Renin System Activity as a Determinant of Response to Treatment in Hypertension and Heart Failure

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SUMMARY In hypertension, irrespective of its underlying etiology, the baseline pretreatment renin-sodium profile predicts the antihypertensive action or the lack of it for five major types of antihypertensive drugs: 1) diuretic agents; 2) beta-receptor blockers; 3) converting-enzyme inhibitors; 4) the alpha, postsynaptic blocker, prazosin; and 5) the calcium channel blockers, verapamil and nifedipine. Moreover, vigorous compensatory activation of the renin-angiotensin system in response to therapy often explains initial drug ineffectiveness or resistance to treatment by diuretics and nonspecific vasodilators. This correlation between renin system behavior and antihypertensive drug efficacy likely reflect basic pharmacologic-physiologic interactions. This correlation is also observed in congestive heart failure without hypertension, where operant renin-aldosterone profiles may help to explain both drug efficacy and drug resistance to commonly administered therapeutic agents. Accordingly, a control system analysis of the renin axis has broad applications in therapy. The analysis is also conceptually significant since it exposes the operation of fundamentally different mechanisms of increased vascular resistance to flow occurring in different patients with hypertension or heart failure. One form is renin-angiotensin-mediated whereas the other, in the absence of renin, is associated with sodium-volume excess and/or abnormal alpha-adrenergic and calcium channel activity. Further definition of these two mechanisms of increased peripheral resistance could lead to a better understanding of the pathogenesis of some forms of essential hypertension and congestive heart failure. (Hypertension 5 (supp III): III-36-III-42, 1983)

KEY WORDS • dietary sodium • converting enzyme inhibitors • calcium channel antagonists • alpha adrenergic blockade • diuretics • systemic vascular resistance

I t has been our working hypothesis that all essential hypertension is not alike pathophysiological-ly, a viewpoint that is supported by a growing body of evidence. Thus, while the height of the blood pressure is generally inversely related to prognosis, there are numerous exceptions, so that the risks of cardiovascular events and of shortened survival are not evenly distributed among equally hypertensive persons. An impressive piece of evidence expressing the heterogeneity of essential hypertension comes from observations frequently made by clinicians that different hypertensive individuals can exhibit entirely different responses to a given drug regimen.

More recently it has been possible to define the heterogeneity of essential hypertension more precisely in biochemical terms using the technique of renin-sodium profiling. This measurement defines an abnormal splay of renin patterns among people with so-called essential hypertension. Approximately 30% have subnormal values, often well below the normal range, and another 15% to 20% have abnormally high values. Only about half of patients with essential hypertension have renin values that fall within the normal range.

We shall evaluate the impact of renin system activity on drug efficacy, how it may identify patient subgroups where specific forms of therapy may be highly effective, and also, how it may play a role in the development of drug resistance.

Basis For Poor Drug Responses

With considerations of compliance to treatment and drug interactions aside, there are two possible reasons why an antihypertensive drug will be ineffective. First, it may be that the antihypertensive activity of the drug is through a mechanism that is not operating to support the high blood pressure in a particular patient. Second, the drug may act on a mechanism that is supporting the hypertension but its effect is offset by a drug-induced...
compensatory response, sufficient to counteract the primary drug action. In this discussion, we will consider and provide examples of both of these types of drug resistance.

The Vasoconstriction-Volume Spectrum of Human Hypertension

These phenomena will be analyzed in terms of the renin-angiotensin-aldosterone control system, where abnormal patterns in individual patients point to pathophysiologic mechanisms at work that are responsible for the hypertension. We assume that the operating blood renin level is a true measure of its active vasoconstriction.\(^1\) We also assume that the urinary sodium value on the day of the study reflects the concurrent state of sodium intake and therefore can be used to evaluate the appropriateness of the renin value in relation to the concurrent volume status when compared with normal control data.\(^1,4\)

Figure 1 illustrates the operation of the renin system and how two fundamental factors support blood pressure (i.e., the vasoconstriction and the volume elements), and enable the assessment of their quantitative contribution to hypertension in individual patients.

In hypertension, several factors may stimulate renin release from the juxtaglomerular cells of the kidney into the circulation. Renin then instantly results in angiotensin I formation, and this is converted via a single passage through the lungs to angiotensin II, which vasoconstricts the arterial tree to raise the blood pressure. At the same time, over a slower limb, angiotensin II activates aldosterone secretion, which causes, during the subsequent 24 hours, salt and water to be retained to further support the blood volume and pressure. The vasoconstriction factor defines the extent of vascular resistance, as determined largely by changes in arteriolar caliber. The volume factor is determined by the amount of sodium and water filling the vascular bed at any point in time. This analytical model does not exclude other factors influencing blood pressure, such as catecholamines, prostaglandins, vasopressin, kinins, emotion, or posture. But all of these factors, in the final analysis, have to exert their effect by changing either the size of the arterial bed (the vasoconstriction factor) or the amount of sodium and water filling the vascular bed (i.e., the volume factor).

The simplest example of this is the patient with low renin essential hypertension, where intra- and extravascular sodium excess are associated with increased vascular resistance and suppression of the renin system. Hypertension in these patients is often completely corrected by inducing sodium depletion and normalization of renin.\(^3\)

Other patients with essential hypertension exhibit medium or high renin levels instead. In them, sodium depletion is less effective, and their blood pressure is often corrected by drugs that either suppress renin secretion (beta-blockers) or block angiotensin formation (converting-enzyme inhibitors).\(^5\) Therefore, the vasoconstriction-volume model allows one to quantify the contribution of renin system activity to the increased vascular resistance, for individual patients, by using appropriate pharmacologic probes. Any drug that affects either the blood pressure or sodium-volume status ought to act by either blocking the renin system at some point, or by blocking an alternate mechanism, producing predictable reactive changes in the renin system.

Renin System Patterns to Identify the Efficacy of Antihypertensive Drug Therapy

The first inkling that there was a relationship between renin status and drug response came from studies of patients with low renin forms of hypertension. Crane et al.,\(^6\) suspecting an unidentified mineralocorticoid as an etiologic factor, first reported that these patients were uniquely responsive to the aldosterone antagonist, spironolactone. Subsequently, this observation has been abundantly confirmed and extended, and it has been shown that it is not the blockade of aldosterone that is crucial. The common denominator for correcting high pressure in these low renin patients is the induction of sodium-volume depletion by whatever means.\(^7\)

In 1972, a breakthrough in this area occurred when Büchler and associates\(^8\) showed that a reciprocal to the above observation existed. They demonstrated that the beta-receptor blocking drug, propranolol, was largely ineffective in lowering blood pressure in low renin patients but was increasingly effective in medium and
high renin patients according to the height of the baseline renin level. Thus, it became possible to understand the variable antihypertensive response to beta-blockers observed in patients with essential hypertension in terms of their differing underlying renin patterns. At the same time, these findings incriminated for the first time an inappropriate or absolute excess of plasma renin in the pathogenesis of high blood pressure in approximately 50% of the patients with so-called essential hypertension.

Table 1 summarizes a number of studies in which these relationships have been evaluated. In these studies, low renin essential hypertension was uniquely responsive to sodium-depleting drugs whereas medium and high renin hypertension was instead especially responsive to beta-receptor blocking drugs that suppressed renin secretion. Additional support is given to these observations by companion reciprocal findings. Thus, beta-blockers are ineffective or even pressor in low renin forms of hypertension, and diuretics are ineffective or even pressor in high renin states. Moreover, there are reasonable physiologic explanations for all of these patterns. Thus, for example, in low renin patients where there is no renin factor to suppress, a major consequence of beta-blockade is unopposed alpha tone, which can actually raise the pressure. Conversely, in high renin patients, preexisting active renin secretion will react to diuretic-induced volume depletion with a further increase in renin. This can counteract the favorable antihypertensive response to diuretics and actually increase blood pressure. Of course, all of these effects are most pronounced and apparent at the extremes of the renin-volume spectrum. They become less impressive or inapparent in patients with medium renin levels. But it is the changes occurring at the extremes of a range of physiologic deviations that allow us to understand the spectrum as a whole. In addition, this issue is confounded by the fact that beta-blockade may have consequences other than suppression of renin release, so that antihypertensive activity is not always related to baseline renin values.

Figure 2 summarizes our experience in 166 hypertensive patients given captopril. It describes the relationship between the induced drop in diastolic pressure 2 hours after the first dose of treatment and the pretreatment renin level. What these data demonstrate is a good relationship between the control renin level and the degree of reduction of diastolic pressure in an acute testing situation. When one considers the difficulties with such an experiment, such as the inaccuracies of indirect blood pressure readings and the changes in overlying sympathetic activity, these data nonetheless illustrate the predictability of the response to a converting enzyme inhibitor, based on the control renin. Thus, when the control renin level is less than 1.0 ng/ml/hr, only minor or insignificant changes in diastolic pressure occur, but significant pressure reduction occurs as the renin values go higher. A similar relationship was described in other studies using saralasin. Altogether, our experience indicates that the extent of baseline renin activity is an accurate predictor of the antihypertensive effectiveness of beta-blockers, saralasin, or of the converting-enzyme inhibitors. Therefore, clinical trials that compare the effects of these drug groups without preliminary renin profiling could produce misleading impressions.

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<tr>
<th>Beta-blockers are preferentially effective in high- and normal-renin patients</th>
<th>Diuretics are preferentially effective in low-renin patients</th>
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<tr>
<td>Karlberg et al., Am J Cardiol 27:642, 1976</td>
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Beta-blockers can actually raise pressure in low-renin patients

Drayer et al., Am J Med 60:897, 1976

Diuretics can actually raise pressure in high-renin patients

Baer et al., Ann Intern Med 86:257, 1977
More recent studies of alpha,-adrenergic blockade and of calcium channel antagonism have provided a broader applicability to this concept. It has been shown that the alpha, postsynaptic receptor blocking drug, prazosin, is especially effective in low renin patients and less effective in high renin states.15,16 Furthermore, the calcium channel antagonists, nifedipine and verapamil, have the same selectivity, being most effective in low renin patients and least effective in high renin states.17,18 These findings have theoretic as well as practical value, because they indicate a close connection between postsynaptic alpha adrenergic activity and calcium channel influx and they suggest that both of these mechanisms are active in low renin hypertension and relatively inactive in high renin patients. Whether the same low renin patients who respond best to diuretics also respond best to calcium channel or alpha blockade remains to be determined. It could be that the low renin state is not homogenous but embraces several subgroups. Furthermore, the role of postsynaptic alpha, receptors in the regulation of calcium channel blockade requires further clarification.19

**REACTIVE PATTERNS OF RENIN SYSTEM ACTIVITY**

**A MECHANISM OF RESISTANCE TO DIURETICS**

In addition to predicting the efficacy of specific drug therapy in renin subgroups, inadequate responses to treatment can be analyzed in light of reactive renin responses to drug therapy. In this context, let us consider why diuretics may be ineffective in lowering blood pressure. Figure 3 illustrates a study published in 1974 by Dr. Gavras and our group,11 demonstrating the effects of the intravenous converting-enzyme inhibitor teprotide, or SQ 20,881, in hypertensive patients. While the patients were ingesting a normal sodium intake, both systolic and diastolic blood pressures were increased in the basal state and teprotide caused a modest reduction of blood pressure. Two key observations were made when sodium depletion was instituted. First, a stringent low sodium diet had no appreciable effect on the resting level of blood pressure. Second, sodium depletion and activation of the renin system made these patients exquisitely sensitive to teprotide. Thus, dietary sodium depletion was ineffective in the reduction of blood pressure, and simply converted the genesis of vasoconstriction in these patients from a nonrenin- to a renin-mediated mechanism. Our group has described a similar relationship in a one-kidney, one clip animal model of renovascular hypertension,20 and similar clinical results have now been reported by other groups. Finally, these data also explain why hypertension that is poorly controlled by diuretic mono

**Figure 2.** Change in seated diastolic pressure 90 minutes after a single oral dose of captopril 25 mg in 166 patients with all forms of hypertension.

**Figure 3.** Blood pressure reduction (±SE) induced by converting-enzyme inhibition in five patients maintained on a normal sodium intake and during sodium depletion. Further reduction was achieved after 2 to 4 days of sodium depletion and readministration of the inhibitor. Sodium depletion per se did not affect control blood pressures (see ref. 12).
therapy will often be normalized when converting enzyme inhibitors are added to diuretics.

It is more readily apparent why diuretics fail to lower blood pressure when such poor responses are observed in clinical studies. Figure 4 is from a study by Weber and colleagues, in which hypertensive patients received the diuretic chlorthalidone, 100 mg daily for 2 weeks. Plasma renin and aldosterone were compared at the control and 2-week treatment stages, and patients were divided into responder and nonresponder groups based on blood pressure control. The reactive increase of plasma renin was almost twofold greater in the nonresponder group compared to the responders. Possibly more important was the fact that the nonresponders had a much greater increase of aldosterone excretion compared to the responders. In the nonresponders, therefore, this vigorous stimulation of the renin system was most likely a factor in completely opposing the reduction of blood pressure induced by sodium depletion. This is one explanation for the inadequate blood pressure response to diuretics.

These data indicate that diuretics are most likely to lower pressure in patients whose renin levels have been suppressed, presumably by a long-standing sodium surfeit. Conversely, in high renin patients, the already stimulated juxtaglomerular apparatus undergoes further abrupt stimulation in the setting of sodium and volume depletion so that the antihypertensive effects in this subgroup of patients is markedly attenuated.

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**Renin System Patterns and Reversal of Vasoconstriction Responsiveness in Congestive Heart Failure**

The relationships just described gain an additional physiological dimension when one examines similar studies made in patients with congestive heart failure. We have evaluated the role of the renin-angiotensin system in 52 patients with chronic congestive heart failure. Figure 5 illustrates that, in these patients, there occurs a wide range of baseline plasma renin activity, ranging from very suppressed levels to markedly elevated levels. These observations are entirely analogous to what we see in the spectrum of patients with hypertensive disorders.

To define and quantify the role of renin-mediated vasoconstriction in patients with chronic congestive heart failure, we administered a single 25 mg dose of captopril and followed hemodynamic changes serially over the ensuing several hours (fig. 6). The induced reversal of vasoconstriction, as assessed by the percent decrease in systemic vascular resistance, was highly determined by the baseline or pretreatment plasma renin activity value. That is, in those patients with markedly elevated plasma renin activity values, there was a marked reversal of vasoconstriction or vasodilation, and in those patients where there was minimal plasma renin activity, captopril was usually not effective as an unloading agent. This relationship held true...
not only for those patients maintained on diuretics but also for patients in whom diuretics were discontinued and in whom sodium balance studies were performed.23

In heart failure patients, possibly unlike most patients with hypertension, more than one mechanism of vasoconstriction may operate simultaneously. We have previously observed that both plasma renin activity and sympathetic nervous system activity, the latter revealed by plasma catecholamine levels, may be increased simultaneously.24-26 In such patients, a favorable hemodynamic response could be observed with either captopril or prazosin. Furthermore, preliminary data indicate that those patients with both increased plasma renin activity and sympathetic tone will respond favorably to calcium channel antagonism by nifedipine.27 Finally, sodium intake per se, may have profound effects on vasoconstriction.28 In such patients, a favorable hemodynamic response could be observed with either captopril or prazosin. Furthermore, preliminary data indicate that those patients with both increased plasma renin activity and sympathetic tone will respond favorably to calcium channel antagonism by nifedipine.27 Finally, sodium intake per se, may have profound effects on vasoconstriction.28 In such patients, a favorable hemodynamic response could be observed with either captopril or prazosin.

Discussion

We have reviewed herein a body of evidence that indicates that the response to beta-receptor blockers, saralasin, teprotide, and the orally active converting-enzyme inhibitors is greatly dependent on the underlying renin system activity and sodium volume status, as revealed by renin-sodium profiling. With diuretic therapy, perhaps the most commonly used antihypertensive agents, there is a close but inverse relationship between response to therapy and the operant baseline renin profile. These agents are most effective in patients with little or no renin activity and progressively less effective to ineffective as the renin level rises.

Recent evidence has further reinforced the value of the renin system analysis for predicting the response to drug therapy and mechanisms of drug action. Thus, experience with alpha receptor blockers and calcium channel antagonism indicates that these two types of agents, like diuretics, are most effective in low renin forms of hypertension, and are relatively to completely ineffective when the baseline renin levels are higher.

It is perhaps easy to explain why converting enzyme inhibitors and beta receptor blockers are more effective depending on the height of the renin level, since these agents act respectively to either suppress renin secretion or block its activity. However, it is a bit more of a challenge to understand why sodium and volume depletion with diuretics lowers blood pressure in low renin patients, and an even greater challenge to understand why calcium channel and alpha blockers are also most effective in these same low renin states. Reasoning backward, one can presume that the low renin state is one that is probably associated with a total body excess of sodium and water, since diuretic effectiveness is obviously related to the depletion of this volume excess. Yet, this leaves unexplained the fundamental question of how a putative sodium excess in the body induces an increase in peripheral resistance in the first place. It also leaves unexplained why alpha receptor blocking drugs and calcium channel blockers as drug classes also have their greatest antihypertensive
action in this setting. However, the fact that both calcium channel blocking drugs and alpha receptor blockers seem to act most effectively in the same circumstances suggests the possibility, at least, that the postsynaptic alpha receptor and the calcium channel-mediated vasoconstriction share something in common and that this in turn is related in some way to the postulated sodium surfet of the low renin state.

While all of these findings produce an exciting new perspective for understanding responsiveness to antihypertensive therapy, it should be restated here that the problem is still far from completely solved. A whole variety of older drugs with seemingly nonspecific actions such as the vasodilators (hydralazine, minoxidil, and nitroprusside), ganglion blockers (quanethidine, bethanidine), and the centrally acting antihypertensive drugs (metyrapol, clonidine, and reserpine) might exert their antihypertensive actions independently of the status of the renin system and also appear to act considerably less selectively. While these older agents have not been systematically or completely studied in modern terms, it does seem that they exhibit much less individual variation in patient response. Furthermore, an obviously important though still undefined role of the autonomic nervous system in mediating or opposing antihypertensive drug action requires much more study before definitive statements can be made. We should note, however, that in congestive heart failure where catecholamine levels are sometimes markedly increased, it is possible to demonstrate in this subset of patients companion abnormalities of autonomic control and of their baroreceptor function.

In summary, an understanding of renin-angiotensin-aldosterone activity in hypertension and heart failure not only provides a useful means to identify patient subgroups that are most likely to respond to specific classes of drug therapy, but also provides a discrete framework to analyze the occurrences of inadequate or ineffective response to drug therapy in individual patients.

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Hypertension. 1983;5:III36
doi: 10.1161/01.HYP.5.5_Pt.2.III36

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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