Increased central blood volume: a possible pathophysiological factor in mild low-renin essential hypertension

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Summary
1. Patients with mild low-renin hypertension characteristically have increased central blood volume. The total blood volume is normal; the larger central blood volume reflects a shift of the blood from peripheral to central (cardiopulmonary) segments of the capacity system.

2. A relationship between central blood volume and plasma renin activity is demonstrable during tilting in normal and hypertensive subjects. In thirteen individuals there was a strong correlation between the decrease of the central blood volume and the increase in plasma renin activity in response to 12 min of 35° head-up tilt.

3. We propose that the elevated central blood volume causes greater stretch of cardiopulmonary mechanoreceptors and this in turn depresses renin release in mild low-renin hypertension.

Key words: essential hypertension, haemodynamics, renin.

Introduction
Approximately 25% of patients with essential hypertension have low plasma renin activity (Crane, Harris & Johns, 1972). A similar proportion of low-renin cases has been reported in patients with borderline hypertension (Esler, Julius, Randall, Ellis & Kashima, 1975). The question of the aetiology of the low-renin state has attracted considerable interest. The following possible causes of low-renin hypertension have been proposed: excessive ingestion of sodium, inability of the kidney to excrete sodium, impaired renal excretion of potassium, increased secretion of an unidentified adrenal mineralocorticoid (Laragh, 1973) and sclerosis of the renal vasculature (Swales, 1975).

In this report we demonstrate that in mild low-renin hypertension there is an abnormal distribution of the blood; more blood is maintained in the central (cardiopulmonary) portion of the capacitance system. It is postulated that in these patients the low-renin state stems from an excessive stimulation of cardiac mechanoreceptors by the expanded central blood volume.

Methods
Nine patients with mild low-renin hypertension (average casual blood pressure range 150-165/90-105 mmHg) were compared with seventeen normotensive volunteers and twelve hypertensive patients with normal plasma renin activity. Patients with low-renin hypertension were chosen from a larger pool of thirty-three patients with mild hypertension. The remaining patients with normal or elevated renin did not differ from control subjects in regard to variables analysed in this report. All subjects were young men (23 ± 3 years in controls and 27 ± 4 years in patients).

Haemodynamic measurements were performed in the resting recumbent position 10 min after all catheters were introduced. A Swan-Ganz catheter was introduced into a forearm vein and situated in the right atrium. Cardiogreen was injected through this catheter and the brachial arterial blood withdrawn through a Gilson densitometer for determination of the cardiac output. Plasma volume was determined by Evans Blue. Total blood volume was
calculated from plasma volume and arterial packed cell volume. Central blood volume was calculated by multiplying cardiac output by mean transit time corrected for the delay in the withdrawal system (Ellis & Julius, 1973).

The plasma renin activity was determined by a radioimmunoassay for generated angiotensin I (Haber, Koerner, Page, Kliman & Purnode, 1969). Samples for plasma renin activity were drawn after 1 h of standing; the blood was immediately chilled, cold-centrifuged and the plasma frozen for subsequent determination. A ‘nomogram’ of the relationship of the 24 h urinary sodium to the 1 h standing plasma renin value was derived from healthy normotensive subjects (Esler et al., 1975). The renin status of patients was determined by reference to this nomogram.

In another group of three normotensive subjects and ten patients with mild hypertension (casual blood pressure 160–180/95–115 mmHg) the effect of tilt on haemodynamics and plasma renin activity was investigated. Patients were resting in recumbency and were then tilted at a 35° angle. Haemodynamic measurements were performed and the blood was drawn for renin determination at rest and after 12 min of tilt.

Results

Low-renin hypertension

The results are given in Table 1. In patients with low-renin hypertension, the total blood volume was not different from that of control subjects but their central blood volume was significantly increased. Consequently, the ratio of the central to total blood volume in low-renin hypertension was increased. Furthermore, Table 1 shows that patients with low-renin hypertension exhibited the appropriate haemodynamic correlates of the increased central blood volume (Ellis & Julius, 1973). Thus their cardiac output was increased through a substantially larger stroke volume.

Tilt

In thirteen subjects who were tilted, changes in the central blood volume and in the plasma renin activity from recumbency to 12 min of tilt were analysed. A decrease of central blood volume and an increase of plasma renin activity occurred and were strongly correlated ($r = -0.872, P < 0.001$).

Discussion

This discussion will centre around the hypothesis that in low-renin hypertension there is a peripheral to central redistribution of blood. Such a redistribution causes increased cardiac filling and the cardiac mechanoreceptors are thereby stimulated. Stimulated mechanoreceptors reduce the sympathetic discharge to the kidneys, which then causes a decreased release of renin.

The central blood volume as determined in this study represents the volume between the tip of the venous catheter and all points temporally equidistant to the brachial artery sampling site. The major determinant is the combined volume of the pulmonary vessels and the heart. Thus a higher central blood volume in the presence of a normal

<table>
<thead>
<tr>
<th>Table 1. Haemodynamic and volume measurements at rest</th>
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<tbody>
<tr>
<td>Mean values ± sd are shown. Significance values (* $P &lt; 0.05$, ** $P &lt; 0.01$) refer to the differences between normal subjects and hypertensive patients (Student’s t-test).</td>
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<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Blood pressure (mmHg)</th>
<th>Blood volume index</th>
<th>Cardiac index (ml/m²)</th>
<th>Stroke volume index (ml/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
<td>Total</td>
<td>Central</td>
</tr>
<tr>
<td>Normotensive</td>
<td>16</td>
<td>122 ± 8</td>
<td>68 ± 6</td>
<td>2773 ± 294</td>
<td>828 ± 115</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Low renin</td>
<td>9</td>
<td>151 ± 13**</td>
<td>87 ± 9**</td>
<td>2784 ± 172</td>
<td>1049 ± 131**</td>
</tr>
<tr>
<td>Normal renin</td>
<td>12</td>
<td>143 ± 9**</td>
<td>82 ± 8**</td>
<td>2730 ± 304</td>
<td>780 ± 124</td>
</tr>
</tbody>
</table>
total blood volume, as seen in patients in this study, is indicative of a redistribution of the blood from peripheral to the central portions of the capacity space. The pathophysiology of this redistribution is not clear. Changes in venous compliance in hypertension (Simon, Pamnani, Dunkel & Overbeck, 1973) or increased venotor tone could be responsible.

A redistribution of blood from the peripheral to the central portion of the capacity space causes an increased cardiac filling; in a number of studies a positive correlation between the central blood volume and the stroke volume has been reported (Ulrych, Frohlich, Tarazi, Dustan & Page, 1969; Tarazi, Ibrahim, Dustan & Ferrario, 1974; Julius, Randall, Esler, Kashima, Ellis & Bennett, 1975). In the present study, as would be expected, the increased central blood volume was associated with a larger stroke volume. The increased stroke volume presumably reflects a larger end-diastolic fibre stretch associated with the increased central blood volume. It is reasonable to assume that under such conditions the cardiopulmonary mechanoreceptors are also subjected to a greater degree of stretch. Ample evidence for the existence of cardiac mechanoreceptors has been accumulated (Pelletier & Shepherd, 1972; Linden, 1973). Stimulation of atrial (Karim, Kidd, Malpus & Penna, 1972) and ventricular (Öberg & Thorén, 1973) receptors in animals causes a decrease of the renal vascular resistance by a withdrawal of the sympathetic tone. The sympathetic tone is apparently withdrawn more from the kidneys than from other vascular areas (Öberg & Thorén, 1973; Mancia, Shepherd & Donald, 1975). The important role of the sympathetic nervous system for renin release is well recognized (Vander, 1965). Decreased renin secretion upon inflation of right atrial balloons, presumably through a withdrawal of sympathetic tone, has been demonstrated in dogs (Brennan, Malvin, Jochim & Roberts, 1971).

The existence of cardiopulmonary mechanoreceptors in humans has recently been demonstrated. Lower body negative pressure was carefully applied to cause a decrease of the right atrial pressure but not to affect the systemic arterial pressure. In two independent studies such a lowering of the right atrial pressure caused a reflex decrease of the forearm vascular resistance (Zoller, Mark, Abboud, Schmidt & Heistad, 1972; Rowell, Wyss & Brengelmann, 1973).

This evidence for the existence of cardiac receptors and for their effect on renin release as well as the evidence for functioning cardiopulmonary receptors in humans provides a reasonable framework for our hypothesis that in low-renin hypertension the increased central blood volume induces a bigger stretch of cardiopulmonary receptors, which causes a decrease of renin release. This hypothesis pertains only to patients with mild low-renin hypertension, similar to those in this study; it does not claim to be applicable to the whole spectrum of low-renin hypertension in larger patient populations. The hypothesis cannot be directly substantiated, but is further supported by the observed correlation between the decrease of the central blood volume and the increase of plasma renin activity during tilt. This strong correlation suggests that there is a relation between the central blood volume and the stretch of cardiopulmonary mechanoreceptors, which in turn relates to the renin release. It should also be mentioned that during the tilt there was no correlation between changes in blood pressure or changes in heart rate and the plasma renin changes. Thus the high-pressure baroreceptors did not appear to participate in the control of renin release.

References


