given increase in cardiac output, arterial blood pressure remains within normal limits because of appropriate adjustments in the vagal and sym-

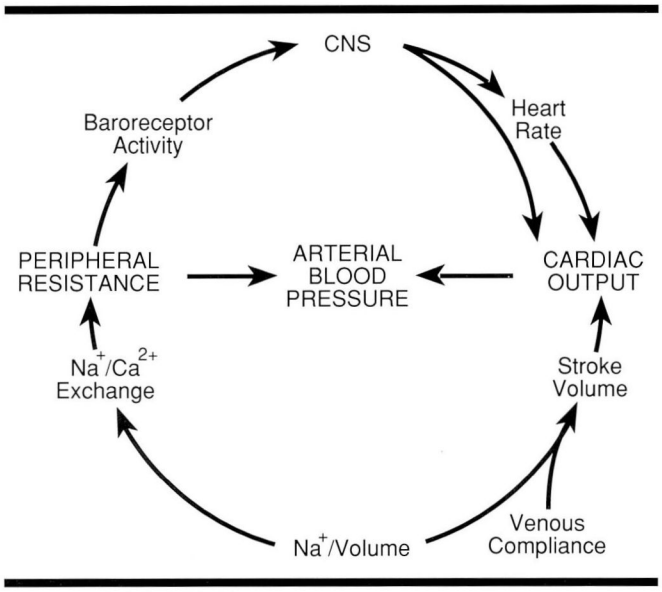

FIGURE 1. The direct determinants of arterial blood pressure (cardiac output × peripheral resistance).

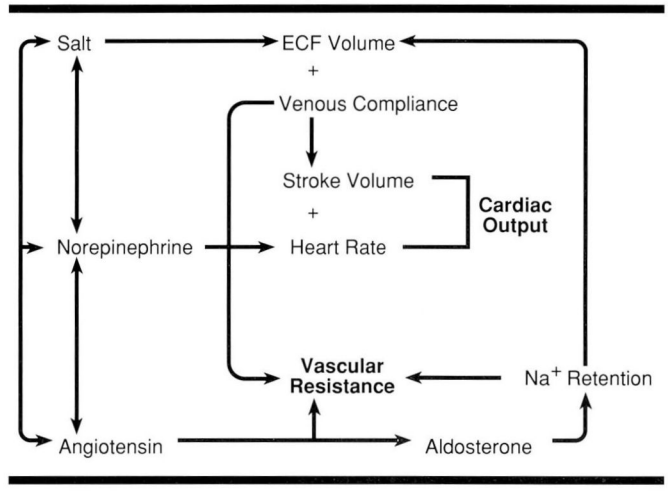

FIGURE 2. Interrelationships between direct and indirect determinants (extracellular fluid [ECF] volume, neural activity, renal pressor system, mineralocorticoids) of arterial blood pressure.

pathetic outflow to the heart, and the sympathetic outflow to the resistance and capacitance vessels and kidneys.[1]

The regulation of these two factors requires a complex set of interactions among the nervous, excretory, endocrine, and circulatory systems (*Figure 2*). Besides these, local chemical mediators have recently been found to be modulators of vasoconstrictive mechanisms. In this latter respect, a key role for calcium recently has been identified and partly characterized.

FACTORS THAT INITIATE AND MAINTAIN ELEVATED ARTERIAL PRESSURE

The increases in mean arterial pressure and peripheral vascular resistance that characterize established primary hypertension may develop by a primary increase in resistance and/or an initial elevation in cardiac output that is secondarily transformed into an increase in resistance.

Primary increase in peripheral vascular resistance: the role of salt/calcium

There is little question that an increase in peripheral vascular resistance is the hallmark of chronic hypertension. The question is: how does resistance rise and how is peripheral vascular resistance regulated?

Evidence of primary alterations in vascular smooth muscle function (leading to increased primary resistance) in primary hypertension has emerged from very different lines of work. The calcium ion (Ca^{2+}) is now believed to play an important role in primary alterations in vascular smooth muscle that eventually result in hypertension.[2] Vascular smooth muscle seems to contain quite small Ca^{2+} stores, so that much of this activator ion must enter from the outside on depolarization. The increased cytosolic free calcium forms a complex with calmodulin that results in activation of myofibrillar ATPase leading to contraction.

The control of cytosolic calcium levels in smooth muscle is a complex process that is regulated by modulation of calcium entry into the cell, release of internally bound calcium, sequestration of calcium within the cell, and extrusion of calcium from the cell. This important Ca^{2+} influx and the expulsion events are poorly understood. However, Blaustein's interesting concept may reflect the principal events reasonably well (*Figure 3*).[2] According to this hypothesis, the Na^+, K^+-ATPase system that keeps $[Na^+]_i$ low and $[K^+]_i$ high has a parallel Na^+/Ca^{2+} exchange pump that expels Ca^{2+}. Energy from the hydrolysis of ATP can be stored in the Na^+ electrochemical gradient and then harnessed to enhance Ca^{2+} extrusion against a large electrochemical gradient. If enhanced Na^+ permeability and/or reduced Na^+, K^+-ATPase activity occurs, $[Na^+]_i$ increases and the Ca^{2+} expulsion is correspondingly dampened. On the whole, any tendency toward increased Ca^{2+} influx versus efflux will increase $[Ca^{2+}]_i$. This results in increased myogenic tone as well as smooth muscle responsiveness to neuro-

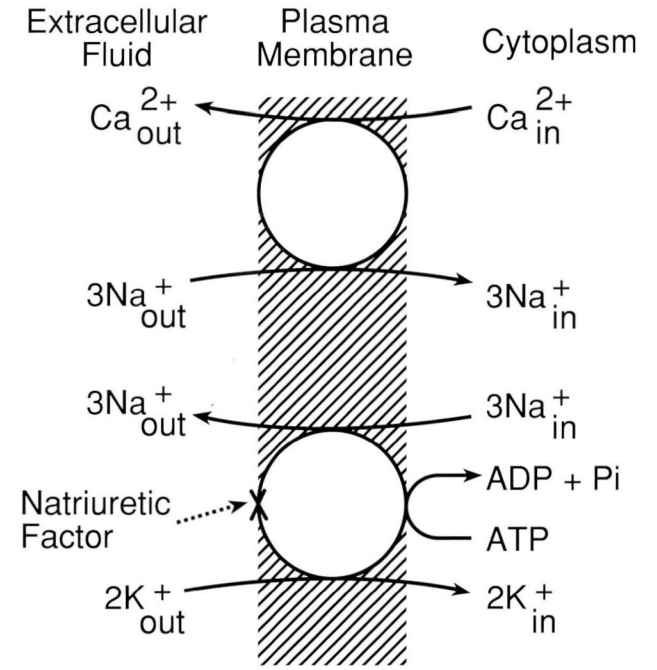

FIGURE 3. The parallel operation between the Na^+/Ca^{2+} exchanger and the Na^+/K^+ exchanger (the site of action of the natriuretic hormone).

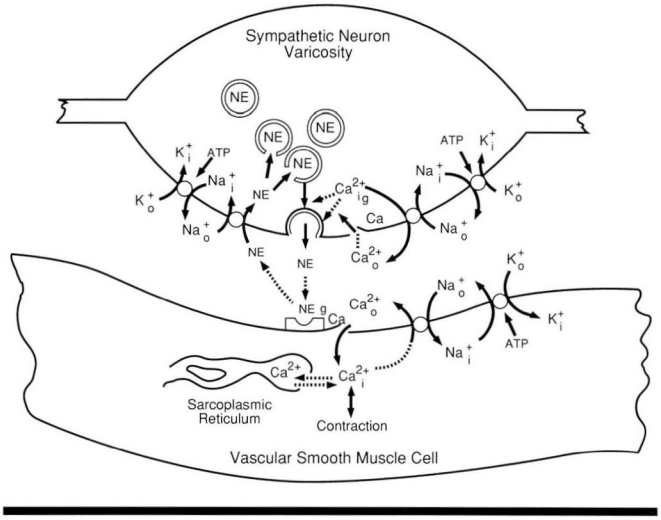

FIGURE 4. Catecholamine release from adrenergic neurons through increases in $[Ca^{2+}]_i$ and regulation of norepinephrine (NE) reuptake mediated by a Na^+/NE cotransport system.

humoral stimuli.

There is evidence to suggest that volume expansion leads to release of a Na^+-pump inhibitor.[3,4] The direct effect of a circulating Na^+-pump inhibitor is to increase $[Ca^{2+}]_i$. A decline in the Na^+ electrochemical gradient will cause a concomitant decline in the Ca^{2+} electrochemical gradient. Because $[Ca^{2+}]_o$ is normally well regulated, $[Ca^{2+}]_i$ will increase. With a stoichiometry of about three Na^+ ions exchanging for one Ca^{2+} ion, a 15% to 20% increase in $[Na^+]_i$ should cause about a 55% to 80% increase in $[Ca^{2+}]_i$, leading to enhanced contractility.

The normal trigger for the release of catecholamines from adrenergic neurons is an increase in $[Ca^{2+}]_i$ (*Figure 4*).[3] Ca^{2+} transport across the neuronal plasma membrane depends in part upon a counterflow exchange of Na^+ for Ca^{2+}. The primary mechanism for terminating the postsynaptic action of norepinephrine (NE) is its nearly complete reuptake by the sympathetic neurons. This reuptake is mediated by a Na^+/NE cotransport system that derives its energy from the Na^+ electrochemical gradient across the neuronal plasma membrane. Partial inhibition of the neuronal sodium pumps by the circulating pump inhibitor should cause the Na^+ electrochemical gradient to decline primarily as a result of an increased $[Na^+]_i$. As a result, the rate and net extent of NE reuptake will be reduced and more NE will remain in the interstitial space, thereby prolonging the activation of the vascular smooth muscle effector cells.

Figure 5 schematizes the interaction between Na^+ and Ca^{2+} in elevating arterial pressure, incorporating the concepts previously discussed. It begins with net salt retention that leads to an increase in extracellular fluid volume and the release of a circulating Na^+-pump inhibitor in subjects that may already have a genetically induced increase in membrane permeability to Na^+. These two factors act in concert to increase $[Na^+]_i$ and, in turn, to increase $[Ca^{2+}]_i$. Increased $[Ca^{2+}]_i$ can lead to enhanced vascular smooth muscle contractility, decreased venous compliance, and increased myocardial contractility. The normal trigger for the release of catecholamines from adrenergic neurons is an increase in $[Ca^{2+}]_i$. NE itself can enhance vascular smooth muscle contractility, increase venous compliance, and increase myocardial contractility. In addition, it can increase release of Ca^{2+} from cellular stores, contributing to sustained increases in $[Ca^{2+}]_i$. These links may eventually provide an explanation of the well-documented relationship between sodium and hypertension.

Role of the sympathetic nervous system

The autonomic nervous system is by far the most powerful and fastest of the extrinsic control systems.

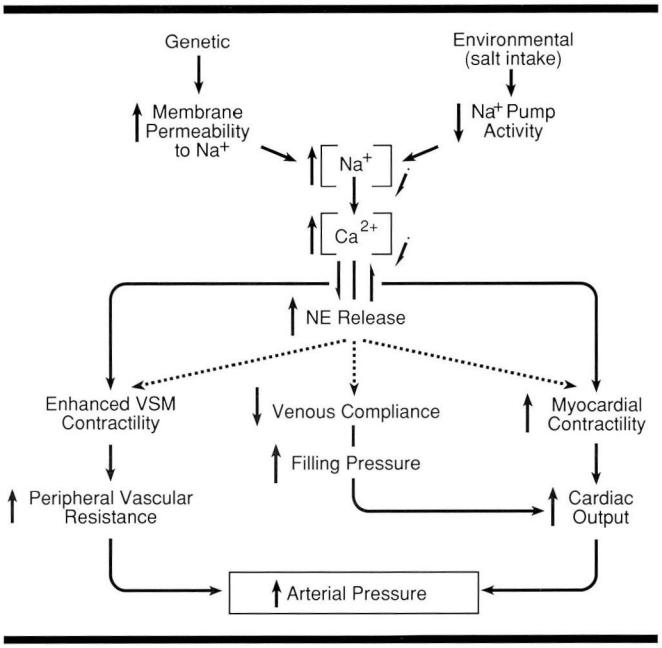

FIGURE 5. Interaction between Na^+ and Ca^{2+} in elevating

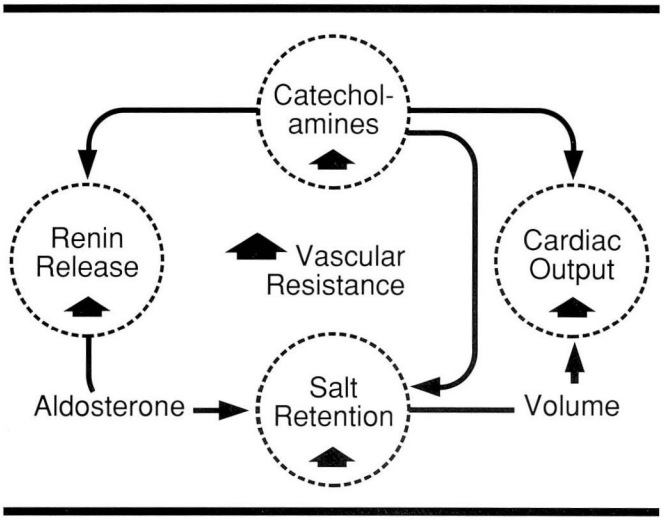

FIGURE 6. Hemodynamic and neurohumoral responses to activation of the sympathetic nervous system.

The sympathetic nervous system (SNS) is closely linked to renin release, which, via angiotensin II, influences aldosterone production and thus salt and water retention by the kidneys. Catecholamines, of themselves, can influence sodium retention by the kidneys (*Figure 6*). Thus, increased cardiac output that gradually shifts to elevated resistance could ensue from selective chronotropic-inotropic cardiac stimulation augmented by elevated venous return from expanded volume and decreased venous compliance.[1]

In human hypertension, investigation of the SNS is complicated by the fact that one must rely on indirect means of investigation. The hemodynamic pattern, the increased vascular responsiveness to exogenous catecholamines, and the hypotensive effect of sympatholytic drugs in many hypertensive patients have constituted the main indirect evidence of the importance of the SNS in maintaining elevated blood pressure. However, since various other factors can influence the hemodynamic status, and since the enhanced responsiveness to catecholamines could be secondary to morphologic changes in the arterial wall, these observations do not necessarily reflect a functional abnormality of the sympathetic system.

Nonetheless, newer approaches to the question have taught us that a significant causal role for the SNS can by no means be dismissed. Some studies further suggest the possibility that hypertension, initiated by a variety of mechanisms, needs the involvement of the SNS to allow it to become sustained. Such a conclusion is entirely consistent with the therapeutic experience demonstrating that drugs that attenuate or block sympathetic control of blood pressure are among the most effective means of treating hypertension.[5]

Role of the renin-angiotensin system

Angiotensin II, aside from its direct vasoconstrictor effects on vascular smooth muscle and its aldosterone-stimulating activity, can exert important excitatory effects on strategically important sites in the brain stem, potentiating ganglionic transmission and NE release (*Figure 7*). Thus angiotensin II can increase arterial blood pressure by directly stimulating vascular smooth muscle and increasing cardiac output through increases in blood volume and venous return.[6]

Cardiac output as the initiating factor

As outlined in *Figure 8*, elevation of cardiac output leads to increased arterial blood pressure. Mainly because of "luxury" perfusion, a secondary resistance increase occurs by whole-body autoregulation. A gradual shift toward normalized cardiac output and raised resistance ensues when hypertension reaches the established phase.[7,8]

The initial cardiac output elevation that gradually shifts to a resistance elevation can be achieved in different ways. First, it could ensue from central neurogenic excitatory patterns that induce not only constriction of

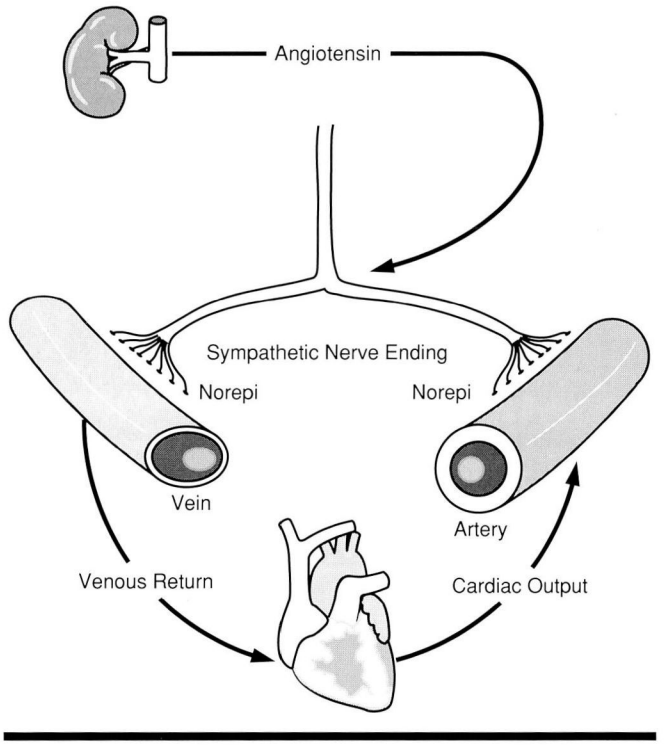

FIGURE 7. Hemodynamic and neurohumoral responses to angiotensin II. (*NOREPI* = norepinephrine)

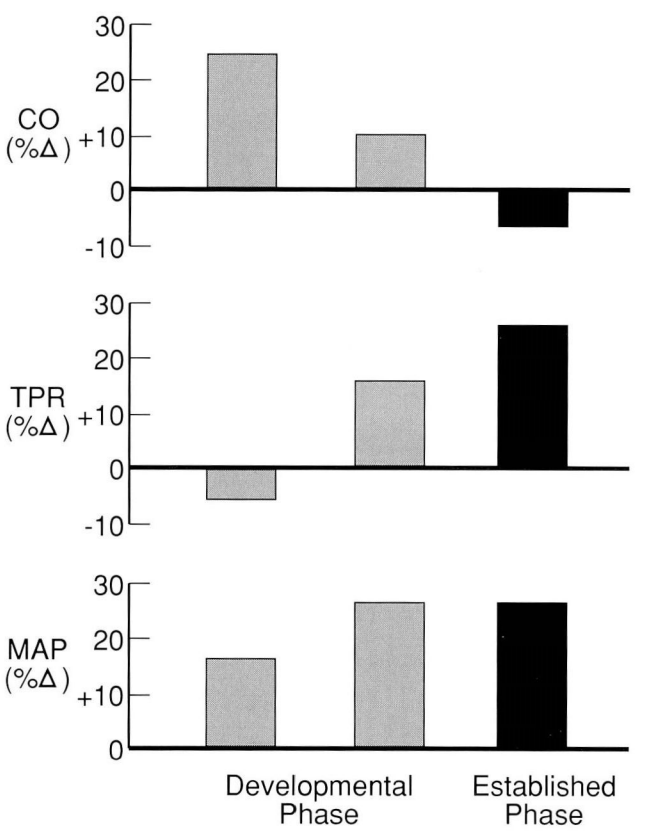

FIGURE 8. Postulated role of cardiac output (CO) in the genesis of hypertension. (*TPR* = total peripheral resistance; *MAP* = mean arterial pressure)

capacitance vessels and selective chronotropic-inotropic cardiac stimulation but also neurogenic resettings of short-term and long-term barostat functions. These changes lead to improved venous return and often cardiac output changes. If barostat functions do not entirely offset the primary events, arterial blood pressure rises. This concept is based purely on a neurogenic mechanism and should not be confused with the "pure" volume alternative.

Second, volume expansion, and hence cardiac output increase, may initiate the rise in arterial pressure. Here the kidneys seem to play the central role. If kidney function is normal, the increased cardiovascular filling also returns towards normal through pressure diuresis. By such means, the kidneys exert a dominating, long-term barostat function because, if other things remain constant, their diuretic capacity determines the final mean arterial pressure. When, however, the excretion function of the kidney is impaired and/or cardiovascular reflexes fail to offset the effects of volume overload, an insidious rise of arterial pressure may ensue. In pure form, such volume variants occur in only a minority of humans, though elements of this nature may be blended with or reinforced by neurogenic elements.

RATIONAL THERAPY BASED ON PHYSIOLOGICAL CHARACTERISTICS OF TYPES OF HYPERTENSION

Primary abnormalities in vascular smooth muscle

Increased peripheral vascular resistance is the hemodynamic hallmark of chronic hypertension. Evidence to date suggests that Ca^{2+} plays a vital role in mediating this vasoconstrictive mechanism. The ideal therapy, therefore, is one that would correct the particular abnormal vasoconstrictor mechanism and not be associated with unwanted tradeoffs. The calcium channel blockers appear to have fundamental pharmacologic advantages over older agents since they act more specifically on the fundamental arteriolar mechanism involved (*Table 1*). Calcium ions are of fundamental importance

TABLE 1
HEMODYNAMIC AND NEUROHUMORAL RESPONSES TO NIFEDIPINE

Measurements	Basal	Treatment
Systolic BP (mmHg)	183 ± 5	136 ± 6*
Diastolic BP (mmHg)	111 ± 2	82 ± 4*
Heart rate (beats/min)	70 ± 4	69 ± 2
Cardiac index (L/min)	2.8 ± 0.2	3.1 ± 0.2
Stroke volume (mL)	75 ± 4	86 ± 4*
Peripheral resistance (U x m^2)	48 ± 3	32 ± 2*
Mean transit time (sec)	7.6 ± 1	7.6 ± 2
Cardiopulmonary volume (mL)	665 ± 40	743 ± 51
Ejection fraction (%)	61 ± 3	58 ± 3
Plasma volume (%N)	96 ± 2	97 ± 2
Plasma renin activity (ng/mL)	2.6 ± 0.6	7.5 ± 1.2*
Plasma aldosterone (ng/dL)	14 ± 2	18 ± 3
Plasma norepinephrine (pg/mL)	260 ± 12	386 ± 42*

Values are mean ± SE (n = 12).
*Statistically different from baseline.

in excitation-contraction coupling. Smooth muscle needs continual replenishment of Ca^{2+} from extracellular sites. This discrepancy on transmembrane Ca^{2+} influx permits manipulation with calcium antagonists.

Volume variants

Human primary hypertension probably includes related volume variants in which renal influences dominate the initiation of elevated arterial pressure. Here the kidneys seem to be a major starting point, presumably because of genetic deviations favoring a tendency to salt and water retention. In other volume variants an initial increase of mineralocorticoid release helps to start the pressure rise. These salt- and water-dependent hypertensions respond to diuretic therapy. Although blood volume measurement is necessary to establish the diagnosis, this type of hypertension is found most frequently in tall and obese subjects, in the elderly, in blacks, and in patients with significant renal impairment. Large doses of diuretics may be necessary to control the hypertension.

Neurogenic variants

Sympatholytic drugs are indicated for several types of hypertensive patients, among them, those with orthostatic hypertension, some with tachycardia and increased cardiac output, and a subset with significant neurohumoral influences (as reflected by increased circulating catecholamines) (*Figure* 9). A sympathetically mediated hypertensive state is most frequently found in young (≤35 yr old) hypertensives and in thin, tall individuals.

The renin-angiotensin II system has been the target of modern therapeutic modalities. At least a third of

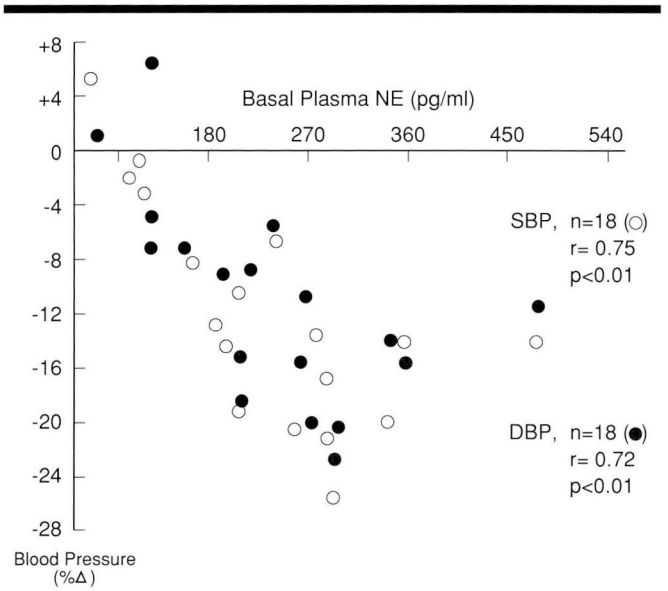

FIGURE 9. Relationship between the circulating levels of norepinephrine (NE) and the arterial pressure response to a centrally acting α_2-agonist (clonidine). The higher the basal plasma NE, the greater the depressor response to the

patients with primary hypertension are characterized as having high plasma renin activity and respond favorably to converting enzyme inhibitors.[9] Increased renin (and thus angiotensin II) release may be an integral part of neurogenic variants where a sympathetically mediated renin release is one of many adjustments constituting the neurohumoral influences. Sympatholytics, by diminishing sympathetic outflow to the kidneys, can inhibit renin release and reduce arterial pressure. Propranolol has been particularly effective in suppressing renin release.[10]

SUMMARY

A clear understanding of cardiovascular physiology, biochemistry, and pharmacology permits an assessment of the possible cause(s) of hypertension and forms the basis for rational and specific therapy. The availability of newer antihypertensive agents with specific and selective actions allows rational and individualized therapies using a minimal number of drugs in their minimal effective doses.

Patients in whom a sodium/volume form of vasoconstriction is predominant are likely to respond to a calcium channel blocker or to a diuretic alone. Those in whom renin-mediated vasoconstriction predominates

can be treated with either an α- or β-receptor blocking agent or with converting enzyme inhibitors. Combinations will be necessary only for those with poor responses to selected monotherapy. This therapeutic approach will, in turn, teach us more about different pressor mechanisms and take us closer to a full understanding of causation.

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