Relation between Plasma Renin Activity, Angiotensin, and Aldosterone and Blood Pressure in Mild Untreated Hypertension

W. Gordon Walker, M.D., John S. Horvath, M.D., Michael A. Moore, M.D., Paul Whelton, M.D., and R. Patterson Russell, M.D.

SUMMARY Plasma renin activity, arterial and venous angiotensin II (A II), plasma aldosterone, and sodium excretion were measured in a group of 101 patients with mild essential hypertension. For the total hour; arterial A II was 5.2 ± 1.0 pg/ml; venous A II was 4.2 ± 0.6 pg/ml; and plasma aldosterone was 5.0 ± 0.45 ng/100 ml. All values were lower than corresponding values for normal subjects on a high salt intake despite the fact that salt intake in the normal subjects exceeded that for the hypertensive group more than 3-fold. Moreover, when the range of diastolic blood pressure up to 114 mm Hg was divided into three successive class intervals of increasing severity, there was a negative correlation between diastolic blood pressure and both PRA and plasma aldosterone. Arterial A II showed an anomalous increase in the class interval 105-114 mm Hg; despite the fact that this group exhibited the lowest level of PRA. At diastolic blood pressures above 114 mm Hg, the PRA appears to rise again. The anomalous increase in arterial A II in the presence of marked suppression of PRA is consistent with the presence of a renin activator or accelerator factor in hypertensive plasma as postulated by others. It also identifies a possible mechanism whereby even small increases in PRA could exert an adverse effect on the hypertensive state.

HELMER’S early observation that plasma renin activity (PRA) is suppressed in some patients with essential hypertension identified an interaction between the renin-angiotensin system and the altered physiology of essential hypertension. Subsequent estimates of the incidence of suppressed PRA in groups of hypertensive patients have yielded frequencies ranging from 9% to 53%. More recently, Brunner et al. reported that patients with markedly suppressed PRA form a subset of hypertensives with a significantly lower incidence of cerebral vascular accidents and myocardial infarction. These findings have not been supported by the studies of Doyle et al. or Mrozek et al. who failed to find any difference in the incidence of end organ disease between hypertensive patients with suppressed, normal, or elevated PRA. Sampling differences must be considered as a possible explanation for these discordant findings.

These studies and others examining mineralocorticoid activity have sought to characterize low renin hypertension. Much of what has been written on this subject implies that low renin hypertension is a distinct nosological entity or a unique subset in the spectrum of essential hypertension. Evidence for this classification must be regarded as suggestive rather than conclusive at present.

If low renin hypertension is a unique entity, i.e., a form of hypertension that always can be identified by the exhibition of abnormally low renin activity, then stratification of a sample of patients according to blood pressure levels should yield the same frequency of low renin values at different levels of blood pressure. Conversely, demonstration of a correlation between blood pressure and renin activity would represent evidence that the renin status of patients with essential hypertension reflected, in some manner, the severity of the disease and could be expected to change as the disease progressed in severity. Because long-term observations on a group of untreated hypertensive patients cannot be justified in view of the recognized hazards of withholding treatment even in mild essential hypertension, we have sought evidence permitting a choice between these alternate hypotheses by measuring PRA in a group of patients with mild untreated hypertension.

The vascular toxic effects of renin are mediated through A II; hence, characterization of renin activity in hypertension is incomplete without simultaneous measurements of plasma A II levels. Since sensitive radioimmunoassays for A II have become available, a number of investigators have reported values for A II in normal and hypertensive subjects. These observations were made on small samples of patients, and the hypertensive patients exhibited a wide range of diastolic pressure. Some had features of malignant hypertension or were being treated with antihypertensive agents; these factors are known to influence the renin-angiotensin system. Dustan's observation that the relation between plasma volume and blood pressure changes remarkably with treatment underscores the importance of studying hypertension in the untreated state.

In the present study we have attempted to define the behavior of PRA, arterial and venous A II, and plasma aldosterone in 101 patients with mild, untreated essential hypertension and to compare these findings to findings for a group of normal subjects who were volume-expanded by oral salt loading.

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METHODS

PATIENT POPULATION AND SELECTION

Preliminary screening identified patients presenting at the Johns Hopkins Hospital Emergency Room for minor medical complaints and who were found to be hypertensive. These were referred to the Hypertension Screening Clinic for further study and follow-up. The demographic characteristics of patients studied were identical to those of previously surveyed groups utilizing the outpatient facilities and thus may be considered a representative sample of the large urban adult population dependent upon The Johns Hopkins Hospital for its medical care. Between July 1972 and August 1973, 459 subjects were referred to the Screening Clinic for further evaluation; 51%, or 232 patients, appeared and preliminary studies included a complete history and physical examination and urinalysis. Criteria for entering patients into this study were: (1) Diastolic blood pressure was equal to or greater than 90 mm Hg, verified by three separate observers. The blood pressure used for purposes of data evaluation was the supine blood pressure obtained just prior to drawing the blood samples. (2) No patient was studied who had received antihypertensive drugs or diuretics in the previous 4 weeks, nor were patients accepted who currently were receiving any other medications. This included all women who had taken oral contraceptives in the previous 6 months. (3) There was no hypertensive end organ disease as judged by screening history, physical examination, and urinalysis, and confirmed by laboratory studies. (4) The subjects ranged in age from 17-47 years.

On the basis of these criteria, 101 patients were accepted for this study. Of the 131 not accepted, 46.6% were too old, 24.4% were receiving drugs, 17.3% had evidence of other disease such as diabetes mellitus, renal disease, alcoholism, or end organ disease, and 11.5% were normotensive at their first clinic visit. Additional studies were carried out on those accepted; blood for serum electrolytes and urea nitrogen routinely was drawn, chest x-rays and electrocardiograms were obtained for more than half, and one-third had intravenous pyelograms performed. To rule out secondary causes of hypertension or other associated illness, appropriate investigations were performed when indicated.

The patients at the time of study were ambulant and on an unrestricted diet; specifically, no attempt was made to influence their sodium intake. All studies were performed between 9 a.m. and 12 noon. Consent was obtained from all patients after the nature and hazards of arterial puncture had been explained.

Control data on normal individuals provided a baseline for evaluation of the data in hypertensive subjects and have been reported in detail in a separate communication.17

COLLECTION OF BLOOD SAMPLES

All subjects had been ambulant for at least 2 hours prior to the blood collection. An indwelling 19-gauge needle was placed in a vein of the forearm and was used for all venous sampling. Blood for PRA, immunoreactive A II and aldosterone was drawn from the vein and immediately afterward a radial artery was punctured to obtain blood for A II.

Blood for PRA and A II was drawn into chilled plastic syringes containing ethylenediaminetetraacetic acid (EDTA), immediately transferred to chilled centrifuge tubes, and centrifuged at 4°C for 15 minutes at 2,000 rpm. The plasma was separated and samples for PRA and A II were stored separately in polystyrene tubes at -20°C until assayed. Blood for plasma aldosterone determinations was collected into chilled plastic syringes containing 1,000 units of purified beef lung heparin and subsequently handled in the same manner as the blood for PRA and A II determinations.

ASSAY TECHNIQUES

PRA was measured by radioimmunoassay using a modification of the technique described by Haber and associates.18 Six replicate determinations on a sample of purified human renin containing 1 × 10^-4 Goldblatt units gave a mean value for angiotensin I (A I) of 4.6 ± .3 (SD) ng/ml per hour when assayed in anephric human plasma. The limit of sensitivity of this assay was 0.1 ng/ml per hour of A I generated when the assay was performed at pH 7.4 with an incubation time of 3 hours. A II was measured by radioimmunoassay carried out on an ultrafiltrate of plasma as previously reported from our laboratory.19,20 Plasma aldosterone was measured by a method previously described from this laboratory.21

URINE COLLECTIONS AND ASSESSMENT OF SODIUM BALANCE

Sodium intake was assessed from the sodium-creatinine (Na/Cr) ratio (mg/mg) for a sample of urine collected when the patients presented themselves at the clinic for blood collections. All urine samples were collected between 9 a.m. and 9:30 a.m. to minimize fluctuations in the ratio. Reliability of this index of sodium excretion was evaluated by comparison of a spot collection to simultaneously obtained 24-hour timed specimens from 18 normal individuals on varying salt intakes (r = +0.62; P < 0.025). A similar correlation was evaluated for 37 patients, comparing spot urine collections with 24-hour collections, yielded an r = +0.56; P < 0.005. In this study spot collections obtained at 6:30 a.m. and at 10:30 a.m. yielded nearly identical correlation coefficients. The Na/Cr ratio also was compared to PRA in another group of 22 normal subjects on various sodium intakes and yielded a significant negative correlation coefficient (r = -0.42; P < 0.025). Thus this ratio provides a useful and reasonable guide to sodium intake although the correlation coefficients reveal significant variation between these two estimates of sodium intake.

RESULTS

STUDY POPULATION

A total of 232 patients were screened in the Hypertension Clinic and 131 were excluded from the study because of failure to meet the criteria outlined under Methods. Analysis of the age, race, and sex distribution of the entire hypertensive population screened showed that the patients excluded differed from the patients studied only in that they were somewhat older. The age, race, and sex of the 101 patients with uncomplicated, mild, untreated essential hypertension are shown in Figure 1. The mean age of the subjects was 31.9 (± 0.6) years. Black subjects comprised 76.4% of the
presents distribution according to race. Inset table contains distribution according to sex and the right half of each bar class intervals of diastolic blood pressure. The left half of each bar group. Males (51.5%) and females (48.5%) were equally divided overall.

Of the patients studied 35.6% had no previous knowledge of their hypertension and 43.8% had prior knowledge of their categories of recumbent diastolic blood pressure at the time of blood drawing is represented in Figure 1. The clustering of diastolic values of 100 and 110 mm Hg. The influence of this clustering tendency on analysis of the data was minimized by division of the range of diastolic blood pressure into four intervals: <95; 95-104; 105-114; and 115+ mm Hg.

Distribution of the hypertensive sample among the four blood pressure categories (Table 2) revealed additional information of interest. Inspection of the distribution of recorded blood pressures revealed a tendency toward digit preference with some clustering of diastolic values of 100 and 110 mm Hg. The influence of this clustering tendency on analysis of the data was minimized by division of the range of diastolic blood pressure into four intervals: <95; 95-104; 105-114; and 115+ mm Hg.

Distribution by race and sex of patients as a function of diastolic blood pressure. The left half of each bar presents distribution according to sex and the right half of each bar presents distribution according to race. Inset table contains distribution according to age.

The majority (84%) of our patients had mild hypertension, diastolic blood pressure <115 mm Hg. Sixteen patients with diastolic pressures in excess of 114 mm Hg exhibited diastolic blood pressures ranging from 115 to 140 mm Hg. These were excluded from the intergroup comparisons because of the much wider class interval which they represented. They were included in all analyses which used the entire hypertensive sample, i.e., in calculating mean values of PRA, angiotensin, and aldosterone for the total hypertensive sample.

Possible sampling artifacts were tested by performing chi-square analyses of the distribution of race, sex, and age among the blood pressure class intervals. No unexpected aggregations with respect to age, sex, or race were encountered within any of the class intervals, indicating that there were no obvious sampling errors or maldistributions to account for the observed differences between the blood pressure class intervals. All the blood pressure subgroups exhibit a distribution of these attributes no different from that in the overall sample.

RENIN, ARTERIAL AND VENOUS A II, AND ALDOSTERONE

Studies from our laboratory on normals have demonstrated that a sodium intake in excess of 200 mEq/day causes no further suppression of PRA, A II, or plasma aldosterone. The sodium intake of all normal subjects included in Table 1 was in excess of 200 mEq/day; these subjects thus display values for PRA, A II, and aldosterone that represent uniformly and maximally suppressed values for normotensive controls. Table 1 presents the mean values (± SE) for PRA, arterial and venous A II, plasma aldosterone, and urinary sodium: creatinine ratio for hypertensive patients. Table 1 presents the mean values (± SE) for PRA, arterial and venous A II, plasma aldosterone, and urinary sodium: creatinine ratio for hypertensive patients.

The Table 1 summary of mean values (± SE) for Plasma Renin Activity (PRA), Arterial and Venous Angiotensin II (A II), Plasma Aldosterone, and Urinary Sodium: Creatinine Ratio in Control Subjects and Hypertensive Patients

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Hypertensives</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (ng/ml per hour)</td>
<td>1.58 (±0.34)</td>
<td>0.83 (±0.13)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Arterial A II (pg/ml)</td>
<td>12.1 (±4.5)</td>
<td>5.2 (±1.0)</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Venous A II (pg/ml)</td>
<td>8.7 (±2.5)</td>
<td>4.2 (±0.65)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Aldosterone (ng/100 ml)</td>
<td>6.7 (±1.2)</td>
<td>5.0 (±0.45)</td>
<td>NS</td>
</tr>
<tr>
<td>Urine Na/Cr Ratio</td>
<td>0.265 (±0.031)</td>
<td>0.083 (±0.006)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>16</td>
<td>101</td>
<td></td>
</tr>
</tbody>
</table>

* P denotes probability based upon comparison of group means by unpaired t-test; NS = not significant.
The distribution of PRA within each of the hypertensive categories is shown in Figure 2 and Table 2. Mean values for PRA in each of the high blood pressure groups are significantly less than in the normotensive control group on a high sodium intake. Moreover, the mean value of PRA decreases with each successive class interval of increasing diastolic blood pressure. When these apparent trends are examined statistically, very strong evidence is obtained that the renin suppression cannot be attributed to differences in Na intake. In addition, the preponderance of blacks in the study population will tend to exhibit lower values and thus serve to depress the mean PRA value even further.

Although the group with diastolic blood pressures >114 mm Hg were excluded from all the statistical analyses because they represented a more heterogeneous group with a much wider range of blood pressure, it is of interest that the mean value of PRA in this group was 1.0 ± 0.4, representing a significant increase over the mean value of 0.28 exhibited by the group with diastolic blood pressure 105–114 mm Hg.

This latter mean value may appear somewhat low, but it should be emphasized that the experimental design and the population studied act in concert to yield such a low value. We have excluded individuals with higher blood pressures and vascular complications who tend to have abnormally high values for PRA, thus ensuring that the group studied will tend to exhibit lower values. In addition, the preponderance of blacks in the study population will tend to yield lower values and thus serve to depress the mean PRA value even further.

### ANGIOTENSIN II

The entire group of hypertensive subjects had significantly lower values for mean arterial and venous A II than the volume-expanded controls (Table 1), and considerable differences between blood pressure categories and their arterial angiotensin values were noted (Fig. 3 and Table 2). The venous values for the three categories were not different but arterial A II levels were increased in the higher blood pressure category. Analysis of variance revealed no difference between the venous A II in different groups but...
TABLE 3  Distribution of Plasma Renin Activity (PRA) Values among Hypertension Categories

<table>
<thead>
<tr>
<th>PRA (ng/ml per hour)</th>
<th>Recumbent diastolic blood pressure categories (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;95</td>
</tr>
<tr>
<td>≤0.1</td>
<td>6</td>
</tr>
<tr>
<td>&gt;0.1</td>
<td>17</td>
</tr>
</tbody>
</table>

Comparison of PRA values in the separate blood pressure class intervals. The frequency of low values for PRA increases as diastolic blood pressure increases; chi-square = 8.25; \( P < 0.02 \).

intergroup variance of arterial determinations was significantly greater (\( P < 0.05 \)) than the intragroup variance. Comparison of PRA and arterial A II as a function of systolic blood pressure (Fig. 4) reveals an inverse relationship between PRA and arterial angiotensin (\( P < 0.01 \)).

The data in Table 2 reveal a much greater difference between arterial and venous A II levels in the group with the highest diastolic blood pressure. Since this appeared inconsistent with the low renin values in this group, the individual arteriovenous differences for A II were compared with their corresponding renin values and a significant negative correlation was obtained (\( r = -0.29; P < 0.025 \), Fig. 5); at higher PRA values, venous A II exceeded arterial values more often than chance would predict. Chi-square analysis (Table 4) was also performed on these data to exclude the possibility that calculation of the correlation coefficient was unduly influenced by extreme values. This analysis showed that the likelihood of this aggregation of arteriovenous differences and PRA values occurring by chance was less than 2%.

PLASMA ALDOSTERONE

The plasma aldosterone values for the whole group showed a highly significant correlation (\( r = +0.40, P < 0.001 \)) with corresponding PRA, and a progressive fall in plasma aldosterone was observed (Table 2) as the diastolic blood pressure rose. It also is evident that a paradoxical inverse relationship appears to exist between aldosterone and A II, a finding in contrast to the highly significant positive correlation between aldosterone and A II in normal subjects.\(^7\)
The unexpected finding of an inverse relation between PRA and A II is in sharp contrast to the findings for normal subjects and may provide clues to the mechanism for the increased risk associated with an elevated renin in essential hypertension. Arterial A II was clearly increased in the group with diastolic pressure in the range of 105–114 mm Hg, despite the fact that this group exhibited the lowest mean value for PRA. Moreover, at the higher blood pressure levels, there was a large arteriovenous difference for A II, indicating both increased peripheral uptake or conversion as well as increased central or pulmonary production at markedly suppressed levels of PRA. The data in Figure 5 and Table 4 strongly suggest a change in A II metabolism as blood pressure increases. Despite the fact that arterial A II in the group of hypertensives with the highest blood pressure is lower than that observed in sodium-replete normal subjects, the arteriovenous difference in this group of hypertensives appears to be nearly twice as great (Tables 1 and 2).

If the ratio of A II to PRA is taken as an index of the in could be supported from the present study. The possibility of an inhibitor in plasma that produced artifactually low values for PRA also must be considered.

Volume expansion is suggested by the exaggerated natriuresis seen in hypertension after a sodium load and the remarkable hypotensive response induced by small doses of diuretics. Direct measurement of blood volume and extracellular fluid volume have, in general, failed to provide evidence for such expansion. Indeed, Dustan and colleagues report normal or reduced blood volume in essential hypertension with an inverse relation between blood volume and blood pressure, and between blood volume and systemic vascular resistance. Since most studies report normal extracellular fluid volumes in essential hypertension, this implies an altered relation between blood volume and interstitial fluid volume with the latter being relatively, but not absolutely increased. Thus, the untreated patient with essential hypertension exhibits a number of features of volume expansion, but direct evidence for such expansion is lacking. Possible consequences of this state are discussed below.

This study provides no support for the existence of excess aldosterone in mild essential hypertension. The inverse relationship between plasma aldosterone concentration and blood pressure indicates that aldosterone is suppressed in similar fashion to renin as blood pressure increases (Fig. 4). It is of interest that discordant behavior between A II and aldosterone appears at the higher blood pressure levels, identifying a possible pathological counterpart to the dissociation between the vascular effects of A II and the adrenal effects as demonstrated by Hollenberg.

The present data do not, however, exclude the possibility of an unidentified mineralocorticoid accounting both for possible sodium retention and progressive suppression of aldosterone and PRA. It would appear from Figure 4 that the second blood pressure class interval, 95–104 mm Hg, may be the most profitable blood pressure range in which to search for novel mineralocorticoid activity since this is the group exhibiting the greatest decrease in aldosterone levels.

<table>
<thead>
<tr>
<th>Table 4 Comparison of Plasma Renin Activity (PRA) and Angiotensin II (A II) Arteriovenous Difference</th>
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<tbody>
<tr>
<td>PRA (ng/ml per hour)</td>
</tr>
<tr>
<td>≤0.1</td>
</tr>
<tr>
<td>&gt;0.1</td>
</tr>
</tbody>
</table>

Distribution of values for arteriovenous A II difference compared with distribution of PRA values below 0.1 ng/ml/hour. The frequency with which arterial exceeds venous values in the low renin group is significantly greater than expected by chance; chi-square = 5.22; P < 0.02.

SODIUM EXCRETION

The level of sodium excretion did not correlate with diastolic pressure, PRA, circulating A II levels, or plasma aldosterone, and no significant difference in sodium excretion was observed between the different blood pressure groups. Sodium excretion for all hypertensives was below the range exhibited by the normal volume-expanded controls; this finding is of considerable interest in view of the fact that the hypertensive group exhibited values for PRA, A II and aldosterone well below the values for maximally suppressed normal subjects.

CLINICAL CORRELATIONS

Correlations between clinical data and determinations of PRA, A II, and aldosterone showed no difference in the values for PRA, A II, and plasma aldosterone between patients who had or did not have either a prior knowledge of hypertension, a remote history of intermittent therapy for hypertension, a remote history of intermittent therapy for hypertension, or a remote history of intermittent therapy for hypertension.

Discussion

These data establish an inverse relationship between PRA and diastolic blood pressure in patients with mild untreated essential hypertension (diastolic blood pressure < 115 mm Hg), at least in the present study. Chi-square analyses failed to disclose any unexpected aggregations by sex, race, or age within any of the blood pressure class intervals. Although the composite values shown in Tables 1 and 2 may reflect a maldistribution of blacks or Caucasians within a given group. In particular, the blood pressure class interval 105–114 mm Hg did not contain an unexpected excess of blacks, nor did the <95 mm Hg group have an excess of Caucasians. Thus, these data support the conclusion that PRA correlates inversely with diastolic blood pressure in untreated hypertensive subjects with diastolic blood pressures less than 115 mm Hg. This inverse relationship also holds for systolic blood pressure in the group studied. Possible explanations for this apparent suppression of PRA with increasing elevation of blood pressure include volume expansion, inappropriate mineralocorticoid excess, neurogenic suppression of renin release, increased renin catabolism or, perhaps, altered angiotensin metabolism. The possibility that the increase in blood pressure exerts a direct inhibitory effect on renin release also...
vivo vasoconstrictive potential of a given level of renin activity, the hypertensive group with the highest blood pressure in this study has a ratio that exceeds the ratio in sodium-loaded normal subjects by nearly 5-fold (9.9-0.28 = 35.4 for the hypertensives; 12.1/1.6 = 7.6 for the normals). This would appear inconsistent with the existence of a renin inhibitor in essential hypertension. It is, however, consistent with the data of Sambhi et al., demonstrating an accelerated rate of A II production by renin in the presence of plasma from hypertensive subjects. They postulate the presence of a renin activator in the plasma of hypertensive subjects to account for this phenomenon. Similar differences between plasma from normal subjects and hypertensive subjects were observed by Kotchen et al., although they endorsed the alternate explanation that an inhibitor of renin, present in normal plasma, decreased or disappeared in hypertension. Our data are perhaps more consistent with the interpretation of Sambhi and colleagues, since an inhibitor in normal plasma, which disappears in hypertensive subjects, should result in a progressive increase in apparent renin activity in essential hypertension.

It has been demonstrated that sodium-replete humans exhibit an enhanced blood pressure increase in response to exogenously administered A 11 and this response may be quantitatively greater in essential hypertension. The apparent increase in A II production at a given renin level demonstrated in the present study would suggest that hypertensive patients are extremely vulnerable to small increments in circulating renin.

The most significant findings of the study were a negative correlation or inverse relationship between diastolic pressure and both PRA and plasma aldosterone. In contrast, arterial A II was highest in the group with the highest diastolic blood pressure, despite the fact that this group had the lowest PRA. The distortion of the blood pressure data by evidence of digit preference in blood pressure recording and the preponderance of blacks in the present sample dictate caution in generalizing from the present study. Nevertheless, the inverse relationship between blood pressure and both PRA and aldosterone appear to indicate that progressive suppression of renin and aldosterone occur as blood pressure increases in untreated essential hypertension. The anamnestic increase in A II levels in the higher blood pressure range identifies a mechanism whereby even small increases in PRA may be particularly deleterious in hypertension.

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