Functional Correlates of Plasma Renin Activity in Hypertensive Patients

By Harriet P. Dustan, M.D., Robert C. Tarazi, M.D., and Edward D. Frohlich, M.D.

SUMMARY
Correlates of peripheral plasma renin activity were studied in 31 normotensive subjects and 93 untreated hypertensive patients. The latter were grouped according to apparent type of hypertension: essential (58), renovascular (21), renal parenchymal disease (11), and primary aldosteronism (3). Plasma renin activity was inversely correlated with total blood and plasma volumes in normal men, men with essential hypertension, and patients with renal arterial stenosis; no correlations were found in normal and essential hypertensive women and patients with renal parenchymal disease. Serum sodium and potassium concentrations were significantly and inversely related to renin activity only in renovascular hypertension and not in the other hypertensive or normal groups. Relationships of plasma renin activity to arterial pressure and other hemodynamic functions were studied in hypertensive patients. Only in the renovascular group did diastolic pressure correlate positively and significantly, indicating participation of the renal pressor system in this form of hypertension throughout a wide range of pressures. Cardiac index and left ventricular ejection rate were directly related to renin activity in essential hypertensive men and patients with renal arterial and parenchymal diseases. The data show that plasma renin activity in hypertensive patients should not be judged alone but along with factors modifying it.

Additional Indexing Words:
Essential hypertension Renovascular hypertension Renal parenchymal disease
Primary aldosteronism Hemodynamics of hypertension Renal pressor system
Blood volume in hypertension Serum sodium in hypertension

Among factors known to influence renin release or plasma renin activity, or both, in dogs or man are arterial pressure,1-3 hemorrhage,4-6 sympathetic vasomotor function,7-9 body posture,10,11 plasma sodium concentration,12,13 and body sodium balance.14,15 With the possible exception of plasma sodium concentration, these factors do not act alone but are interrelated through modifications of intravascular volume, hemodynamic functions, and sympathetic vasomotor tone. For example, upright posture,16 negative sodium balance in hypertensive patients,17 and severe hemorrhage,18 all of which elevate plasma renin activity, have in common decreased intravascular volume and cardiac output and increased sympathetic vasomotor tone. Another example of these possible interrelations relates to increased plasma renin activity found after administration of diazoxide and hydralazine.3,19 Although both drugs reduce arterial pressure, they also increase cardiac output20,21 but the relationships of changes in cardiac functions to increases in plasma renin activity have not been studied. Further, although the low plasma renin activity found in patients with primary aldosteronism has been related to an expanded blood volume,22 there has been no examination of the quantitative relations...
between intravascular volume and renin activity in primary aldosteronism or any other type of hypertension. Recently, we have found differences among various diagnostic groups of hypertensive patients in plasma volume and cardiac output, and the possibility arose that renal pressor, intravascular volume, and systemic hemodynamic factors, as well as being different, might be interrelated in different forms of hypertension. This report describes the functional correlates of plasma renin activity in normal subjects in regard to intravascular volume and serum sodium and potassium concentrations, and in hypertensive patients to these same indices, as well as to arterial pressure, cardiac output, left ventricular ejection rate, and estimates of sympathetic vaso-motor activity.

**Methods**

The subjects of this study were 31 normotensive laboratory personnel and 93 hypertensive patients who were either untreated or had not received any antihypertensive drugs for at least 1 month. The control group was comprised of 19 men and 12 women, and the hypertensive group of 54 men and 39 women. Two control subjects were Negro, as were six hypertensive men and three hypertensive women. Plasma renin activity and blood volume were measured in all, serum sodium and potassium concentrations in 15 control subjects and all the patients, and cardiac output, left ventricular ejection rate, and estimates of neurogenic activity in 56 patients. The control subjects were studied in the course of their daily activity; although the hypertensive patients were hospitalized, their activity was not further restricted. Daily dietary sodium intake was 100 mEq or greater. None of the normal women were taking contraceptive medication, but information concerning such treatment was not available in all the hypertensive women because some were studied before it was emphasized that these drugs can elevate plasma renin activity. 

In hypertensive patients causes for elevated arterial pressure were investigated as completely as locally feasible. Intravenous urography and renal arteriography were performed in all, whereas urinary excretion rates of aldosterone and catecholamines were measured only in those patients who were thought likely to have primary aldosteronism or pheochromocytoma, respectively. The results of these studies form the basis for an etiologic classification of hypertension (table 1). Fifty-eight patients were considered to have essential hypertension because no cause for elevated pressure could be found. In 21, hypertension was associated with renal arterial stenosis; these were classified as having renovascular hypertension although there is no way of making this diagnosis short of demonstrating the effect of hypertension after renal arterial reconstruction or nephrectomy. Eleven patients had renal parenchymal disease—glomerulonephritis, pyelonephritis, or polycystic disease—and three had primary aldosteronism. None of the patients had papilledema at the time of the study, although three of the essential hypertensive patients had had malignant hypertension many years previously that had remitted after adequate antihypertensive drug therapy. Four of the patients had retinal hemorrhages or exudates, or both—one man each with essential hypertension, renal arterial disease, and renal parenchymal disease, and one woman with renal arterial disease. Of the remaining patients, eight were considered to have normal retinal arterioles, while the rest had varying degrees of retinal arteriolar constriction and sclerosis. Although many patients had radiographic and electrocardiographic signs of hypertensive heart disease, none had any evidence of cardiac failure.

During hospitalization, brachial arterial pressure was measured in the supine position four times daily, and weekly averages of diastolic and mean pressure (diastolic pressure plus one-third pulse pressure) were used for correlation with

<table>
<thead>
<tr>
<th>Diagnostic groupings</th>
<th>Total no.</th>
<th>Men: Age range (years)</th>
<th>Women: Age range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>31</td>
<td>19 (26–49)</td>
<td>12 (21–50)</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>58</td>
<td>42 (16–68)</td>
<td>16 (25–63)</td>
</tr>
<tr>
<td>Renal arterial disease</td>
<td>21</td>
<td>5 (41–61)</td>
<td>16 (22–66)</td>
</tr>
<tr>
<td>Renal parenchymal disease</td>
<td>11</td>
<td>4 (17–58)</td>
<td>7 (17–55)</td>
</tr>
<tr>
<td>1° Aldosteronism</td>
<td>3</td>
<td>3 (37–42)</td>
<td></td>
</tr>
</tbody>
</table>

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other measurements. In the normal subjects, only one or two arterial pressure readings were taken.

**Plasma Renin Activity, Total Blood and Plasma Volumes, Serum Sodium and Potassium Concentrations**

All measurements were made in the morning, usually following an overnight fast, and after 30 to 45 minutes of supine rest. Plasma renin activity was estimated by the method of Pickens and associates26 with two modifications: (1) EDTA was used as the anticoagulant instead of heparin, which, in high concentrations, has been shown to interfere with generation of angiotensin,27 and (2) the supernatant obtained after stopping the reaction by boiling was evaporated to dryness under nitrogen in a water bath at 80°C instead of being evaporated in a rotary evaporator at reduced temperature and pressure. The amount of angiotensin (ng/ml) generated during a 4-hour incubation was used as the estimate of plasma renin activity.

Plasma and total blood volumes were measured from the diluent volume of 5 microcuries of 131I human serum albumin and the venous hematocrit, which was determined in duplicate by capillary microcentrifugation. Results were expressed in milliliters per centimeter height to minimize influences of weight.28 Details of the method as used in this study have been previously published.29 Serum sodium and potassium concentrations were determined by internal standard flame photometry from venous blood samples obtained without stasis.

**Hemodynamic Studies**

These were performed without premedication in the morning following an overnight fast and immediately after blood had been obtained for the above measurements. Cardiac output was measured by the indicator-dilution technic by means of indocyanine green and expressed as cardiac index (CI), liters per minute per square meter. Procedural details of the methods used have been previously reported.30 Intra-arterial pressure was recorded and the mean arterial pressure calculated from the sum of the diastolic pressure and one-third pulse pressure. Heart rate was counted from a continuously recorded electrocardiogram. Left ventricular ejection time was measured from rapidly recorded arterial pulses (100 mm per sec) and used to calculate mean rate of left ventricular ejection (MRLVE)—stroke index divided by ejection time and expressed in milliliters per second per square meter.

In addition to the above, arterial pressure and heart rate were measured on a supine patient and during 5 minutes of 50° head-up tilt and in response to the Valsalva maneuver. Changes in pressure and pulse rate during the tilt were taken as indices of sympathetic vasomotor activity, as was also the increase in diastolic pressure during the overshoot phase of the Valsalva maneuver.30 Statistical analyses were carried out by the standard t-test for comparing means and the F test for evaluating the significance of correlation coefficients.

**Results**

**Plasma Renin Activity** (Table 2)

In the normotensive men plasma renin activity averaged 1.08 ng/ml, with a range of 0.2 to 2.5 ng/ml; in the women the mean value was 0.8 ng/ml, with a narrower range of 0.1 to 1.1 ng/ml. The difference between the two groups was not significant.

In the essential hypertensive patients, mean value for plasma renin activity was less in men (1.0 ng/ml) than in women (1.5 ng/ml) but

<table>
<thead>
<tr>
<th>Diagnostic groupings</th>
<th>Sex</th>
<th>No.</th>
<th>Mean</th>
<th>SEM</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Men</td>
<td>19</td>
<td>1.08</td>
<td>±0.15</td>
<td>0.2–2.5</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>12</td>
<td>0.8</td>
<td>±0.10</td>
<td>0.1–1.1</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>Men</td>
<td>42</td>
<td>1.0</td>
<td>±0.14</td>
<td>0.1–3.9</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>16</td>
<td>1.5</td>
<td>±0.32</td>
<td>0.2–4.5</td>
</tr>
<tr>
<td>Renal arterial disease</td>
<td>Men</td>
<td>5</td>
<td>0.5</td>
<td>±0.49</td>
<td>0.4–2.1</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>16</td>
<td>0.5</td>
<td>±0.21</td>
<td>0.5–2.1</td>
</tr>
<tr>
<td>Renal parenchymal disease</td>
<td>Men</td>
<td>4</td>
<td>1.2</td>
<td>±0.32</td>
<td>1.2–3.2</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>7</td>
<td>0.7</td>
<td>±0.22</td>
<td>0.7–2.2</td>
</tr>
<tr>
<td>1° Aldosteronism</td>
<td>Men</td>
<td>3</td>
<td>0.3</td>
<td>±0.07</td>
<td>0.3–0.7</td>
</tr>
</tbody>
</table>

*Circulation, Volume XLI, March 1970*
Table 3

Group Averages for Total Blood Volume, Serum Sodium and Potassium Concentrations, Mean Arterial Pressure, Cardiac Index, and Left Ventricular Ejection Rate

<table>
<thead>
<tr>
<th>Diagnostic groupings</th>
<th>Sex</th>
<th>TBV</th>
<th>Serum Na+ and K+</th>
<th>Hosp. MAP</th>
<th>CI and MLVER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>ml/cm</td>
<td>No.</td>
<td>Na+(mEq/L)</td>
<td>K+(mEq/l)</td>
</tr>
<tr>
<td>Normal</td>
<td>Men</td>
<td>19</td>
<td>29.1 ± 0.537*</td>
<td>17</td>
<td>140 ± 0.899</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>12</td>
<td>24.5 ± 0.603</td>
<td>7</td>
<td>141 ± 0.801</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>Men</td>
<td>42</td>
<td>30.7 ± 0.809</td>
<td>41</td>
<td>141 ± 0.511</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>16</td>
<td>23.4 ± 0.824</td>
<td>16</td>
<td>139 ± 0.713</td>
</tr>
<tr>
<td>Renal arterial disease</td>
<td>Men</td>
<td>5</td>
<td>31.0</td>
<td>5</td>
<td>141 ± 0.548</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>16</td>
<td>20.8 ± 0.864</td>
<td>16</td>
<td>140 ± 0.793</td>
</tr>
<tr>
<td>Renal parenchymal disease</td>
<td>Men</td>
<td>4</td>
<td>29.4</td>
<td>4</td>
<td>135 ± 4.19</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>7</td>
<td>22.8 ± 0.608</td>
<td>7</td>
<td>141 ± 1.36</td>
</tr>
<tr>
<td>1° Aldosteronism</td>
<td>Men</td>
<td>3</td>
<td>37.6</td>
<td>3</td>
<td>145 ± 2.9</td>
</tr>
</tbody>
</table>

* Standard error of the mean; values not presented for groups with less than seven patients.
Abbreviations: TBV = total blood volume; Hosp. MAP = a week's average of hospital mean arterial pressure; CI = cardiac index; MLVER = mean rate of left ventricular ejection.

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The difference was not statistically significant. In the patients with renal arterial disease, the plasma renin activity ranged widely from normal to markedly elevated levels. With such a range, the group averages seem no value because they obscure the heterogeneity of the data. Thus, the variation in plasma renin activity was wider than normal range of renin activity. In the patients with renal arterial disease, the plasma renin activity was also found in patients with renal parenchymal disease, but for the most part the values were normal. Of the four men, in whom the plasma renin was elevated, one had uremia, the other three men, and hypertension, elevated plasma renin was observed in association with renal hemor- rhages and exudates. In all of the 16 women, plasma renin ranged widely, and the highest value (21 ng/ml) was in the patient with the highest value (21 ng/ml). The patients with primary aldosteronism, values were low, as has been previously reported.

<table>
<thead>
<tr>
<th>Diagnostic groupings</th>
<th>Number</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>19</td>
<td>0.100</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>12</td>
<td>0.02</td>
</tr>
<tr>
<td>Renal arterial disease</td>
<td>5</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

For calculation of correlation coefficients (r), the logarithm of plasma renin activity was used instead of the absolute value since the relationship was exponential.
Table 5

Statistical Evaluation of the Relationship of Plasma Renin Activity to Mean and Diastolic Arterial Pressures

<table>
<thead>
<tr>
<th>Diagnostic groups</th>
<th>Number</th>
<th>Mean r</th>
<th>Mean P value</th>
<th>Diastolic r</th>
<th>Diastolic P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>42</td>
<td>-0.151</td>
<td>n.s.</td>
<td>-0.168</td>
<td>n.s.</td>
</tr>
<tr>
<td>Women</td>
<td>16</td>
<td>-0.002</td>
<td>n.s.</td>
<td>-0.170</td>
<td>n.s.</td>
</tr>
<tr>
<td>Renal arterial disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men and Women</td>
<td>21</td>
<td>+0.446</td>
<td>&lt;0.05</td>
<td>+0.515</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Renal parenchymal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men and Women</td>
<td>11</td>
<td>+0.070</td>
<td>n.s.</td>
<td>+0.073</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

* Average of four supine daily pressures for one week in hospital.

total blood volume ($P < 0.001$) and with plasma volume ($P < 0.01$). An inverse correlation was also found in normal men ($P < 0.05$) as well as in men and women with renal arterial stenosis ($P < 0.02$) (fig. 1). However, no relationship between intravascular volumes and plasma renin was found in either normal or essential hypertensive women or in patients with renal parenchymal disease.

**Arterial pressure** (tables 3, 5, and 6). The relation of plasma renin activity to brachial arterial pressure was studied only in the hypertensive patients because multiple pressure readings taken over several days were available, whereas in the normal subjects one, or at the most two, measurements had been obtained.

In patients with renal arterial disease, both mean and diastolic arterial pressures were positively and significantly correlated with plasma renin activity ($P < 0.05$ for both pressures) (fig. 2). In those with essential hypertension and renal parenchymal disease, there was no association of renin activity with either pressure (table 5).

The question arose whether this association merely reflected the fact that the patients with renal arterial disease had more severe vascular disease than did the other hypertensive subjects. To answer this, we paired patients with essential and renal hypertension by sex and height of diastolic pressure and were able to study 15 pairs (table 6). Values for serum sodium and potassium were similar in the two groups, and mean plasma renin activity was only slightly higher for the one with renovascular hypertension. In spite of these similarities, the two groups differed sharply in the relationship of plasma renin activity to diastolic blood pressure in that there was a positive correlation ($P < 0.01$) between these two variables among the patients with renal arterial disease and no relationship among those with essential hypertension.

Table 6

Relationship of Plasma Renin Activity to Diastolic Arterial Pressure in 15 Pairs of Renovascular and Essential Hypertensive Patients Matched for Sex and Diastolic Pressure Level

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>Renovascular</th>
<th>Essential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Men: women</td>
<td>5:10</td>
<td>5:10</td>
</tr>
<tr>
<td>DBP</td>
<td>108</td>
<td>107</td>
</tr>
<tr>
<td>MAP</td>
<td>131</td>
<td>127</td>
</tr>
<tr>
<td>K +</td>
<td>4.12</td>
<td>4.03</td>
</tr>
<tr>
<td>Na +</td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td>PRA</td>
<td>1.92</td>
<td>1.48</td>
</tr>
</tbody>
</table>

Correlation of PRA with DBP:

- $r = +0.671$  
- $F = 10.64$  
- $P < 0.01$  
- $P = 0.85$  
- $P = n.s.$

Abbreviations: DBP = diastolic arterial pressure, mm Hg; MAP = mean arterial pressure, mm Hg; K + and Na + = serum potassium and sodium concentrations, mEq/L; PRA = plasma renin activity, ng/ml.
Cardiac index and left ventricular ejection rate (tables 3 and 7). These were positively correlated with plasma renin activity at a high level of significance ($P < 0.001$) in the 28 essential hypertensive men in whom hemodynamic measurements were made. In contrast, no association was found between these hemodynamic functions and renin activity in the 10 women with essential hypertension.

These correlations could be studied in nine patients with renal arterial disease; no relationship of renin activity with cardiac index was found, but a correlation coefficient of $+0.568$ for plasma renin with left ventricular ejection rate suggested a positive relationship (fig. 3) even though the observations were too few to allow judgment of statistical significance. In six patients with renal parenchymal disease, both cardiac index and ejection rate seemed associated with plasma renin activity (figs. 3 and 4).

Responses to tilt and the Valsalva maneuver. In men with essential hypertension, there was no association of arterial pressure changes during tilt with renin activity, but a positive correlation ($P < 0.05$) was found between plasma renin activity just before tilt and increase of heart rate during tilt (table 7). Numbers of observations in essential hypertensive women and patients with renal arterial stenosis and parenchymal disease were too small to permit any meaningful analysis.

Heart rate in the supine position is also influenced by cardiac nervous activity, but neither in essential hypertensive men and women nor in patients with renovascular

<table>
<thead>
<tr>
<th>Table 7</th>
</tr>
</thead>
</table>

| Statistical Evaluation of the Relationship of Plasma Renin Activity to Cardiac Index, Left Ventricular Ejection Rate, Supine Heart Rate, and Increase in Heart Rate with Head-up Tilt |

<table>
<thead>
<tr>
<th>Essential hypertension</th>
<th>28 men</th>
<th>10 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>$P$ value</td>
<td>r</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>+0.642</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Ventricular ejection rate</td>
<td>+0.593</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Supine heart rate</td>
<td>+0.262</td>
<td>n.s.</td>
</tr>
<tr>
<td>Heart rate increase with tilt</td>
<td>+0.383</td>
<td>$&lt; 0.05$</td>
</tr>
</tbody>
</table>

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hypertension could supine heart rate be correlated with renin activity. If, however, the essential hypertensive men were divided into two groups depending on whether heart rate was greater or less than 70 beats per minute, plasma renin activity was found to be significantly higher in patients with faster heart rates than in those with slower rates (1.21 ± 0.20 and 0.65 ± 0.14 ng/ml, respectively, *P* < 0.05).

Rise in diastolic pressure in response to the Valsalva maneuver is a function of neurogenic activity. This was studied in relation to plasma renin activity in the essential hypertensive patients, but no association was found.

**Serum sodium and potassium concentrations** (tables 3 and 8). No correlation of plasma renin activity with serum sodium or potassium concentrations was found in normal subjects or patients with essential hypertension. Study of these relationships in patients with renal parenchymal disease points up a difficulty inherent in analyses involving small groups. When data for the entire group of 11 were analyzed, both sodium and potassium correlated inversely with plasma renin (*P* < 0.01); however, when values of the one severely uremic man were deleted, the correlation coefficients (*r* = −0.514 for sodium and −0.312 for potassium) failed to indicate a significant relation (table 8). In contrast, the patients with renal arterial stenosis showed a highly significant negative correlation of renin activity with both sodium (*P* < 0.01) and potassium (*P* < 0.01) concentrations.

**Discussion**

Only two methods for determining plasma renin attempt to measure enzyme concentration by the use of column separation and incubating with excess substrate. Another two also provide a measurement of concentration but do not separate the enzyme from inhibitors or activators. The remaining methods give only a quantitative estimate of enzyme activity; there is a number in common use and a variety of ways to express activity. This usually makes impossible a precise comparison of values obtained by different laboratories but does not vitiate a study of factors affecting plasma renin activity because, with all methods, similar changes in activity have been reported under conditions such as variations in dietary sodium intake, supine versus upright posture, and blood pressure reduction.

In all studies of plasma renin activity in hypertension, one outstanding feature has been the wide range of values found within the various types. Even in renal arterial stenosis, where the renal pressor system seems a likely determinant of elevated arterial pressure, both plasma renin concentration and activity have been normal in some patients. These findings, coupled with the fact that values much higher than those occurring in hypertension have been found in certain

<table>
<thead>
<tr>
<th>Diagnostic grouping</th>
<th>Number</th>
<th>Sodium</th>
<th>Potassium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><em>r</em></td>
<td><em>P</em> value</td>
</tr>
<tr>
<td>Normal</td>
<td>15</td>
<td>−0.431</td>
<td>n.s.</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>58</td>
<td>−0.116</td>
<td>n.s.</td>
</tr>
<tr>
<td>Renal arterial disease</td>
<td>21</td>
<td>−0.600</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Renal parenchymal disease</td>
<td>10*</td>
<td>−0.514</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

* With multivariate analysis, one patient's values fell outside the 95% ellipse and were therefore removed for calculation of correlation coefficients (*r*).
nonhypertensive conditions—such as hepatic cirrhosis and adrenal insufficiency—have raised questions as to the role of the renal pressor system in hypertension. However, it has been amply demonstrated that many stimuli affect renin release, suggesting that a value for renin activity should not be judged alone but along with factors that may modify it. The present study indicates this to be the case.

Although values for plasma renin activity seem to have little relevance by themselves, it should be pointed out that our normal range from 0.1 to 2.5 ng/ml is considerably narrower than our previously reported 0 to 5.5 ng/ml. This probably reflects the supine rest that was a condition of the study. These results can be compared with those of del Greco and associates because the same method and presampling rest period were used. (Dividing their values by 10 expresses plasma renin activity as in this study—ng/ml/4 hr incubation.) Their normal values ranged from 0.5 to 3.4 ng/ml, and only three were above 2.5 ng/ml, the upper limit found in our study. The results in patients with renal arterial and parenchymal diseases were similar to ours, with values ranging widely. In their 33 essential hypertensive subjects, only three values were above normal, whereas in our study increased levels were found in four of 42 men and nine of 16 women.

Plasma renin activity in women with essential hypertension tended to be higher than in men. There is a possibility that some women were taking contraceptive drugs, which could have been responsible for the higher values. Renin substrate levels would have helped in assessing this possibility because estrogen administration can increase renin substrate, which, in turn, increases measured activity. Brown and associates have reported that plasma renin rises during the last half of the menstrual cycle, and such a hormonal influence might explain the sex difference found. If this had been so, normal women should have had higher values than normal men, but such was not the case. Finally, mention should be made of the possible contribution of uterine renin to activity measured in plasma. Although no information concerning this is available in women with kidneys, renin-like activity has been described by Capelli and associates in four anephric patients treated by hemodialysis.

One of the early observations in animals was the renin-releasing effect of hemorrhage. That this was not dependent on arterial pressure reduction was shown by Bunag and associates, who demonstrated that slow bleeding without hypotension evoked a sharp increase in release as long as renal innervation was intact. More recently, Skillman and associates have reported increased plasma renin activity in normal men following hemorrhage of 15% of total blood volume that did not, however, reduce arterial pressure significantly. These results suggest that intravascular volume is a determinant of plasma renin in man as well as animals. Body sodium balance is also an influence, with a negative balance increasing and a positive balance decreasing plasma renin activity. Although it seems likely that these changes reflect alterations in intravascular volume, Romero and associates, in reporting the effects of a 5 mEq sodium diet in normal men, attributed increased plasma renin activity to decreased renal blood flow. However, Newsome and Bartter have shown that variations in plasma renin during manipulations of sodium and water intake are related to changes in some body fluid compartment, probably the intravascular. Meyer and associates have demonstrated that the increases producible by a diuretic can be prevented by giving enough polyvinylpyrrolidone or Dextran to prevent plasma volume reduction; and both Meyer and associates and Pickens and Enoch have reported that acute plasma volume expansion decreases renin activity. It now seems clear that changes in intravascular volume occurring over hours or days can modify plasma renin, but there has been no previous demonstration that the intravascular volume plays a role under ordinary circumstances.
PLASMA RENIN ACTIVITY

Our results indicate that in both normal and essential hypertensive men there was an inverse association between blood volume and renin activity. Further, a similar relation seemed to exist in most of the patients with renal arterial disease. In contrast, these two variables were not significantly correlated in patients with renal parenchymal disease. The present study does not eliminate the possibility that the extracellular fluid volume per se is a determinant of plasma renin activity. However, we have recently shown in a group of essential hypertensive subjects that plasma renin correlated inversely with plasma volume but not with interstitial fluid volume.49

Reasons for lack of association between blood volume and renin in normal and essential hypertensive women are not apparent. It may be, as indicated above, that plasma renin activity in women is influenced by cyclic variations in estrogen and progestosterone secretion as well as uterine renin—both influences being unaffected by the intravascular volume. If this is the case, women should differ from men in plasma renin responses to dietary sodium restriction and administration of diuretic drugs, but such differences have not emerged.

The possibility that contraceptive drugs destroyed the blood volume-renin relation in women with essential hypertension does not appear likely because, although we do not have information concerning such treatment in all patients, none of the normal women were taking contraceptives and they showed no evidence of an association. Further, if the women with renal arterial disease were taking these drugs, they did not abolish the effect of blood volume.

The renal pressor system seemed to participate only in the hypertension of patients with renal arterial disease because of the positive correlation between diastolic arterial pressure and plasma renin activity (fig. 2). The significance of this association was emphasized by analyzing the two variables in 15 pairs of patients with renovascular and essential hypertension matched for sex and diastolic arterial pressure, and it was found that the correlation coefficients (r) were not statistically significant because of the small numbers of observations, this representation suggests a significant association.

Figure 2
Regression lines and formulas for the relationship of plasma renin activity (PRA) to diastolic arterial pressure in patients with renal arterial stenosis. Line A indicates the relationship for all 21 patients of the group; line B for 19 patients, excluding the two with the highest values for renin activity.

Figure 3
The relationship of plasma renin activity (PRA) to mean rate of left ventricular ejection (MRLVE) in nine patients with renal arterial stenosis and six with renal parenchymal disease. Although the correlation coefficients (r) were not statistically significant because of the small numbers of observations, this representation suggests a significant association.
arterial pressure. A positive correlation ($P < 0.01$) was found only in the renal hypertensive persons, indicating a causal relation between plasma renin and arterial pressure. The fact that this association has not been shown previously may reflect a failure to consider the wide range of diastolic pressure found in groups of patients with renal arterial stenosis.$^{50}$

The correlations of cardiac index and left ventricular ejection rate with plasma renin activity were highly significant in men with essential hypertension. In patients with renal parenchymal disease, similar correlations were suggested, but in those with renal arterial stenosis only a relationship with left ventricular ejection rate was indicated (fig. 3). This latter finding seems related to the fact that cardiac index in such patients tends to be elevated$^{51}$ and that in those included in this study, the range of values was too narrow to demonstrate an association. However, when the data are plotted with those of the essential hypertensive men and patients with renal parenchymal disease (fig. 4), the association seems clear.

Reasons for correlations of plasma renin activity with these hemodynamic functions were not revealed by this study. One explanation would be a direct relation between cardiac output and renal blood flow, but evidence for this is not available. It seems more likely that these hemodynamic-renin associations are not causal but reflect a common influence. Venous return and shift of blood to the central circulation determine cardiac output and are controlled by sympathetic vasomotor activity,$^{52}$ which also affects left ventricular ejection rate.$^{53}$ Thus, it could be that the correlations of plasma renin activity with cardiac index and ejection rate are indications of neurogenic control of cardiovascular functions and renin release. In accord with this possibility is our finding that essential hypertensive men with heart rates greater than 70 beats per minute had significantly higher plasma renin activity than did those with slower heart rates.

Both diazoxide and hydralazine administration have been shown to elevate plasma renin activity.$^{5, 19}$ Both elevate cardiac output$^{20, 21}$ and stimulate beta-adrenergic receptors.$^{54-56}$ In the case of diazoxide, elevation of cardiac output is, in part at least, a reflex response to arterial pressure reduction.$^{55}$ Thus, it seems likely that increased plasma renin activity might relate either to a direct or indirect neural stimulation. Reflex stimulation through arterial pressure reduction may also account for the renin-releasing effect of sodium nitroprusside-induced hypotension.$^{57}$

Augmentation of sympathetic vasomotor outflow permits hemodynamic adjustments in the upright position and is considered one explanation for increased plasma renin that
normally occurs with standing. As an estimate of neurogenic activity, we took the heart rate increase during 50° head-up tilt and found that this correlated positively with supine plasma renin activity in the 28 essential hypertensive men studied (P < 0.05). This finding suggests that the amount of neurogenic activity mobilized during upright tilt was a function of supine sympathetic vasmotor tone. In this regard, we have previously shown that patients with orthostatic hypertension, when supine, also had exaggerated increases in diastolic arterial pressure during the Valsalva overshoot and exaggerated depressor responses to transient ganglion blockade. Failure to correlate supine plasma renin activity with arterial pressure changes during tilt and the Valsalva maneuver suggests that these responses are not such sensitive indices of neurogenic influences as is a change in heart rate.

The foregoing discussion indicates an important role for sympathetic vasmotor activity in determining plasma renin. Yet the finding of normal plasma renin responses to dietary sodium restriction and upright posture in patients following kidney transplantation has suggested that the renal nerve supply is unimportant. However, until there is a way to test for intact renal innervation other than demonstrating increases in plasma renin activity, its role cannot be examined critically.

Brown and associates have emphasized the inverse relation of serum sodium with renin concentration and Nash and associates have shown in dogs that reducing the sodium concentration of blood perfusing a kidney will augment renin release that can, in turn, be abolished by using a hypernatremic perfusate. However, the relation of serum sodium to plasma renin activity in clinical situations seems not so straightforward. Thus, although del Greco and associates found a negative correlation between these two variables in hypertensive patients, plasma renin activity was better correlated with severity of vascular disease than with plasma sodium concentration. Further, Newsome and Bartter showed that overhydrating normal subjects reduced plasma renin activity even though plasma sodium was lowered to levels often found in patients with severe vascular disease; also, Brown and associates have reported normal plasma renin concentrations in a patient with gross hyponatremia associated with inappropriate ADH secretion.

Among the hypertensive patients in this study, an inverse relation between serum sodium and renin activity was found only in those with renal arterial disease who also, as a group, had lower serum potassium concentrations than the others, suggesting presence of secondary aldosteronism, a condition recognized as being associated with some diminution of serum sodium.

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