SUMMARY Abnormalities of renin release and of venous distensibility have been described in essential hypertension. We have postulated that decreased venous distensibility could contribute to the blunted renin response to upright posture in hypertension. Stiffer veins might prevent venous pooling in the lower extremities, which in turn might affect the stretch on cardiopulmonary mechanoreceptors, thereby influencing the reflex release of renin. We investigated this hypothesis in the present study of 47 patients with mild hypertension and 26 (male) healthy volunteers of similar age and race. To induce isolated changes in the stretch of cardiopulmonary mechanoreceptors, systemic hemodynamics were measured before and after thigh cuff inflation at 60 mm Hg for 30 minutes. Cardiac output was determined by dye dilution. Before the intervention, variable thigh cuff pressures were used to measure venous pressure volume with mercury-in-Silastic strain gauge plethysmography. Venous distensibility was diminished in hypertension, as evidenced by a shift in the calf venous volume/pressure curve toward the pressure axis. During the 30-minute experiment, the hypertensive subjects had less blood pooling in their legs in response to thigh cuff inflation, as compared with the control subjects. The hemodynamic and renin responses reflected this diminished effect of thigh cuff inflation on venous return. The smaller increase of renin in the hypertensive group was associated with a smaller fall in the stroke index and right atrial pressure; the reflex rise in the heart rate was also decreased. By pooling blood in the lower extremities, thigh cuff inflation simulates upright posture. It is customary to classify the renin status of hypertensive patients according to the renin response to upright posture. Our study suggests that abnormal venous distensibility, through its effect on cardiopulmonary receptors, may be partly responsible for the low renin values frequently observed in hypertension. (Hypertension 8 [Suppl II]: II-36-II-43, 1986)

KEY WORDS • renin • venous distensibility • essential hypertension • hemodynamics • cardiopulmonary mechanoreceptors

Most investigations \(^1\) have demonstrated that venous distensibility is reduced in borderline and established hypertension, although some studies,\(^5,6\) using small numbers of subjects, have been inconclusive. The functional importance of less compliant veins in hypertension remains uncertain. Ulrych et al.\(^7\) postulated that the exaggerated natriuresis observed in hypertensive subjects during an intravenous volume load was due to reduced peripheral vascular compliance. Several investigators\(^8-11\) have demonstrated redistribution of blood from the peripheral to the central compartment in renovascular and borderline hypertension, which they assumed to be secondary to decreased peripheral vascular capacitance. This redistribution was found to occur in a group of low-renin hypertensive subjects.\(^11\) Since cardiopulmonary mechanoreceptors play an important part in the control of renin release,\(^12,13\) it was postulated that in hypertensive persons, renin responses to physiological maneuvers that unload cardiopulmonary mechanoreceptors might be influenced by abnormal venous distensibility. In none of the above studies were the hemodynamic and hormonal correlates of abnormal venous compliance directly assessed. The only study attempting such a correlation\(^3\) failed to find an association among abnormal forearm venous distensibility, resting hemodynamics measured noninvasively, and the renin profile in hypertensive subjects. The present study was designed to investigate the effect of venous distensibility on hemodynamic and hormonal responses to inflation of cuffs around the thighs, a maneuver that selectively unloads the cardiopulmonary mechanoreceptors.\(^12\)
Methods

Subjects
Study participants included 47 patients who had borderline or mild hypertension, without known secondary causes of high blood pressure or overt cardiovascular disease, and 26 healthy paid volunteers, all between the ages of 18 and 50 years. Borderline hypertension was defined as at least one recorded blood pressure measurement above 140/90 mm Hg in the preceding year. According to the traditional nomogram of upright renin versus urinary sodium values, 10 patients had low-renin hypertension. Hypertensive subjects were recruited from the Hypertension Clinic at the University of Michigan and by public advertisement.

The normotensive subjects were recruited in a similar manner and selected so that the mean age of the normal group was similar to that of the hypertensive group. They had a normal physical examination, no family history of hypertension, and no abnormality on screening laboratory tests.

Demographic and clinical data for each group are summarized in Table 1. Before enrollment in the study, 29 hypertensive patients had been treated with antihypertensive medications, but all drugs were withdrawn at least 4 weeks before the study. Thirty-two patients had a positive family history of hypertension in first-degree relatives.

All participants read, understood, and signed an informed consent form approved by the institutional review committee for the use of human subjects for experimental purposes.

Study Protocol
At the time of enrollment, all study subjects were instructed in the self-determination of blood pressure with an aneroid sphygmomanometer. Blood pressure was recorded twice daily for a week, then all readings were averaged to obtain a mean home blood pressure value. For 4 days before the hemodynamic study, subjects were placed on a diet containing 20 mEq of sodium, which was supplemented with salt tablets, for a total of 100 mEq of sodium per day. The 24-hour urinary sodium excretion on the last day of the diet was 104 ± 12 mEq (mean ± SEM) for the normal group and 92 ± 8 mEq for the hypertensive group.

All laboratory investigations commenced at 0800 and were completed by 1300. Laboratory temperature was maintained in the range of 21 to 24°C. Upon arrival, the subjects' height and weight were determined, and supine blood pressure (clinic blood pressure) was measured after 3 minutes of rest. A 21-gauge butterfly needle was inserted into the brachial vein, then the subject assumed the upright position for 15 minutes. At the end of this period, blood samples were drawn for the determination of plasma renin activity, blood screening, and biochemistry values. After removal of the butterfly needle, the left arm was prepared for cannulation. A polyethylene catheter with an internal diameter of 0.58 mm (Clay Adams, Division of Becton, Dickinson and Company, Parsippany, NJ, USA) was inserted into the basilic vein, advanced to the right ventricle, and withdrawn to the right atrium. An 18-gauge, 5-cm Teflon catheter (Angiocath, Deseret, Sandy, UT, USA) was introduced percutaneously into the brachial artery. Hewlett-Packard quartz pressure transducers (Model 1290A) for the recording of right atrial and brachial artery pressures were placed at the midaxillary level in the fourth intercostal space. Readings were recorded on a Hewlett-Packard 4578 polygraph (Hewlett-Packard, Palo Alto, CA, USA). Cardiac output was measured by dye dilution (Cadiogreen, Hynson, Westcott and Dunning, Baltimore, MD, USA) with an Electronics for Medicine densitometer (Honeywell, Van Nuys, CA, USA). Details of hemodynamic measurements performed in our laboratory have been documented elsewhere. 14

Once the catheters were in position, plasma volume was determined by the Evans’ blue dilution technique, as previously described. 14 Total blood volume (TBV) was calculated from the arterial hematocrit (Hct) and the plasma volume (PV): TBV = PV/(1.0 - 0.96 x Hct). Venous distensibility in the left calf was determined with the subject in the supine position by calculating venous volume changes, using a mercury-in-Silastic strain gauge plethysmograph (Hokanson EC-4, Issaquah, WA, USA). A congesting cuff (1 x 85 cm) was placed around the thigh while the calf was elevated above the level of the body with foam wedges. Calf circumference was measured and then an appropriately sized gauge was positioned at the point of maximum circumference. The congesting cuff was inflated to 50 mm Hg (Hokanson rapid cuff inflator) while the increase in calf volume was recorded continuously and expressed as milliliters per 100 g of tissue, according to standard plethysmographic procedures. Once a plateau had been achieved, at 3 minutes, the congesting pressure was deflated by

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Table 1. Demographic and Clinical Data in Normotensive and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>26</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.2 ± 1.8</td>
<td>36.9 ± 1.2</td>
<td>NS</td>
</tr>
<tr>
<td>Race (white/black)</td>
<td>23:3</td>
<td>40:7</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>177.7 ± 1.0</td>
<td>179.4 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.8 ± 1.8</td>
<td>92.1 ± 2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body surface area (m^2)</td>
<td>1.94 ± 0.02</td>
<td>2.11 ± 0.02</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home blood pressure:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>116.6 ± 1.3</td>
<td>136.3 ± 1.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>73.5 ± 1.5</td>
<td>87.9 ± 1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clinic blood pressure:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mm Hg)</td>
<td>124.5 ± 1.6</td>
<td>146.0 ± 2.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>69.8 ± 1.2</td>
<td>88.2 ± 1.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Family history (+/-/?/?)</td>
<td>0/26</td>
<td>32/14/1*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SEM. NS = not significant.
*This subject was adopted.
10 mm Hg for 2 to 3 seconds, to facilitate emptying of the veins, and was then reinflated by 5 mm Hg with sufficient time allowed to establish a new plateau (usually <20 seconds). This sequence was repeated to the lowest congesting pressure of 10 mm Hg. Duplicate volume/pressure curves were recorded, and the results averaged. The minimum occlusion pressure was determined by extrapolating the mean volume/pressure curve for each subject through zero volume change, as described by Walsh et al. The venous volume at a congesting pressure 30 mm Hg above the minimum occlusion pressure was derived from the volume/pressure curve for each subject. Adequate tracings were recorded in 43 hypertensive patients and 23 normal controls. Tracings were rejected if there was a movement artifact during the recording period or if the venous volume/pressure curve could not be extrapolated to determine the minimum occlusion pressure.

Sixty minutes after the catheterization had been completed, hemodynamic and hormonal measurements were obtained while the subjects were in the supine position. Plasma renin activity was measured by radioimmunoassay of angiotensin I generated after a 60-minute incubation period at a pH of 6.0. Plasma catecholamines were determined by the radioenzymatic method. Once baseline measurements had been performed, cuffs around both thighs were inflated to 60 mm Hg for 30 minutes, the hemodynamic and hormonal measurements were repeated, and the cuffs deflated. During cuff inflation and deflation, changes in calf volume were determined by strain gauge plethysmography, as described above. After inflation of the cuff, there is a period of rapid filling, which usually lasts less than 2 minutes. To minimize possible differences in capillary filtration, the change in calf volume was measured 4 minutes after cuff inflation and 30 seconds after cuff deflation, and the two values were then averaged.

Statistics

Demographic, hemodynamic, and hormonal data for the normal and hypertensive groups were compared by one-way analysis of variance. Profile analysis and repeated measures analysis of variance were used to compare the venous volume/pressure curves. When a significant time-diagnosis interaction occurred, further comparisons were performed with t tests, using the appropriate mean square error terms from the analysis of variance. Regression analysis was performed by the least-squares method. Data were analyzed on the computer system of the University of Michigan (MTS), using the MIDAS and BMDP statistical packages. A p value of less than 0.05 was considered to be significant.

Results

Baseline Hormonal, Hemodynamic, and Biochemical Data

Baseline renin and hemodynamic data are shown in Table 2. With the subjects in the supine position, plasma renin activity was similar in both groups. In the standing position, however, plasma renin activity was significantly lower in the hypertensive group (p<0.05). The hypertensive subjects had a higher mean arterial pressure (p<0.0001), and although their right atrial pressure and cardiac index were similar to the values in the control group, their heart rate was higher (p<0.005) and their stroke index lower (p<0.05), as compared with the normotensive controls. The central blood volume index was also lower (p<0.05) in the hypertensive subjects, but covariate analysis demonstrated that this was due to differences in body size, with no independent effect of hypertension. The plasma volume index and total blood volume index did not differ significantly between the two groups. Not shown in Table 2 are plasma norepinephrine and epinephrine levels, which also did not differ significantly between the two groups (norepinephrine, 231 ± 11 pg/ml in the hypertensive group vs 220 ± 11 in the normotensive group; epinephrine, 93 ± 5 vs 96 ± 4 pg/ml, respectively).

Although most biochemical indexes were similar in the two groups, some differences were noted. Plasma potassium and phosphate were lower in the hypertensive group than in the normotensive group (4.32 ± 0.05 vs 4.57 ± 0.009 mEq/L, p<0.01, and 3.0 ± 0.1 vs 3.5 ± 0.1 mEq/L, p<0.001; respectively), whereas plasma urate and serum albumin levels

Table 2. Baseline Renin and Hemodynamic Data in the Normotensive and Hypertensive Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma renin activity* (ng/ml/hr)</td>
<td>2.09 ± 0.23</td>
<td>1.69 ± 0.15</td>
<td>NS</td>
</tr>
<tr>
<td>Standing plasma renin activity* (ng/ml/hr)</td>
<td>4.12 ± 0.55</td>
<td>3.07 ± 0.15</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>85.2 ± 1.1</td>
<td>100.3 ± 1.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>2.8 ± 0.2</td>
<td>2.4 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>59.0 ± 1.5</td>
<td>64.9 ± 1.6</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Cardiac index (L/min/m²)</td>
<td>2.89 ± 0.11</td>
<td>2.91 ± 0.10</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke index (ml/beat/m²)</td>
<td>48.8 ± 1.0</td>
<td>45.1 ± 1.2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Central blood volume index (ml/m²)</td>
<td>795 ± 16</td>
<td>748 ± 19</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Plasma volume index (ml/m³)</td>
<td>1580 ± 33</td>
<td>1517 ± 22</td>
<td>NS</td>
</tr>
<tr>
<td>Total blood volume index (ml/m³)</td>
<td>2855 ± 53</td>
<td>2789 ± 40</td>
<td>NS</td>
</tr>
<tr>
<td>Δ Calf volume (ml/100 ml)</td>
<td>1.53 ± 0.12</td>
<td>1.26 ± 0.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Minimum occlusion pressure (mm Hg)</td>
<td>6.2 ± 0.8</td>
<td>6.3 ± 0.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SEM. NS = not significant; VV₀ = change in calf volume at 30 mm Hg above the minimum occlusion pressure; Δ calf volume = change in calf volume induced by thigh cuff inflation to 60 mm Hg (see text).

*After the subjects had rested in a supine position for 1 hour.
were higher (7.0 ± 0.2 vs 6.1 ± 0.2 mEq/L and 4.97 ± 0.05 vs 4.75 ± 0.05 mmol/L, respectively; p < 0.01).

**Venous Distensibility**

Venous distensibility, corrected for differences in the minimum occlusion pressure, was significantly lower in the hypertensive group (p < 0.05, see Table 2). Similarly, the mean calf volume change during the 30-minute inflation period was decreased in the patients with hypertension. The venous volume/pressure curves for the two groups were also different (Figure 1). A profile analysis showed that the curves were not parallel (p < 0.01), and analysis of variance indicated that the venous volume at the four highest congesting pressures was lower in the hypertensive group.

The hypertensive subjects were more obese, had a larger calf circumference (39.5 ± 0.5 cm vs 37.2 ± 0.2, p < 0.01), and presumably had a greater thigh circumference. Despite these differences, the calculated minimal occluding pressure was similar in the normal and hypertensive groups (see Table 2). Moreover, at the lowest occluding pressure, the volume changes actually measured were the same for the two groups (see Figure 1). These findings suggest that the observed differences were not secondary to an artifact, such as reduced transmission of the congesting pressure through the tissues in the heavier hypertensive subjects.

**Hemodynamic and Hormonal Responses to Thigh Cuff Inflation**

In the normal subjects, inflation of the thigh cuffs to 60 mm Hg reduced the right atrial pressure, stroke index, cardiac index, and central blood volume index, while increasing the heart rate (Table 3). Mean arterial pressure was not significantly altered, but the systemic vascular resistance increased by 17%. Significant rises in plasma renin activity, norepinephrine, and epinephrine (93%) were observed. All changes were highly significant (p < 0.0001), as determined by Student's paired t test.

The hemodynamic and renin responses of the hypertensive subjects differed significantly from those of the normal group (see Table 3). The differences suggest that thigh cuff inflation provoked a smaller decline in venous return in the hypertensive group. The right atrial pressure and stroke index declined less (p < 0.005 and p < 0.01, respectively). The reflex tachycardia was attenuated, and consequently, the fall in the cardiac index was similar in both groups. Changes in arterial pressure, pulse pressure, and systemic vascular resistance were similar in the two groups (data not shown). Plasma renin activity increased less in the hypertensive subjects than in the normal controls (p < 0.005). However, the renin response to right atrial pressure changes was similar in both groups. Even though baseline plasma renin activity was slightly (not significantly) lower in the hypertensive subjects (see Table 2), the rise in plasma renin activity, expressed as the percentage of change from baseline, was smaller in the hypertensive group (p < 0.05). Norepinephrine responses were similar in both groups (data not shown).

**Correlation of Hemodynamic and Hormonal Responses to Thigh Cuff Inflation in the Hypertensive Group**

To determine whether the reduced renin response to thigh cuff inflation in the hypertensive group was related to a difference in venous distensibility and its hemodynamic consequences, we performed linear

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensive</th>
<th>Hypertensive</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrial pressure (RAP, mm Hg)</td>
<td>-2.5 ± 0.2</td>
<td>-1.5 ± 0.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stroke index (ml)</td>
<td>-10.8 ± 1.2</td>
<td>-7.2 ± 0.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiac index (L/min)</td>
<td>-0.36 ± 0.07</td>
<td>-0.33 ± 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>8.2 ± 1.3</td>
<td>4.0 ± 0.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Central blood volume index (ml)</td>
<td>-86 ± 4</td>
<td>-73 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma renin activity (PRA, ng/ml/hr)</td>
<td>1.1 ± 0.2</td>
<td>0.57 ± 0.09</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>132 ± 82</td>
<td>90 ± 46</td>
<td>NS</td>
</tr>
<tr>
<td>PRA/RAP</td>
<td>0.44 ± 0.1</td>
<td>0.38 ± 0.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Responses are changes in absolute values (compared to the supine baseline), expressed as means ± SEM. NS = not significant.

| Figure 1. Venous volume/pressure curve for normal subjects (closed circles) and hypertensive subjects (open circles). △ Calf volume = the change in calf volume induced by thigh cuff inflation at each distending pressure. Note that the curve for each group is extrapolated to the minimum occlusion pressure, a variable derived from individual curves (see text). *p < 0.05.
TABLE 4. Correlation Coefficients for Thigh Cuff-Induced Hemodynamic and Renin Changes in the Normotensive and Hypertensive Groups

<table>
<thead>
<tr>
<th></th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Stroke index</td>
<td>-0.11</td>
<td>-0.52*</td>
</tr>
<tr>
<td>Δ Cardiac index</td>
<td>-0.02</td>
<td>-0.56*</td>
</tr>
<tr>
<td>Δ Central blood volume index</td>
<td>0.11</td>
<td>-0.41†</td>
</tr>
<tr>
<td>Δ Pulse pressure</td>
<td>-0.48‡</td>
<td>-0.30‡</td>
</tr>
<tr>
<td>Δ Calf volume</td>
<td>-0.01</td>
<td>-0.35‡</td>
</tr>
</tbody>
</table>

Normal and hypertensive subjects were analyzed separately.

PRA = plasma renin activity.

*p < 0.001; †p < 0.01; ‡p < 0.05.

regression analysis on the data from the hypertensive group (Table 4). With thigh cuff inflation, the change in renin correlated with changes in the stroke index (p<0.0005), cardiac index (p<0.0001), central blood volume index (p<0.005), calf volume (p<0.05), and pulse pressure (p<0.05) but did not correlate with changes in the heart rate or right atrial pressure. After the effect of changes in stroke volume on changes in pulse pressure had been eliminated by partial correlative analysis, a significant relationship no longer existed between changes in renin and pulse pressure. The change in renin during cuff inflation correlated with plasma renin activity in the upright position (r = 0.40, p<0.01). Similar correlations were not found in the normotensive group. This lack of correlation is due to a few "outliers" in the data from the group of normal subjects in the study. However, our previous work leaves no doubt that changes in right atrial pressure and cardiopulmonary volume across a wide range of conditions are closely related to plasma renin changes. There were no relationships between baseline values or changes in norepinephrine or epinephrine and the hemodynamic changes in either group.

To facilitate examination of the above relationships, we arbitrarily divided the hypertensive subjects into two groups of equal size according to the change in renin with thigh cuff inflation. Those with changes above the mode (0.507 ng/ml/hr) were labeled "normal responders," and those with changes below the mode were labeled "low responders." Calf volume and hemodynamic changes for each hypertensive subgroup are displayed in Figure 2, along with the results in the normotensive control group for comparison. As compared with the normal controls and normal renin responders, the low renin responders pooled less blood in their legs during the 30 minutes of thigh cuff inflation and had smaller reductions in cardiac, stroke, and central blood volume indexes. The venous volume/pressure curve for the low renin responders was shifted toward the pressure axis, as compared with the curve for the normal controls (p<0.05) but was not significantly different from the curve for the normal renin responders, although a trend in this direction was evident. Changes in arterial pressure, pulse pressure, heart rate, and right atrial pressure were not significantly different. Plasma renin activity in the upright position was also lower in the low renin responders (2.56 ± 0.35 ng/ml/hr, p<0.05).

Using the traditional criterion of standing plasma renin activity below the distribution of values in our normal group after correction for sodium intake, we identified 10 low-renin hypertensive subjects. These patients had hemodynamic abnormalities that were similar to those seen in the low renin responders, but most changes did not achieve statistical significance. Thus, the change in calf volume was smaller in the low-renin hypertensive subjects than in the normal-renin hypertensive subjects (1.54 ± 0.25 vs 1.98 ± 0.11 ml/100 ml tissue, respectively; p = 0.07), and the falls in the central blood volume index (−39 ± 20 vs −84 ± 14 ml/m², p = 0.05) and stroke index (−5.9 ± 1.7 vs −7.7 ± 1.0 ml/beat/m², p = 0.19) were also smaller.

Effect of Prior Medical Treatment, Race, and Severity of Hypertension

Since plasma renin activity may be altered for some time after cessation of medical treatment, the effect of prior therapy in the hypertensive group was assessed.
Patients who had taken agents likely to suppress renin (β-blockers and sympatholytic agents), activate renin (diuretics or vasodilators), or have a variable effect on renin (a diuretic combined with a β-blocker or sympatholytic agent) were grouped together and compared with those who had received no treatment (Table 5). Prior treatment had no significant effect on plasma renin activity in the supine or upright position or on the renin response to thigh cuff inflation. Prior therapy also did not affect any other hemodynamic, hormonal, or biochemical measurement, including plasma potassium, urate, and phosphate.

All 29 treated patients and 4 others had clinic diastolic pressure values consistently exceeding 90 mm Hg. The remaining 14 had diastolic readings oscillating below and above 90 mm Hg (borderline hypertension). There were no differences between these two groups in regard to baseline renin, renin responses, baseline hemodynamics, or hemodynamic responses. Plasma renin activity was lower in the normal and hypertensive black subjects than in their white counterparts. Exclusion of data from the black subjects did not alter the results of any of the statistical analyses, and they are therefore reported together with the data from the white subjects.

**Discussion**

The major finding of the present study is that in hypertensive patients decreased venous distensibility is associated with a decrease in renin responsiveness to thigh cuff inflation. We conclude that the decreased pooling of blood due to stiffer veins causes a smaller reduction in the stretch of cardiopulmonary mechanoreceptors, which in turn is responsible for the diminished renin response. The supportive evidence for such a conclusion and its limitations are discussed below.

**Venous Distensibility in Hypertension**

A number of plethysmographic studies have demonstrated that the veins are less distensible in hypertensive patients than in their normal counterparts. Unlike the other groups, we measured venous distensibility in the lower limb rather than the forearm, since the veins of the lower limbs play a much greater part in the physiological adaptation to postural changes. Two other studies have examined venous pooling in the legs of hypertensive subjects. In one study, the calf volume changes were not documented, but in the other study, hypertensive subjects were found to have less pooled blood in their legs than their normal counterparts.

In measuring venous distensibility plethysmographically, one must remember that this technique provides a measure of changes in volume but does not measure absolute vascular volume. Theoretically, therefore, group differences in the venous volume/pressure curves could have been influenced by differences in the initial venous volume of the leg, resulting from differences in the venous return to the heart. We avoided this problem by raising the leg above the bed equally for all subjects. Furthermore, the central venous pressure was similar in both groups. The hypertensive subjects in our study were more obese; thus, the proximal cuff pressure may not have been transmitted equally to the deep veins in both groups. Since the transmural venous pressure was not measured directly, this effect cannot be totally discounted. However, the minimum occlusion pressure was similar in the two groups, and the venous volume/pressure curves were similar at lower levels of distending pressure. Thus, all evidence suggests that methodological factors do not account for the plethysmographic differences and that the observed results reflect true differences in venous distensibility.

The underlying mechanism (or mechanisms) for diminished venous distensibility in hypertension remains uncertain. In this study, no relationship was found between plasma catecholamines and any index of venous distensibility. If plasma catecholamine levels are used as an index of "global" sympathetic tone, then the differences between normal and hypertensive subjects in our study cannot be explained on the basis of increased sympathetic tone. Plasma norepinephrine is at best a poor index of sympathetic tone; thus, it is not surprising that investigations using different methods have demonstrated that elevated neurogenic tone contributes to reduced venous compliance in hypertension. In these studies, sympatholytic agents were found to increase venous capacitance, but not to normal values, implying that structural changes are also important determinants of venous distensibility in human hypertension, as they are in experimental hypertension.
to total blood volume for the hypertensive group was similar to that for the normal group. Thus, we were unable to confirm earlier reports from our laboratory and others suggesting a relationship between venous distensibility and the resting blood volume distribution. Low-renin hypertensive subjects did not have an increased ratio of central to total blood volume either, in contrast to our earlier report, but the number of low-renin hypertensive subjects in the present study was small.

In contrast to baseline hemodynamics, the central hemodynamic response to thigh cuff inflation in our study was influenced by the reduction in venous distensibility. The hypertensive group had less pooled blood in their calves. The hemodynamic consequence of this diminished decrease in venous return was a smaller fall in the right atrial pressure and stroke volume index in hypertensive patients. However, possibly because of the smaller change in their cardiopulmonary receptor load, the patients had a diminished reflex increase in the heart rate. These opposing changes in stroke volume and heart rate explain the similar decrease in the cardiac index observed in the two groups.

Although the hemodynamics of many physiological interventions have been examined in hypertension, few studies have found differences from normal values that can be explained on the basis of reduced venous distensibility. Most maneuvers, especially the head-up tilt, produce more marked changes that stimulate a number of reflexes, making it difficult to differentiate the effect of stiffer veins from other pathophysiological abnormalities in hypertension. Lower-body negative pressure, on the other hand, produces minor hemodynamic changes similar to those produced by thigh cuff inflation. This intervention has been shown to cause less venous pooling in the legs of hypertensive subjects and to be associated with a smaller fall in right atrial pressure. Our study, using a different method of venous pooling in a substantially larger group of patients, confirms these initial observations.

**Relationship of Hemodynamic Factors to Decreased Renin Responsiveness in Hypertension**

The hypertensive subjects in the present study had an attenuated renin response to thigh cuff inflation that was associated with a decrease in venous distensibility and an abnormal hemodynamic response secondary to reduced pooling of blood in the legs. We confirmed the association of reduced renin responsiveness with the venous abnormality by analyzing the responses in the hypertensive group. Thigh cuff inflation induced changes in plasma renin activity that were inversely correlated with changes in the stroke index, cardiac index, and central blood volume index. We have previously described a similar finding in the hemodynamic and renin responses to the head-up tilt maneuver. Division of our hypertensive group according to their renin response to thigh cuff inflation corroborated the relationships noted above (see Figure 2). Comparison of low- and normal-renin hypertensive subjects (identified by traditional criteria on the basis of standing renin values and 24-hour sodium profiles) showed the same trends.

Theoretically, the decreased renin response observed in this study could have stemmed from a diminished decrease in the stretch of the cardiopulmonary receptors or from the smaller decline in cardiac output. To address this question, we must turn to a considerable body of work regarding the role of cardiopulmonary mechanoreceptors in the control of renin release in animals and humans. Afferent nerve fibers from cardiopulmonary mechanoreceptors located in the atria and large pulmonary veins travel through the vagus to the vasomotor center in the medulla, where they have an inhibitory influence. Animal studies have shown that decreasing the stretch of these receptors increases peripheral and renal sympathetic tone. Conversely, increasing the stretch of the cardiopulmonary mechanoreceptors inhibits renin release. Despite an early negative report, it now seems certain that cardiopulmonary receptors do play a greater part than the high-pressure receptors in the reflex control of renin release in normal humans. One of these studies has shown unequivocally that the renin response to thigh cuff inflation in humans is regulated by a reflex and is not related to a decrease in cardiac output.

The gain of the cardiopulmonary receptor reflexes in human hypertension has been investigated in two studies. Both have demonstrated that the responsiveness of these reflexes is well preserved in hypertension, and in the case of borderline hypertension, it is even enhanced. Since the gain of the cardiopulmonary baroreflexes is not decreased in hypertension, the reduced renin response to thigh cuff inflation observed in the present study is best explained by the decrease in venous distensibility. Low-renin responders had less pooled blood in their legs, hence the smaller decrease in the stretch of the cardiopulmonary mechanoreceptors and, consequently, the diminished renin response.

As noted above, the efferent limb of the cardiopulmonary receptor reflex for renin release travels through the sympathetic nerves. Thus, one would expect diminished sympathetic activation and a smaller rise in plasma norepinephrine in association with the attenuated renin response. That this did not occur, however, is not surprising. Plasma norepinephrine is at best an index of global sympathetic tone that provides little or no information on regional tone. Indeed, major changes in regional neurogenic tone may occur without a marked change in plasma norepinephrine. Thus, differences between hypertensive and normotensive subjects may have occurred in our study but may not have been detected in plasma because of a relatively small and variable contribution of the regional “spillover” to overall plasma levels.

**Implications Regarding Low-Renin Hypertension**

Many authors regard renin abnormalities in essential hypertension as markers of underlying pathophysiological processes, even though renin profiling is not routinely used in clinical practice. A physiological or...
pharmacological intervention, such as dietary sodium restriction, upright posture, tilt, thigh cuff inflation, or acute administration of a diuretic, is required to unmask low-renin hypertension. Many theories have been proposed to explain the phenomenon, but the possibility that it may be due to an abnormal hemodynamic response to the unmasking maneuvers has not received sufficient attention.

Our results show that the renin response to thigh cuff inflation and standing is attenuated in hypertension. This blunted response is due to reduced venous distensibility and, consequently, to an altered hemodynamic response. The decrease in the stretch of the cardiopulmonary mechanoreceptors during simulated orthostatic stress (thigh cuff inflation) is diminished in hypertension; thus, the reflex rise in plasma renin activity is also diminished. Since the hemodynamic response to a physiological maneuver used to unmask a renin abnormality is not the same in normal and hypertensive subjects, it is plausible that some low-renin states described in hypertension stem from differences in the hemodynamic stimulus that increases renin secretion.

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Decreased venous distensibility and reduced renin responsiveness in hypertension.

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