Sympathotonia in primary hypertension and in a caricature resembling dysautonomia

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Summary

1. Plasma catecholamines and adrenergic correlates of cardiac function were compared in young men with borderline hypertension, classified according to renin status (group 1). Plasma catecholamines were increased and cardiac pre-ejection periods were shortened in 'high'-renin patients.

2. Plasma catecholamines were raised in 70% of 'high'-renin patients with primary hypertension (group 2), were related directly with age in normotensive females and were related inversely with catecholamine responses to postural stress in both normotensive and hypertensive subjects ($P < 0.01$).

3. The raised catecholamines of four 'high'-renin patients with pronounced features of sympathetic nerve activity-caricatures were elevated further during hypertensive periods. Mean arterial blood pressures were reduced 20-30% after either $\alpha$- or $\beta$-receptor blockade. Catecholamines were reduced after $\beta$-receptor blockade.

4. There appears to be a spectrum of neurogenic 'gain' in primary hypertension; it is suppressed in 'low'-renin hypertension, directly related to blood pressure in 'normal'-renin hypertension, increased in 'high'-renin hypertension and achieves a maximum in caricatures. Neurogenic factors seem to be important in the cause and maintenance of 'high'- and 'normal'-renin hypertension respectively. The caricatures may be examples of a severe form of hypothalamic stimulation.

Key words: autonomic blockade, cardiac systolic time-interval, dysautonomia, hypertension, raised catecholamines, sympathotonia.

Introduction

Plasma catecholamines are increased in a significant number of patients with primary hypertension, suggesting that neurogenic factors may be causative (Engelman, Portnoy & Sjoerdsma, 1970; DeQuattro & Chan, 1972; Louis, Doyle & Anavekar, 1973; DeQuattro & Miura, 1973). Sympathetic tonicity can be assessed from various clinical, haemodynamic, pharmacological and biochemical measurements, some of which are flushing, sweating, tachycardia, cardiac systolic time-intervals, post-Valsalva overshoot, haemodynamic changes after autonomic blockade, urinary and plasma catecholamines, plasma and tissue biosynthetic enzyme activities and by direct nerve recordings of electrical discharge. Further, tonicity influences the activity of the renin–angiotensin system.

Herein are findings of sympathetic nerve activity of young men with borderline hypertension (group 1) and both men and women with labile or sustained hypertension (group 2). To establish clinical homogeneity further, all patients were sub-classified according to their renin status: 'normal', 'low' and 'high'. We assessed the blood pressure responses to $\alpha$- and $\beta$-receptor-blocking agents of four (group 2) patients who had striking clinical manifestations of sympathetic nerve hyperactivity. Although the signs of autonomic discharge in these caricatures strongly suggested phaeochromocytoma, they were thought to have an adult form of dysautonomia.

Methods

Group 1

Subjects were males, ages 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 was categorized on an unrestricted diet by reference of plasma renin activity values while standing to a renin–urinary sodium nomogram derived from twenty-five age-matched normal males. Plasma noradrenaline and cardiac systolic time-intervals were measured in seventeen patients 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).

**Group 2**

All subjects received a diet of more than 100 mmol of sodium for the 3 days before the study. Sodium excretion was measured for the last 24 h. Blood was obtained in the morning (as above) from fifty-four normotensive volunteer subjects, ages 18–50 years, and sixty-six patients with primary hypertension without evidence of cardiovascular sequelae. Another blood sample was taken from sixty patients and twenty normal volunteer subjects on the next morning after 60 min of standing, 12 h after 80 mg of frusemide by mouth.

Plasma catecholamines were measured by the method of either Engelmann, Portnoy & Lovenberg (1968) or Renzini et al. (1970). Concentrations of total catecholamines determined from duplicate specimens of twenty patients with hypertension were similar when analysed by the two methods (Miura, Campese, DeQuattro & Meijer, 1977). Plasma renin was measured by the radioimmunoassay method (Haber, Koerner, Page, Kliman & Purnode, 1969).

Three patients from the ‘high’-renin sub-group and an additional ‘high’-renin hypertensive patient were studied both when relatively symptom-free and normotensive (basal) and when having severe symptoms and hypertension (stress). Plasma catecholamines and renin activities were compared during basal and stress conditions. Maximum blood pressure responses to 5 mg of phentolamine intravenously were compared with blood pressure reduction after 4–6 weeks of therapy with oral α-receptor (phenoxybenzamine) or β-receptor (propranolol) blockade. The average of three mean arterial blood pressures before therapy was compared with that measured during therapy with the blocking agents.

**Results**

**Study 1**

Plasma noradrenaline was elevated in ‘high’-renin hypertensive, 1326 (sd 249) pmol/l (224 ± 42 ng/l), compared with 805 (sd 266) pmol/l (136 ± 45 ng/l) in ‘normal’ subjects (P < 0.01) and 1012 (sd 343) pmol/l (171 ± 58 ng/l) in hypertensive patients with normal plasma renin activity (P < 0.05). Plasma noradrenaline concentrations were related directly with plasma renin activities (r = 0.46, P < 0.05). Left ventricular ejection time was not significantly different from that of normal subjects in either of the two groups of mild hypertensive subjects studied. However, the cardiac pre-ejection period index was shortened in ‘high’-renin hypertensive patients, 119 ± 5 ms compared with 132 ± 6 ms and 134 ± 7 ms in normal subjects and ‘normal’-renin hypertensive patients respectively (P < 0.01).

**Study 2**

Of the hypertensive patients, 39, 46 and 15% were classified as ‘low’-, ‘normal’- and ‘high’-renin patients respectively. They were ‘low’ if renin after frusemide did not exceed 1.2 ng h⁻¹ ml⁻¹ and ‘high’ if the basal renin exceeded 1.1 ng h⁻¹ ml⁻¹. The blood pressures of ‘low’-renin patients were 169 ± 5 mmHg systolic and 103 ± 4 diastolic, 10% greater than those of the other two groups. Plasma catecholamines of patients in all groups were directly related to plasma renin activities (r = 0.43, P < 0.05). The ‘low’-, ‘normal’- and ‘high’-renin sub-groups had catecholamine concentrations of 1520 ± 142, 1437 ± 159 and 2686 ± 325 pmol/l compared with normotensive values of 1225 ± 71 pmol/l. ‘High’-renin values exceeded values of the other three groups (P < 0.01). Catecholamine concentrations of both normotensive and hypertensive females exceeded those of males in the respective groups by approximately 40% (P < 0.001). Basal plasma catecholamines of male and female hypertensive subjects were 1455 ± 822 and 2000 ± 1130 pmol/l respectively compared with 988 ± 319 and 1656 ± 615 pmol/l in normotensive subjects (mean ± sd). Only male
### Table 1: Sympathotonia in hypertensive caricatures: decrease in blood pressure after \( \alpha \)- and \( \beta \)-receptor blockade

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Basal Blood pressure (mmHg)</th>
<th>Renin (ng h(^{-1}) ml(^{-1}))</th>
<th>NE+E (pmol/l)</th>
<th>Decrease in blood pressure with ( \alpha )- or ( \beta )-receptor blockade (( \Delta % ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>G.W.</td>
<td>30</td>
<td>F</td>
<td>120/90</td>
<td>4054</td>
<td>1-8</td>
<td>160/110</td>
</tr>
<tr>
<td>L.S.</td>
<td>38</td>
<td>M</td>
<td>144/96</td>
<td>4.0</td>
<td>0.5</td>
<td>140/98</td>
</tr>
<tr>
<td>C.B</td>
<td>28</td>
<td>M</td>
<td>132/76</td>
<td>2-1</td>
<td>0.5</td>
<td>132/76</td>
</tr>
<tr>
<td>E.R.</td>
<td>55</td>
<td>F</td>
<td>184/144</td>
<td>166/120</td>
<td>166/105</td>
<td>200/105</td>
</tr>
</tbody>
</table>

*Blood pressure before 5 mg of phentolamine was compared with the lowest value during the 2 min after phentolamine. Pre-phentolamine blood pressures were 184/124, 206/144, 166/120 and 200/105 mmHg respectively. Percentage reduction after oral blockade was the mean arterial pressure pre-therapy compared with the average pressure after 4-6 weeks of propranolol (P) or phenoxybenzamine (Ph).*
values are significantly different \((P < 0.01)\). Although plasma catecholamines of normotensive males were similar through the five decades studied, they increased with age in females \((r = 0.72, P < 0.01)\). When plasma catecholamines of hypertensive subjects were compared by age and sex, eight of fifty-six, or 14\%, of the 'low'- and the 'normal'-renin patients, and seven of ten, or 70\%, of the 'high'-renin patients had raised plasma catecholamines (greater than the mean value plus 2 SD of the mean). The increased incidence of raised catecholamines in 'high'-renin hypertension is significant \((P < 0.001)\).

The responsiveness of plasma catecholamines to standing plus frusemide was inversely proportional to the basal plasma catecholamines for both normotensive subjects \((r = 0.81, P < 0.01)\) and hypertensive subjects \((r = 0.48, P < 0.01)\).

Plasma catecholamine concentrations were increased markedly in the four caricatures, especially during hypertensive episodes (Table 1). Each of these patients had a 20–30\% reduction in mean arterial blood pressure after either acute \(\alpha\)-receptor blockade or chronic blockade with \(\alpha\)- or \(\beta\)-receptor blocking agents. Basal plasma catecholamines were reduced 35 and 63\% in two of the caricatures (G.W. and L.S. respectively) after several months of propranolol therapy.

**Discussion**

There is a spectrum of neurogenic gain in primary hypertension. It is manifested in some young men with borderline hypertension and is related to cardiac indices of increased haemodynamic status. It is suppressed in patients with 'low'-renin hypertension and related directly to blood pressure in 'normal'-renin hypertension. It is consistently increased in those with 'high'-renin hypertension. The 'high'-renin subjects appear to manifest their adrenergic overdrive. Neurogenic factors achieve maximum importance in the caricatures. Blood pressures of these patients with striking elevation of plasma catecholamine concentrations as seen in phaeochromocytoma or in familial dysautonomia (V. DeQuattro & L. Linde, unpublished work) respond well acutely to intravenous \(\alpha\)-receptor blockade and chronically to oral \(\beta\)-receptor blockade. This finding suggests that the \(\alpha\)-receptor antagonist blocks the excessive sympathetic toxicity at the peripheral neurovascular cleft and the \(\beta\)-receptor blocker acts centrally, perhaps in the hypothalamus. This explanation fits with the clinical resemblance of the caricatures to syndromes simulating diencephalic stimulation described previously (Page, 1935). The reduction of raised plasma catecholamines of the hypertensive caricatures and the hypertensive subjects studied by H. M. Brecht, F. Banthien, W. Ernst & W. Schoeppe (unpublished work) after \(\beta\)-receptor-blocking therapy lends further support for this concept. The sympathetic nerve fibre appears to be the link in 'high'-renin patients with either borderline, labile or sustained hypertension, having subtle or marked clinical manifestations of their sympathetic nerve toxicity. In the last-named patients it may bridge excessive hypothalamic discharge to cardiac and vascular musculature and renal nerves.

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**References**


