Abnormal Sodium Metabolism and Plasma Renin Activity (Renal Renin Secretion) and the Vasoconstriction Volume Hypothesis: Implications for Pathogenesis and Treatment of Hypertension and Its Vascular Consequences (Heart Attack, Stroke)

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Arterial hypertension is sustained by either of two long-term mechanisms of arteriolar vasoconstriction or by an inappropriate reaction between them. One mechanism is renin-mediated, the other is related to antecedent renal sodium retention. The plasma renin value directly reflects the presence and degree of renin-mediated vasoconstriction, and, inversely, defines the predominance of sodium-related vasoconstriction. A hypotensive response, or lack of it, to angiotensin-converting enzyme inhibitor is similarly informative. Because the normal kidney exposed to high arterial pressure and normal salt intake will reduce its renin secretion to near zero, any renin secretion in a hypertensive setting can be considered abnormal. Typically, high-renin hypertensive patients are more vasoconstricted than low-renin patients with similar blood pressures. The intense vasoconstriction leads to relative hypovolemia, hemococoncentration, hyperviscosity, postural hypotension, and in severe forms even to acrocyanosis, all of which are dramatically reversed with anti-renin therapy. Conversely, low-renin equally hypertensive patients have relatively more sodium volume and are less vasoconstricted; they are generally responsive to natriuretic drugs (e.g., diuretics or calcium antagonists) and appear relatively protected from vascular sequelae such as stroke and heart attack. These observations provide a new means for evaluating prognosis and a basis for mechanistically differentiating and treating hypertensive patients, allowing increasingly simpler and more-specific long-term therapies.

Renin system activity begins with the secretion of the enzyme renin by juxtaglomerular cells reacting to the local perception of reduced perfusion. In the bloodstream, renin triggers a biochemical cascade that yields angiotensin II, which exerts powerful vasoconstrictor properties, stimulates the adrenal cortex to release the sodium-retaining adrenocortical hormone aldosterone, and signals increased sodium reabsorption at the proximal tubules. The normal result of this three-pronged defense against perceived crisis is an appropriate boost in blood pressure, eliminating the local renal perception of reduced perfusion and suppressing the secretion of renin (1).

By now, after three decades of research, the scientific community recognizes the renin system as the principal long-term defender of blood pressure and electrolyte homeostasis. The system's dysfunction is implicated in a sizable portion of hypertensive diseases: this has been made clear by the use of such pharmacologic probes as angiotensin-converting enzyme (ACE) inhibitors, the anti-renin action of which has given them important diagnostic and therapeutic applications. It now is clear that hypertension, once thought to be a monolithic disorder, is a causal spectrum lying between two reciprocal, overlapping extremes, one mediated by inappropriate plasma renin activity and the other by inappropriate sodium retention (2). Sodium retention physiologically suppresses the concentration of plasma renin but at the same time supports higher blood pressures by itself inducing arteriolar vasoconstriction by means still not understood.

The normal variations in sodium intake are reciprocally mirrored in rises and falls of renin secretion (see Figure 1) (1, 3, 4), and the appropriateness of an individual patient's concentration of plasma renin can be evaluated by comparison with that of normal individuals having various amounts of salt intake. A high plasma renin value indicates a renin-mediated hypertension, which will probably respond favorably to anti-renin treatment. Conversely, a low renin value points to a sodium-mediated disorder, which most probably will respond to anti-sodium treatment.

In this laboratory, we have used the renin profile, in which the 24-h urinary sodium value is used as an index of sodium intake, as the basis for an analytical method we call vasoconstriction-volume analysis (5) (see Figure 2), which has been further defined by single-file evaluation of treatment by an anti-renin system drug or a natriuretic hypotensive agent. The method proceeds from the view that all expressions of human hypertension make up a pathophysiological spectrum involving various degrees of inappropriate vasoconstriction relative to volume. Despite its direct sodium-reabsorbing effect at the proximal tubule and its aldosterone stimulation, the most telling effect of angiotensin is systemic and renal vasoconstriction, and we consider that the operative pressor effect of sodium retention is consequent to the hydraulic effects of increased intravascular fluid volume. The extremes of this hypertensive spectrum of abnormal plasma renin–sodium volume products are seen in malignant hypertension (high-renin profile, intense vasoconstriction, and a minimal volume factor) and primary aldosteronism (low-renin profile, a large volume factor, and minimal renin-vasoconstriction).

This method has enabled a useful differentiation of
patients with essential hypertension (3, 4, 7). In the majority—those with either medium (60%) or high (20%) concentrations of plasma renin—inappropriate renin-mediated vasoconstriction sustained the hypertension and tended to yield to anti-renin treatment, whereas diuretics had little or no effect. In the remaining 30%, low-renin profiles were the rule and the hypertension generally yielded to diuretics, with little or no improvement from anti-renin agents. The method has also proved helpful as a screening modality for patients with surgically curable renal hypertension, who characteristically have high plasma renin values emanating from a single stenotic kidney. Indeed, many such patients, previously assigned to lifelong drug treatment but now candidates for relatively noninvasive cure by balloon angioplasty, had been misdiagnosed as having essential hypertension.

Two Forms of Vasoconstriction: the Calcium Connection

In recent years we have expanded the analytical concept to include the realization that the sodium volume component exerts its own unique vasoconstrictive effect. Our analytical and diagnostic format now seeks to identify the pathogenesis of a hypertensive situation in terms of a spectrum between two forms of vasoconstriction, one mediated by renin release and the other by sodium retention (8). The hydraulic action of the fluid accumulation attending sodium retention makes a substantial contribution to blood pressure, but this is first reflected by a higher cardiac output with increased arterial filling. Then in some undefined way, the antecedent excess sodium volume induces arteriolar vasoconstriction that returns the cardiac output to the normal range. How sodium volume content induces long-term vasoconstriction remains a mystery. However, in tracking the biochemistry of vasoconstrictive processes evoked either by angiotensin or sodium, it is increasingly clear that calcium plays a role on both sides of the equation.

Calcium is involved in renin–angiotensin II-mediated events. Available evidence suggests that all factors affecting renin release do so by changing the intracellular concentration of calcium or cyclic AMP, perhaps in coordination with adenosine and prostaglandins (9, 10). Calcium is further involved in the early stages of angiotensin stimulation of aldosterone biosynthesis (cholesterol to pregnenolone (11–14)).

As for sodium-mediated events, several findings suggest that the pressor action of dietary salt may be linked to its ability to alter calcium metabolism. Three lines of evidence support this concept, together with the growing impression that patients with low-renin and hypo-
calcemic hypertension are most likely to be those with sodium-mediated hypertension:

- Calcium feeding can correct the low-renin form of hypertension but is of no value or may even act as a pressor in high-renin patients (15–17). These effects have also been observed in prototype experimental models (18).

- The pressor effect of sodium feeding seen in salt-sensitive patients can be blocked by calcium administration (19).

- The calcium-channel antagonists nifedipine and verapamil have the greatest depressor effect in low-renin and low-calcium patients and the least in high-renin patients with the higher calcium values (20–26).

We have recently undertaken further study of this possible sodium–calcium interaction as a mechanism involved in low-renin vasoconstriction. In metabolic-balance ward studies (26), patients were maintained on constant low-sodium (10 mmol/day) or high-sodium (200 mmol/day) diets for a week before receiving verapamil. Similar results were obtained in an outpatient study involving nitrendipine (27). To our surprise, both drugs were at least as effective when patients were ingesting the high-salt diet (which lowered renin values) as when they were on the low-salt diet—in fact, probably even more so. These findings thus describe the first antihypertensive drug species in which sodium depletion does not add to effectiveness and may actually retard it. Similar results have been obtained by others when using either dietary or diuretic sodium depletion in combination with a calcium antagonist (27–29). These results further confirm that calcium-channel antagonists are most effective in opposing the abnormal vasoconstriction of the nonrenin, sodium-sensitive types identifiable in low-renin patients and are least effective in opposing renin-mediated vasoconstriction.

Our explanation of these events begins with the assumption that, with vasoconstriction, the free calcium in vascular smooth muscle cytosol increases in proportion to the increase in diastolic blood pressure. In the low-renin, sodium-related form of vasoconstriction, the concentration of extracellular ionized calcium is reduced (30) and the intracellular abnormality is opposite to that outside the cells. In this defect, the plasma membrane, for reasons having to do with calcium transport, has become slightly more permeable to calcium, with more calcium accumulating inside the cells from outside sources. The result is the metabolic pattern observed in the low-renin state, with lower extracellular and higher intracellular calcium. We have found that this form of vasoconstriction is "salt sensitive"; i.e., it is induced or amplified by sodium administration (24, 31).

Whatever the final intracellular pathways, patients with renin-mediated vasoconstriction are less sensitive to the depressor effects of calcium-channel blockade (25, 26) because the increased intracellular calcium is not primarily dependent on influx from outside. Second, the pressor effect of salt feeding and the depressor effect of salt depletion are not seen in the high-renin state presumably because these maneuvers operate by modifying calcium influx from outside sources (18, 32).

Calcium may be involved even in neurally mediated vasopressor phenomena, although the contribution of such phenomena to long-term hypertension is moot. The pathways linking neural activity to sodium and calcium transport are poorly understood but may involve a proximity of the transport sites on the cell membrane. Experimental evidence indicates that calcium-channel antagonists may also have a spillover antagonist effect on nearby postsynaptic alpha-adrenergic receptors (33). The effectiveness of calcium blockers, alpha blockers, and diuretics in low-renin hypertensive patients suggests a functional link between sodium, calcium, and alpha-adrenergic receptor activity. The renin profile, backed and confirmed by single-file drug trial, points the way to management even in patients with essential hypertension: high-renin patients will most likely respond to ACE inhibitors or beta-blockers, and low-renin patients to calcium channel blocker, diuretics, or alpha₁-blockers.

"Normal-Renin" Hypertension: an Oxymoron

What can we say about the hypertensive patient with a renin value in the zone occupied by normotensive individuals? Here the presence of a renin factor is often indicated by the fact that many such "normal-renin" patients experience a partial or complete correction of blood pressure when treated with an ACE inhibitor (34–38). Evaluation becomes a bit easier when one realizes that a "normal" plasma renin value in any hypertensive person is abnormal in the context of the patient’s disease and reflects a dysfunction of the renin system. In truly normal, healthy subjects, anything that will raise blood pressure will reduce renin secretion, most often to zero. The use of the word "normal" in this context is misleading; we have come to use the term "medium" instead.

We offer a hypothesis to explain the phenomenon: apparently, kidneys of a large proportion of patients with essential hypertension harbor two functionally abnormal nephron populations: a minor subgroup of hypofiltering nephrons with impaired sodium excretion, which chronically hypersecrete renin, and a larger subgroup of normal but adapting, hyperfiltering nephrons, appropriately reacting to the increase in blood pressure by chronically suppressing renin secretion and increasing the glomerular filtration rate and the distal sodium supply (39). Renin suppression in the normal nephrons compensates the excess production in the impaired nephrons, producing a net output equal to that seen in normotensive individuals; however, the interference with overall sodium excretion results in increased blood pressure. The problem is not met by conventional diuretic treatment but by addressing the renin factor.

Morphological evidence supports this thesis, showing narrowed and dysfunctional afferent arterioles side by side with normal arterioles in patients with uncomplicated hypertension (40). The lesions are similar to those seen in typical Goldblatt-type human hypertension, a
condition in which nephrons in the stenotic kidney have diminished blood flow and reduced perfusion pressure and contain heavily granulated, hyperplastic renin-producing juxtaglomerular cells (41).

Renin as a Risk Factor for Heart Attack and Stroke

We believe there is a special urgency in identifying and treating the renin factor in hypertensive diseases. As long ago as 1972, we first proposed that the baseline value for plasma renin activity could predict vulnerability to heart attack or stroke. Our five-year study of 219 patients with moderate to severe hypertension showed that those with a normal or high plasma renin activity had an 11% and 14% frequency, respectively, of heart attack or strokes (4), whereas none of 59 consecutive low-renin patients had either of these complications, despite a similar increase in blood pressure and left ventricular hypertrophy in the two groups.

A recently reported prospective trial has confirmed and extended this hypothesis that plasma renin activity is directly related to cardiovascular damage (3). In this study, 1717 patients with mild hypertension studied at various worksites were followed prospectively for seven years. After a baseline renin–sodium profile was taken, the patients were all effectively treated with a traditional stepped-care regimen. The baseline renin profile was a powerful independent predictor of a subsequent heart attack. Thus, among 967 patients who had one or more risk factors (e.g., hyperlipidemia, hyperglycemia, tobacco use), a high baseline value for plasma renin was associated with a nearly fourfold greater risk of a heart attack. More importantly, in the 750 patients who had no other risk factors, plasma renin was even a more powerful predictor of risk, with a more than sevenfold greater risk manifest in the high subrenin group, and with no heart attacks observed in all 241 patients with low renin values. Stroke events were too few for meaningful analysis. The pattern of these data raises the possibility that the concentration of plasma renin is related to risk in a continuous manner, because medium- and low-renin patients had proportionally fewer events. Whatever the case, these new findings define plasma renin as a potent independent risk factor for heart attack in patients with mild uncomplicated hypertension and suggest a role for renin testing to evaluate risk and to plan anti-renin system treatment and suggest the need for larger-scale studies of different populations to further define these issues.

At the same time, new experimental evidence relates plasma renin values to the development of stroke. In one of these studies, feeding potassium supplements to stroke-prone spontaneously hypertensive rats caused marked suppression of plasma renin concentrations and this effect was closely associated with marked protection from stroke and from renal vascular injury, even though blood pressure was unchanged from controls (42). The stroke lesions in these animals are extremely similar to the most common form of human stroke. Moreover, in another study, blocking renin activity with an ACE inhibitor also produced marked protection from stroke in animals whose blood pressure was not also reduced (43).

Evidence That Plasma Renin Excess Is Vasculotoxic

Other data have provided circumstantial support for and confirmed different patterns of vascular injury between high- and low-renin states:

- The hypertension of low-renin patients is usually longer in duration and higher in degree than that of high-renin patients, and is just as difficult to control with drugs (44–46). However, patients with low-renin hypertension have better renal function than either the medium- or high-renin patients (44).

- High-renin patients show signs of hemoconcentration: hemoglobin, hematocrit, and total protein values are higher than in low-renin patients or normotensive controls (46).

- Among black subjects, known to be most prone to severe hypertension with vascular sequelae, the young hypertensive patients almost always fall into the medium-renin group, whereas the great majority of patients over age 50 have relatively milder disease and exhibit low renin concentrations (44).

Low-renin hypertensive patients may have a relatively benign type of hypertensive disease. Their sodium-related hypertension is associated with a more positive sodium balance, relatively higher volumes of blood and extracellular fluid, and subsequently, a better tissue perfusion than in medium- or high-renin patients (47). The latter two groups, because of relatively poorer tissue perfusion, are likely to be more susceptible to ischemic vascular damage in such target beds as coronary, cerebral, and renal circulations.

There is also a convincing history of experimental and clinical evidence indicating that excessive or inappropriate plasma renin activity may be vasculotoxic. In 1939, Winternitz et al. (48) showed that injections of renin produced severe vascular damage in nephrectomized dogs, whose sodium balance could be expected to be maximally positive. Since that time, a large experimental and clinical literature has accumulated that relates plasma renin activity to vascular injury. Studies show that malignant hypertension in humans is caused by an abnormal renal–adrenal interaction, causing excess renin and aldosterone secretion (49, 50). This condition is associated with diffuse vascular damage and fibrinoid change. Significantly, the entire syndrome can be reversed by specific anti-renin therapy (34, 36, 51–53), which corrects the hypertension and hyperaldosteronism and leads to healing of the vascular damage.

The case for renin's culpability is also supported by numerous clinical studies showing that total nephrectomy can reverse the malignant syndrome, normalize the blood pressure, and lead to healing of the vascular disease, as shown by biopsy (1). Patients with curable renovascular hypertension due to renin excess are also more prone to malignant vasculitis with vascular damage in the brain and heart (54, 55). Moreover, there is an increasing awareness that high-renin essential hypertension is also associated with more vascular sequelae, a
stormier course, and a shorter survival than low- or medium-renin cases.

Many other clinical situations associated with high plasma renin concentrations are accompanied by striking vascular damage, stroke, or heart attack. These include patients with scleroderma (56), renal trauma, acute closure of a renal artery graft (1), or a renin-secreting tumor (57). After the use of the angiotensin II-blocking agent saralasin in a diagnostic test, four patients with renal hypertension and hyperreninemia developed marked rebound hypertension with encephalopathy in two and coma in one (58). Finally, in patients with scleroderma, marked vascular damage and early demise are correlated with the amount of increase of the plasma renin (56, 59).

The Pressure Factor in Vascular Damage

How can we account for the proposition that renin-mediated hypertension poses a greater risk of heart attack than does sodium-mediated hypertension, despite equal degrees of increases in blood pressure? This thesis goes against the long-held conviction, logical enough on the surface, that the dangers of hypertension stem mainly from the hydraulic force of expanded fluid volume rupturing blood vessels.

It is true that increased pressure, if great enough, might damage any vascular structure; experimentally induced increases in blood pressure can disrupt a blood vessel (60). Both human (61, 62) and animal studies (60, 63, 64) indicate that the malignant phase of hypertension occurs or can be induced when the blood pressure surpasses a critically high value. In this situation, arteriolar necrosis develops, especially in those beds exposed to the high pressure, whereas the vasculature beyond the induced constriction is protected. Also, beyond a critically high pressure, apparently "breakthrough" of autoregulation occurs (65), so that the resistance vessels are no longer able to constrict in response to the increased blood pressure. Instead, they give way, transmitting the high pressure load to the more distal and fragile vasculature, where a blowout occurs.

However, all this does not necessarily mean that the high blood pressure is the critical or only factor in causing vascular damage. Moreover, it may not be appropriate to extrapolate to long-term situations in human subjects what has been observed mostly in acute or short-term animal studies. As is well known, chronic high blood pressure produces adaptive changes in the vascular wall—specifically, hypertrophy—which reduces the lumen-to-wall ratio (66) and may substantially raise the breakthrough point for autoregulation. That this occurs has been suggested by research in hypertensive subjects (67) and by experimental models (60).

Further, many of the acute studies with animal models that have been used to support the pressure hypothesis have induced the high pressure by using vasoconstrictor substances, usually renin–angiotensin or adrenergic agents. This type of study must also be considered to show that administration of vasoconstrictors can induce vascular damage correlated to the degree of hypertension. Rarely do the investigators ask whether a similar degree of hypertension induced by volume expansion would have produced commensurate vascular injury.

There is another, perhaps even more important, criticism of "the pressure hypothesis." Many hypertensive patients and animal models exhibit and tolerate extremely high blood pressures without vascular damage. But marked vascular damage can occur in a variety of clinical and experimental situations at blood pressure readings well below what is thought to be critical. These compelling observations strongly suggest that other factors besides an increased blood pressure may be necessary to induce vascular damage.

Actually, several experiments suggest that vascular damage in hypertensive or normotensive situations may be more closely related to the induction of hypovolemia, with compromised flow and consequent ischemia of the tissues. This impression is supported by observations in animals (68) and humans (69) that indicate that malignant hypertension due to renin excess actually can be remitted by saline infusions. These infusions, even though they may raise the blood pressure, improve flow and relieve hypovolemia and ischemia. Recent studies have defined two animal models in which sustained hypertension is induced or maintained by sodium depletion (70) and corrected by saline administration (71). This broadens the evidence that suggests that sodium depletion and consequent reduced flow can be critical factors for inducing vasoconstriction and hypertension.

Despite the association of high plasma renin concentrations with many hypertensive situations in the clinic and laboratory, most advocates of the "pressure hypothesis" refute a role for renin in vascular damage by citing two situations in which vascular damage occurs with renin either blocked or absent. However, both of these situations are ambiguous. For example, the first type of study shows that when the pressor actions of renin are offset by the concurrent administration of a vasodilator drug such as hydralazine, vascular damage does not occur (72). But this proves nothing, because at the same time the arterial pressure was also reduced, restoring adequate blood flow and creating an entirely different situation.

The second circumstance invoked to discredit the role of renin in vascular damage is the deoxycorticosterone (DOC) acetate–salt hypertension model (73, 74). In this model, vascular damage develops in association with massive sodium retention and a reactively low plasma renin concentration. However, the vascular damage produced by DOC takes much longer to develop than does that induced by renin. In the final analysis, DOC damage is probably also associated with ischemia and reduced flow as consequences of slow edematous deterioration of the vascular wall (74). Actually, onset of the malignant syndrome in DOC acetate–salt-treated rats usually follows paroxysms of natriuresis (75) with re-
sulting hypovolemia, high viscosity, decreased blood flow, and tissue ischemia. Furthermore, good evidence now suggests that both the hypertension and the malignant syndrome of DOC–salt hypertension are sustained by abnormal vasoconstriction caused by excessive vasopressin release (76, 77).

Möhring et al. (68) have further defined the key role of renin in the malignant vasculitis of experimental renovascular hypertension and have demonstrated the beneficial effect of sodium administration in inducing remissions, presumably by restoring flow and suppressing renin. In this model, too, as in the DOC model (74), the malignant phase was preceded by natriuresis with homoconcentration and by higher renin concentrations, whereas blood pressure was unchanged. Accordingly, in both the DOC–salt and renin-induced renovascular models, the findings suggest that sodium depletion with hypovolemia, reactive vasoconstriction, resulting poor flow, and tissue ischemia may be critical in precipitating vascular injury. Altogether, the data also show that severe vascular injury can occur in the absence of renin, as in the DOC model, and that most probably another vasoconstrictor agent, vasopressin, is critically involved instead.

These experiments and others indicate that renin is not necessary for vascular injury to develop in the presence of hypertension. However, before concluding that the cause is purely pressure, one must show that other vasoconstrictor substances besides renin (e.g., vasopressin or catecholamine hormones) are not involved.

Meanwhile, the available evidence suggests that severe vasoconstriction, with its attendant adverse effects, even in the absence of hypertension, may be a key prerequisite for inducing vascular damage. Such vasoconstriction leads to translocation of fluid from the vascular to the interstitial spaces, hypovolemia, homoconcentration, higher blood viscosity, and finally to ischemia from reduced tissue flow, particularly to the microcirculation. This helps explain the many clinical and experimental situations in which vascular damage occurs at pressures well below the so-called critical range. This might also explain results from numerous clinical trials in which successful antihypertensive therapy failed to protect patients from myocardial infarction (78–84). In all such studies, diuretic therapy was part of the regimen. Such therapy would be expected to lower pressure at the price of reducing effective volume and flow and inducing reactive renin-induced vasoconstriction. Conversely, protection from myocardial infarction has been regularly demonstrated in those clinical trials involving beta blockade alone—for example, the large Göteborg trial with 7500 subjects (85). This form of drug therapy can be expected to suppress renin-mediated vasoconstriction (51, 86).

There is no longer a need for speculation on these matters. Today, reliable assays of renin are widely available. Their more frequent use in office practice and in large-scale studies can further clarify the cardiovascular hazards we have related to plasma renin and should set the stage for sharper diagnosis and more aware management of essential hypertension.

References

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