High-renin essential hypertension: adrenergic cardiovascular correlates

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Summary

1. Patients with mild essential hypertension and elevated plasma renin activity, when compared with normal subjects and hypertensive subjects with normal plasma renin, demonstrated features of sympathetic nervous cardiovascular excitation, accompanied by a raised plasma noradrenaline concentration.

2. An elevated heart rate at rest, shortened cardiac pre-ejection period, and greater heart rate reduction with acute β-adrenoreceptor blockade (intravenous propranolol) in high-renin essential hypertension were indicative of adrenergic cardiac excitation. An elevated total peripheral vascular resistance at rest and a greater fall in peripheral resistance with α-adrenoreceptor blockade (intravenous phentolamine) suggested the existence of a neurogenic increase in arteriolar resistance.

3. Blood pressure was normalized by ‘total’ autonomic blockade (atropine plus propranolol plus phentolamine) in the hypertensive subjects with elevated plasma renin activity.

4. These findings suggest that in mild high-renin essential hypertension increased adrenergic drive to the heart and resistance vessels exists. The elevation of blood pressure is sustained predominantly by neurogenic mechanisms. The high plasma renin activity is seen as an expression of sympathetic nervous system overactivity.

Key words: essential hypertension, haemodynamics, noradrenaline, peripheral resistance, phentolamine, propranolol, renin, systolic time-intervals.

Introduction

Plasma renin activity is elevated in some patients with essential hypertension. These typically have either mild hypertension, or severe or accelerated disease (Frohlich, Kozul, Tarazi & Dustan, 1970). In severe high-renin essential hypertension hypertensive retinopathy is invariably present (often haemorrhages or papilloedema) and renal function is usually impaired; the elevated plasma renin activity is presumably an expression of arteriolar damage in the kidney.

Quite distinct from this is the form of high-renin hypertension sometimes noted in young patients with mild essential hypertension (Frohlich et al., 1970; Molzahn, Dissmann, Halim, Lohmann & Oelkers, 1972; Esler, Julius, Randall, Ellis & Kashima, 1975). Here a different pathophysiology seems to underly the elevation of plasma renin activity. The sympathetic nervous system plays an important role in regulating renin release by the kidney (Vander, 1965). Since early essential hypertension is often characterized by sympathetic nervous overactivity (Julius & Esler, 1975), it is possible that an elevated plasma renin activity in this context is an expression of stimulatory neurogenic influences on renin secretion (Dustan, Tarazi & Frohlich, 1970; Esler & Nestel, 1973; DeQuattro & Miura, 1973). As such, the high plasma renin activity could be a marker of a generalized increase in cardiovascular sympathetic nervous tone.

This possibility was explored in the present study, in which the plasma catecholamine concentration, cardiac systolic time-intervals and the haemodynamic response to sequential autonomic blockade were used as indices of sympathetic nervous system
function. With these techniques, sympathetic nervous activity was systematically studied in patients with mild high-renin essential hypertension.

**Methods**

**Subjects**

All experimental subjects were males aged 18–35 years. Patients had mild essential hypertension (average casual blood pressure 150–165 mmHg systolic, 90–105 mmHg diastolic, or both). The renin status in the hypertensive subjects was categorized on an unrestricted diet by reference of PRA values measured while standing to a renin–urinary sodium nomogram derived from twenty-five age-matched normal males. The investigation was performed in two parts, with each subject participating in one study only.

**Haemodynamic response to sequential autonomic blockade**

Ten patients with high-renin hypertension, ten hypertensive patients with normal PRA, and fourteen normal volunteer subjects were studied. The patients were preselected to include equal numbers with elevated and with normal PRA, which was estimated by radioimmunoassay of angiotensin I generated in vitro by the method of Haber, Koerner, Page, Kliman & Purnode (1969). Intra-arterial brachial pressure and cardiac output (by dye dilution) were measured at rest by methods previously described (Julius, Pascual & London, 1971), and then the haemodynamic response to sequential autonomic blockade with atropine sulphate (0.04 mg/kg; 0.058 μmol/kg) intravenously, propranolol hydrochloride (0.2 mg/kg; 0.68 μmol/kg) and phentolamine mesylate (15 mg; 0.04 mmol) was studied. Atropine and propranolol, in the doses used, produce effective cardiac vagal and sympathetic blockade (Julius et al., 1971). Phentolamine was administered in a dose sufficient to achieve substantial blockade of α-adrenoreceptor vasoconstriction (Esler et al., 1975). The fall in heart rate with propranolol was taken to be indicative of the prevailing level of sympathetic cardiac stimulation, the fall in total peripheral resistance with phentolamine to be related to the degree of adrenergic maintenance of vascular resistance, and the fall in blood pressure with ‘total’ autonomic blockade (atropine plus propranolol plus phentolamine) to reflect the overall extent of neurogenic maintenance of blood pressure.

**Plasma noradrenaline concentration, cardiac systolic time-intervals**

In the second study, plasma noradrenaline concentration and cardiac systolic time-intervals were measured in six hypertensive subjects with high renin, ten patients with normal PRA, and seven normal subjects. Plasma noradrenaline concentration in venous blood, after 60 min of recumbent rest, was estimated by the method of Renzini, Brunori & Valori (1970). Cardiac systolic time-intervals were derived from the electrocardiograph, the phonocardiograph and external carotid arterial pressure tracings (Harris, Schoenfeld & Weissler, 1967). Attention was focused on the pre-ejection period index and the left ventricular ejection time, since the duration of these intervals is determined in part by myocardial contractility, and influenced by adrenergic cardiac stimulation (Harris et al., 1967).

**Results**

**Study 1**

The haemodynamic findings at rest, and haemodynamic responses to sequential autonomic blockade, are presented in Table 1. The elevation of blood pressure in the high-renin hypertensive subjects was sustained by an elevated total peripheral vascular resistance. Despite the higher heart rate in this group, cardiac output was normal, owing to a limitation of stroke volume (Table 1).

With sequential autonomic blockade, the high-renin hypertensive group demonstrated a significantly greater fall in heart rate with propranolol, in total peripheral resistance with phentolamine, and in mean blood pressure with total autonomic blockade than normal subjects or hypertensive subjects with normal PRA (Table 1). After total autonomic blockade, mean blood pressure in the high-renin hypertensive subjects, 83 ± 10 (sd) mmHg, did not differ significantly from that of the normal subjects, 76 ± 8 mmHg.

**Study 2**

Plasma noradrenaline concentration was elevated in the high-renin hypertensive subjects, 1326 ± 249
Adrenergic correlates of plasma renin

Mean values ± so are shown. * P < 0.05; ** P < 0.01; hypertensive subjects compared with normal subjects (Student's t-test).

TABLE 1. Haemodynamics at rest and haemodynamic response to autonomic blockade

<table>
<thead>
<tr>
<th>Subjects</th>
<th>PRA (standing) (ng h⁻¹ ml⁻¹)</th>
<th>Urinary sodium excretion (mmol/24 h)</th>
<th>Mean blood pressure (mmHg)</th>
<th>Cardiac index (1 min⁻¹ m⁻²)</th>
<th>Heart rate (min⁻¹)</th>
<th>Stroke index (ml/m²)</th>
<th>Total peripheral resistance (mmHg l⁻¹ min m⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>2.31 ± 0.89</td>
<td>186 ± 72</td>
<td>78 ± 6</td>
<td>2.85 ± 0.37</td>
<td>61 ± 9</td>
<td>47.1 ± 5.3</td>
<td>27.5 ± 3.6</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>5.69 ± 1.24**</td>
<td>199 ± 58</td>
<td>95 ± 11**</td>
<td>2.83 ± 0.39</td>
<td>70 ± 7**</td>
<td>40.3 ± 5.7*</td>
<td>34.3 ± 4.3**</td>
</tr>
<tr>
<td>High-renin</td>
<td>1.58 ± 0.39</td>
<td>199 ± 58</td>
<td>95 ± 11**</td>
<td>2.49 ± 0.32*</td>
<td>62 ± 11</td>
<td>41.4 ± 8.9*</td>
<td>38.9 ± 7.5**</td>
</tr>
<tr>
<td>Normal-renin</td>
<td></td>
<td></td>
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</tbody>
</table>

Haemodynamic response to sequential autonomic blockade

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Change in heart rate (min⁻¹)</th>
<th>Change in total peripheral resistance (phentolamine) (%)</th>
<th>Change in mean blood pressure (total autonomic blockade) (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atropine Propranolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>+54 ± 14 −16 ± 4</td>
<td>0 ± 13</td>
<td>−2 ± 9</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>+43 ± 13 −26 ± 8**</td>
<td>−11 ± 6*</td>
<td>−13 ± 6**</td>
</tr>
<tr>
<td>High-renin</td>
<td>+54 ± 9 −17 ± 6</td>
<td>−3 ± 14</td>
<td>−3 ± 12</td>
</tr>
<tr>
<td>Normal-renin</td>
<td></td>
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</tbody>
</table>

pmol/l (224 ± 42 ng/l), compared with 805 ± 266 pmol/l (136 ± 45 ng/l) in normal subjects (P < 0.01) and 1012 ± 343 pmol/l (171 ± 58 ng/l) in hypertensive subjects with normal PRA (P < 0.05).

Left ventricular ejection time was not significantly different from normal in either of the two groups of mild hypertensive subjects studied. However, the cardiac pre-ejection period index was shortened in high-renin hypertensive subjects, 119 ± 5 ms, compared with 132 ± 6 ms and 134 ± 7 ms in normal and normal-renin hypertensive subjects respectively (P < 0.01).

Discussion

The mild high-renin hypertensives in this study were characterized as a group by (1) increased heart rate and total peripheral resistance at rest, (2) an enhanced heart rate reduction after β-adrenoreceptor blockade with propranolol, (3) reduction in peripheral vascular resistance after α-adrenoreceptor blockade with phentolamine, (4) fall in blood pressure after 'total' autonomic blockade, with normalization of pressure, (5) elevated plasma noradrenaline concentration, (6) shortened cardiac pre-ejection period.

These findings suggest that in mild high-renin essential hypertension increased adrenergic drive to the heart and resistance vessels exists. The elevation of blood pressure appears to be sustained predominantly by autonomic nervous mechanisms. The high plasma renin activity is seen as an expression of sympathetic nervous system overactivity in what may possibly prove to be either a distinct form of neurogenic human hypertension, or a stage in the evolution of the hypertensive disease process.

References


