Interaction between renin and the autonomic nervous system in hypertension

The abnormal distribution of plasma renin values described in established essential hypertension are also found in patients with very early, borderline hypertension. In established hypertension, renin values have been used to draw inferences about the pathophysiology of blood pressure elevation. Within this concept, the low-renin state is considered a volume-dependent (volume expanded) form of hypertension. The high-renin state is viewed as high-resistance hypertension caused by a renin-dependent vasoconstriction. However, the pathophysiology of high- and low-renin borderline hypertension does not follow the prediction from the volume-vasoconstriction theory. The high-renin state is often associated with an increase in cardiac output and normal values of vascular resistance. Even when the cardiac output is normal and the total peripheral resistance is elevated in high renin, the vasoconstriction is not renin-angiotensin dependent. The high-renin borderline and mild hypertension is a state of generalized, increased, sympathetic drive to the heart, blood vessels, and kidneys. After the influence of the autonomic nervous system is removed by pharmacologic blockade, blood pressure in patients with high-renin values becomes normal. To the contrary, pharmacologic antagonization of angiotensin II with a converting enzyme inhibitor does not lead to normal blood pressure values in patients with high-renin. Patients with borderline hypertension with low renin have normal plasma and blood volume values. However, because of decreased compliance of the peripheral capacitance space, the blood volume is shifted from the peripheral to the central (cardiopulmonary) portion of the circulation. Expansion of the cardiopulmonary blood volume causes a larger stretch of cardiopulmonary mechanoreceptors, which, in turn, elicits a preferential inhibition of the sympathetic tone to the kidneys. The low-renin and low sympathetic tone in these patients are the consequence of the expansion of the cardiopulmonary blood volume and not of the total blood volume. (AM HEART J 1988;116:611.)

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John Laragh's[1] classification of hypertension into low-, normal-, and high-renin subgroups represents a major milestone in contemporary thinking about the pathophysiology of hypertension. The concept that patients with hypertension are not a homogeneous group and that this heterogeneity may predict patient's responses to various types of antihypertensive treatment greatly altered our thinking about hypertension. The notion that renin levels may reflect different underlying pathophysiologic processes (e.g., that patients with low-renin values have "volume" hypertension and those with high renin have "vasoconstrictor" hypertension), although helpful as a teaching tool, immediately created vigorous reactions, as one might expect with any new and creative idea. It was pointed out that

although entirely logical, the concept was theoretic and that actual hemodynamic measurements do not support the notion of volume expansion in low-renin hypertension.[2] Similarly, it was found that patients with very mild hypertension and high-renin values have high cardiac output[3] and are only "relatively vasoconstricted;" that is, their resistance is not appropriately dilated to accommodate the increased cardiac output.[4]

Physiologically, the renin-angiotensin system interacts with the autonomic nervous system. A β-adrenergic receptor is involved in the renin release from the kidneys; the renin-angiotensin system has central nervous system effects; peripherally, angiotensin II potentiates sympathetic responses.

Over a period of years, we have been interested in the role of the nervous system in hypertension, particularly in patients with mild and borderline hypertension. This review will show that the renin classification is also applicable to this early stage of hypertension, but that the underlying pathophysiology in these patients does not follow the prediction

from the volume-vasoconstriction concept of hypertension. In low-renin cases the total blood volume is normal, but its distribution is abnormal, causing a volume expansion in the cardiopulmonary portion of the venous capacitance. In high-renin cases observed vasoconstriction depends on the enhanced sympathetic drive. High renin in these patients does not appear to act as a direct vasoconstrictor.

HIGH-RENIN BORDERLINE AND MILD HYPERTENSION

Numerous lines of evidence in our laboratory pointed toward a strong role for the autonomic nervous system in mild and borderline hypertension. These results have been reviewed elsewhere.[5, 6] In short, it was shown that the elevation of cardiac output is neurogenic and that it is caused by a higher sympathetic drive and a lower parasympathetic inhibition of the heart. Since two components (sympathetic and parasympathetic) were abnormal and the change in the tone of these two components was reciprocal, this suggested that the abnormality emanates from the medulla oblongata. Integration of cardiovascular sympathetic and parasympathetic tone does occur in the medulla, and the response characteristically is reciprocal; that is, higher tone in one is associated with lesser tone in the other branch of the autonomic nervous system. Various inputs ascend or descend on the medullary cardiovascular center and are able to change the peripheral cardiovascular autonomic tone.

We investigated the possible role of arterial baroreceptors in the genesis of this autonomic imbalance and found that their sensitivity is not altered in patients with hyperkinetic borderline hypertension.[7] Next, we focused on psychosomatic factors as a possible cause of the observed hemodynamic and autonomic nervous system abnormality. Emotional excitement elicits fast heart rates and elevation of blood pressure. This has been investigated in animals, and it has been shown that induction of the "defense reaction" causes a stereotypic circulatory response. Brod[8] pointed out the similarities between the hemodynamic pattern in patients with hypertension to that of the elicited defense reaction in animals. Our patients with borderline hypertension show a characteristic personality pattern; they are outwardly oriented, submissive to others, but at the same time suspicious.[9, 10] These subjects are also prone to "holding in" their anger,[11] but experience a higher subjective intensity of anger.[12]

Since the autonomic abnormality in borderline and mild hypertension appeared to have a central nervous system origin and could possibly be associated with psychosomatic factors, one would expect

that the abnormality would be widespread. We postulated that conceptually all observed abnormalities in borderline hypertension (increased venous tone, decreased plasma volume, increased vascular resistance, larger stroke volume, faster heart rate, and high plasma–renin activity levels) could be explained by a general increase in the cardiovascular autonomic drive.[5] Consequently, Esler et al.[13] embarked on a systematic investigation of the relationship between the sympathetic tone and the plasma-renin activity in borderline and mild hypertension. These studies[3, 13] culminated in their report in the *New England Journal of Medicine* on patients with mild but established hypertension.[12] In this study, patients with high renin had normal resting cardiac output levels. Nevertheless, when they were given intravenous propranolol, they responded with both a greater decrease in the cardiac index and heart rate and a greater increase in the preejection period compared with patients with normal-renin values and normotensive control subjects. Thus the high-renin state was associated with signs of increased cardiac β-adrenergic drive. This pharmacologic evidence for increased sympathetic drive in patients with high-renin hypertension also confirmed by the biochemical observation that their plasma norepinephrine level was elevated. After cardiac blockade with propranolol and atropine, blood pressure in these patients with high-renin values still remained elevated through a vasoconstrictive mechanism (a high vascular resistance). This vasoconstriction could have been caused either by high-renin levels or by an enhanced α-adrenergic drive. This issue was put to the test with the α-adrenergic blockade with phentolamine. After phentolamine, blood pressure in patients with high renin fell to the normal range. We interpreted this to mean that high renin in these patients reflected the generalized increase of the sympathetic drive, but actual blood pressure maintenance depended on an enhanced α-adrenergic arteriolar tone.

Interestingly, in this study patients with high-renin, mild established hypertension had a personality structure similar to those with hyperkinetic borderline hypertension; for example, they were submissive and prone to holding in their anger.[12] Thus high-renin mild hypertension appears to be an entirely neurogenic form of human hypertension, possibly of psychosomatic origin.

We also tested the effect of intravenous converting-enzyme inhibition with teprotide in a small group of patients with high-renin hypertension compared with patients with normal-renin values. The purpose of the study was to investigate directly
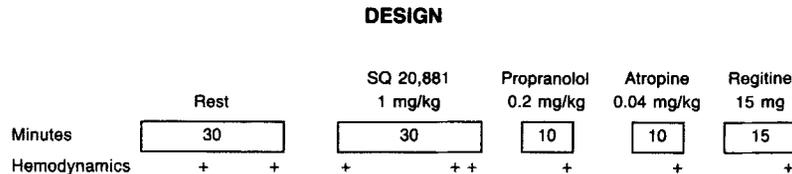
DESIGN

Fig. 1. The study design SQ 20881 is teprotide (Squibb), the first angiotensin-converting enzyme inhibitor available for human use. It was given as an intravenous infusion. The peptide had a very short half-life, and its activity was probably lost 5 minutes after discontinuation of the infusion.

whether high renin could have been the cause of blood pressure elevation in these patients with borderline hypertension. Unfortunately, our supplies of teprotide were limited, and we did not have a control group of normotensive subjects. I retrieved the data from our files and have found that they usefully complement the other studies.

The design of the study, as shown in Fig. 1, was a short-term study of SQ 20881 (teprotide), the first converting-enzyme inhibitor available for human use. The drug was infused in the recommended blocking dose of 1 mg/kg/min. This was then followed by a fast sequence of propranolol, atropine, and regitine. As shown in Fig. 2, the five patients with high-renin values had mean blood pressures similar to the eight patients with low-renin borderline hypertension, but the cardiac index of the high-renin group was significantly elevated. Thirty minutes of teprotide did not alter the hemodynamics or blood pressure levels. After the autonomic blockade, cardiac output in patients with high renin fell to values comparable to patients with low-renin. The autonomic blockade also elicited a fall of blood pressure in patients with high renin to a level significantly below that of the low-renin group. After autonomic blockade, blood pressure in the high-renin group fell to the normotensive range. However, since blood pressure levels of similarly treated normal control subjects are not available, we cannot evaluate the significance of this finding.

Nevertheless, the study permits three conclusions: (1) It shows the difference between the high- and low-renin groups. (2) It proves that antagonizing the angiotensin II does not normalize blood pressure in these patients. (3) It shows that after blockade of angiotensin II, patients with high renin still show an excessive cardiac and vascular adrenergic drive. The study is not only in line with our previous research on the importance of excessive autonomic drive in high-renin hypertension, but it also suggests that renin-angiotensin elevation is not the primary event. We speculate that a primary elevation of angiotensin II is not responsible

(through its central nervous system action) for the higher autonomic tone in high-renin hypertension because the higher tone was still present during blockade of angiotensin II (cardiac output and blood pressure remained elevated during the infusion). These experiments strengthen, but do not prove our contention that an increase in central nervous system drive is the primary event, and renin elevation is only one sign of this generalized increase in sympathetic drive.

LOW-RENIN BORDERLINE HYPERTENSION

Patients with low-renin borderline hypertension studied in our laboratory do not have an increase in plasma volume. However, we confirmed our earlier observation that the cardiopulmonary blood volume is expanded in borderline hypertension.[14] In the new studies it became clear that redistribution of a normal total blood volume from the peripheral to the central portion of the capacitance space is particularly characteristic of patients with low-renin borderline hypertension.[15] It has been noted that in addition to large cardiopulmonary blood volume, these patients also have suppressed sympathetic tone.[16]
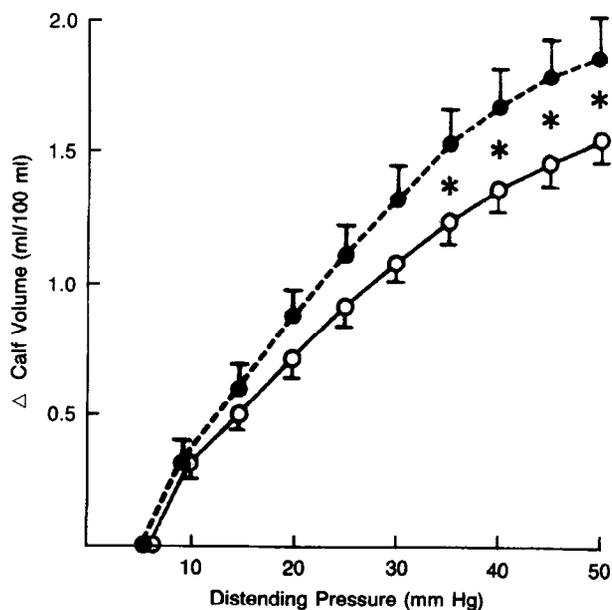
These findings pointed to two possibilities: (1) Some patients with borderline hypertension have a restricted peripheral venous capacitance caused by either a decrease in venous compliance or an increase in the peripheral venous tone. (2) The increase in cardiopulmonary blood volume could cause a larger stretch of cardiopulmonary mechanoreceptors, which, in turn, may inhibit the renal sympathetic tone and thereby lower the plasma-renin values in the upright position. We postulated this hypothesis in 1976,[16] but it took a long detour into the physiologic regulation of renin release in normal humans before the hypothesis could be tested on patients.

Animal experiments clearly demonstrated the existence of stretch receptors in the heart and large pulmonary veins.[17, 18] Stimulation of these receptors causes a generalized withdrawal of the sympathetic
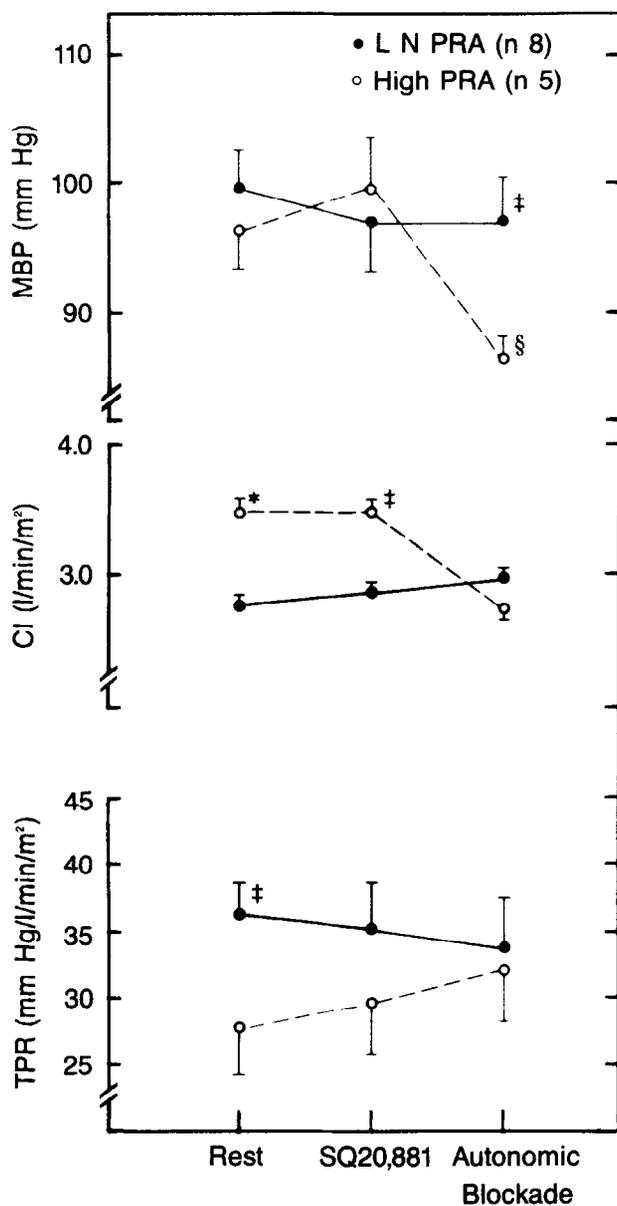
Fig. 2. Hemodynamic effect after teprotide (SQ 20881) and "triple autonomic blockade" with atropine, propanolol, and regitine. $*p = <0.05$ and $\ddagger = <0.01$ difference between the groups (Student t tests), and § denotes $p < 0.05$ by paired comparison within the group. MBP = mean blood pressure; CI = cardiac index; TPR = total peripheral resistance; PRA = plasma renin activity.

Fig. 3. Venous volume-pressure curve for normal subjects *(closed circles)* and hypertensive subjects *(open circles)*. Δ Calf volume = the change in calf volume induced by thigh cuff inflation at each distending pressure. $*p < 0.05$.

output, but the effect on the renal sympathetic tone is most pronounced.[3,5,6] It has been shown that cardiopulmonary mechanoreceptors mediate renin release in animals.[7-10] Thus based on these animal experiments, our hypothesis—that the low-renin state in humans may be caused by an excessive stretch of cardiopulmonary mechanoreceptors— seemed reasonable. Problems came about concern-

ing the issue of whether cardiopulmonary mechanoreceptors function in exactly the same manner in human beings as they do in animals. The existence of these receptors and their physiologic role in humans have been demonstrated,[11,12] but there was some doubt regarding whether they regulate renin release. The main objection came from a group of investigators who used lower body negative pressure to cause peripheral venous pooling and a decrease in the stretch on cardiopulmonary mechanoreceptors.[14] Under these circumstances, a small decrease in the right atrial pressure did not cause an increase in plasma renin. However, an increase was observed when the lower body negative pressure was so strong that it also induced a fall in the arterial pressure. These results suggested that cardiopulmonary mechanoreceptors are not involved in the regulation of renin release in humans, but that arterial baroreceptors are involved. Since in every other aspect the regulation of renin in animals and humans is the same, this particular exception was unexpected. We began to wonder whether the technique of lower body negative pressure induces some artifacts. The lower body vacuum suction requires a tight seal at the interface between the pressure chamber and the body surface. In all such experiments, the chamber is sealed at the level of the iliac crest. This, of necessity, also includes a part of the lower abdomen.

There was ample evidence that this maneuver also decreases the intra-abdominal pressure.[19-22] This negative abdominal pressure could be transmitted to the kidneys and affect the intrarenal renin-regulating baroreceptors. Furthermore, numerous circulatory reflexes can be elicited from the richly innervated abdominal cavity.[23] Consequently, we sought a technique that would permit pooling the blood in the lower part of the body without affecting the pressure in the abdominal cavity. The old technique of using a tourniquet to decrease cardiac preload has been modified, and various degrees of pressure were generated in a pair of narrow inflatable cuffs placed high on the experimental subjects' thighs.[24] This caused the expected pooling of blood in the legs (the right atrial pressure and the cardiopulmonary blood volume decreased) and an increase in renin values. That this increase in renin was reflex mediated has been shown in two ways: (1) The response could be abolished with β-adrenergic blockade, and (2) patients with transplanted and therefore denervated kidneys did not respond to thigh cuff inflation with an increase in renin. This initial encouraging result lead to a series of experiments that are well-summarized by Egan et al.[25, 26] Using various maneuvers (positive lower body pressure, tilting, sitting with legs extended horizontally, and various levels of thigh cuff inflation) Egan et al. provided ample proof that cardiopulmonary mechanoreceptors exert the predominant role in the reflex regulation of renin in human beings. These results have recently been confirmed by Mancia et al.,[27] who used the lower body negative pressure technique and leg raising to explore the full range of the reflex activity. They conclude that the cardiopulmonary mechanoreceptors can both increase and decrease renin from prevailing baseline levels.

When sufficient evidence that the cardiopulmonary mechanoreceptors control renin release in humans had been collected, we decided to reinvestigate the original hypothesis that low renin in borderline and mild hypertension might be caused by a larger stretch of cardiopulmonary receptors because of the expansion of cardiopulmonary blood volume. This was studied by Fitzpatrick et al.[28] Thigh cuff inflation was again used to elicit renin responses and also to measure the compliance of the veins in the legs. Fig. 3 shows that as a group, patients with borderline hypertension had less distensible leg veins. Fig. 4 illustrates that patients with normal-renin values and normotensive control subjects pooled a similar amount of blood in the legs in contrast to the low-renin responders who accumulated less blood in the legs. These differences in
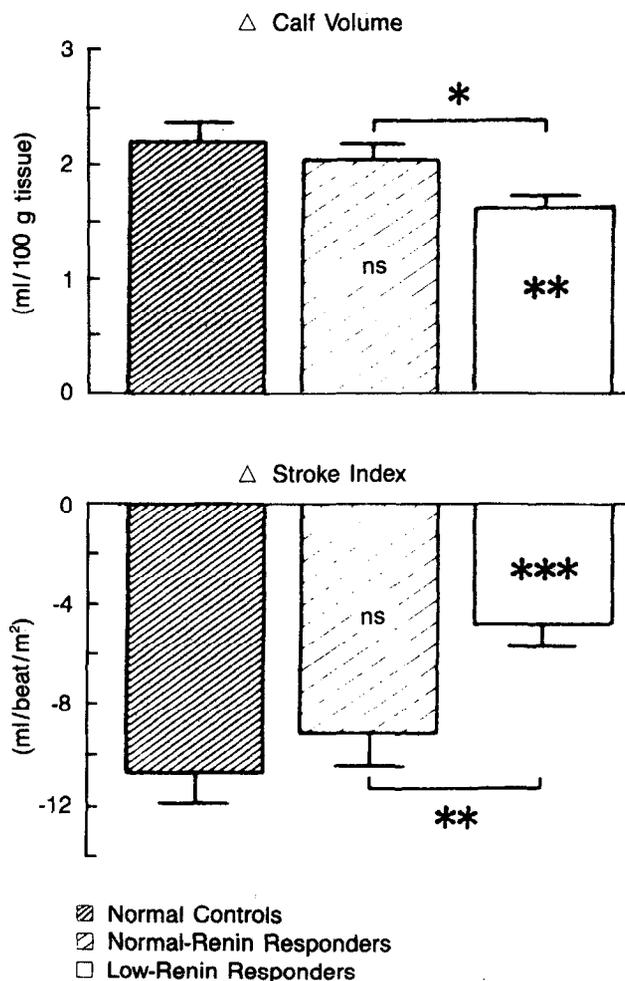

Fig. 4. Changes in calf volume and stroke index induced by thigh cuff inflation in normal controls, normal-renin responders, and low-renin responders. Significant differences between the two hypertensive groups are shown by symbols over bars connecting each column, and differences between either hypertensive group and the normal controls are shown on the column for the hypertensive group. $*p < 0.05$; $**p < 0.01$; $***p < 0.005$.

venous pooling elicited appropriate changes in cardiac preload, as shown in Fig. 4 by the differences in stroke volume.

These experiments clearly indicate that low-renin values in hypertensive patients are the result of a hemodynamic abnormality. Patients with low-renin values are not volume expanded in the true sense of the word. However, they have abnormally stiff peripheral veins, which cause translocation of the intravascular fluid toward the central portion of circulation. It is very likely that this causes a bigger stretch of the cardiopulmonary mechanoreceptors, which leads to low-renin and norepinephrine values. The possibility that an excessive cardiac stretch also causes a larger release of atrial natriuretic factors,

which may affect renin values, has not yet been investigated.

CONCLUSION

An abnormal distribution of plasma-renin values can already be found in the very early phases of hypertension. In these patients the renin values are not simple markers for an underlying volume-vasoconstriction pathophysiology. The total blood volume is not expanded in low-renin hypertension. In high-renin cases, the renin elevation is a consequence of a generalized increase in sympathetic tone, but it is not responsible for excessive vasoconstriction. The cause of vasoconstriction in these patients is an enhanced α-adrenergic drive.

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