Elevated plasma adrenaline reflects sympathetic overactivity and enhanced α-adrenoceptor-mediated vasoconstriction in essential hypertension

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Summary

1. Stressful sympathetic stimulation (cold pressor test) was applied to 18 patients with essential hypertension and 15 normotensive subjects. Intra-arterial blood pressure, heart rate, plasma adrenaline and noradrenaline concentrations as well as forearm blood flow were measured before and during the cold pressor test; tests were repeated after regional postsynaptic α₁-adrenoceptor blockade with prazosin.

2. Under basal conditions mean blood pressure ($P < 0.001$), heart rate ($P < 0.01$), forearm blood flow ($P < 0.001$) as well as adrenaline concentration ($P < 0.01$), but not noradrenaline, was higher in patients with essential hypertension.

3. During the cold pressor test, mean blood pressure, heart rate, plasma adrenaline and noradrenaline concentrations increased and forearm flow decreased (all $P < 0.001$).

4. Stress-stimulated plasma adrenaline was higher in essential hypertensive patients than in normotensive subjects ($P < 0.01$). In the former the stress-induced increase in plasma adrenaline correlated with the increase in mean blood pressure ($r = 0.514; P < 0.05$).

5. Prazosin increased forearm blood flow more in essential hypertension ($P < 0.001$). This increase correlated with the resting plasma adrenaline in the hypertensive ($r = 0.710; P < 0.001$), but not in normotensive, subjects.

6. When the cold pressor test was repeated during postsynaptic α₁-adrenoceptor blockade forearm blood flow did not decrease; instead it increased further in both groups ($P < 0.05$).

7. Thus in essential hypertension elevated plasma adrenaline concentration reflects sympathetic overactivity as also expressed by enhanced α-adrenoceptor-mediated vasoconstriction.

Key words: adrenaline, α-adrenoceptor, cold pressor test, forearm blood flow.

Abbreviations: EHT, essential hypertension; NT, normal blood pressure.

Introduction

Increased sympathetic nervous activity has been implicated in the pathophysiology of essential hypertension (EHT) [1–4], as reflected by elevated plasma adrenaline concentrations observed in some patients [5–7]. Recently we demonstrated a direct relationship between plasma adrenaline and the degree of α-adrenoceptor-mediated vasoconstriction under resting conditions [7], indicating a neurogenic contribution to elevated peripheral resistance in EHT.

To obtain a more dynamic assessment of these inter-relationships we compared plasma catecholamines, blood pressure, heart rate and forearm blood flow during stressful sympathetic stimulation with the cold pressor test before and during postsynaptic α₁-adrenoceptor blockade with prazosin in EHT and NT.

Methods

Patients

Study groups consisted of 18 outpatients (12 males, six females), aged 31–62 (mean 47) years with uncomplicated EHT and of 15 healthy NT (eight males, seven females) aged 30–65 (mean 49) years. Antihypertensive treatment was withdrawn at least 6 weeks before the study. Only
concentrations measured under basal conditions and after a 10 min intra-arterial infusion of prazosin (0.5 μg min⁻¹ 100 ml⁻¹ of forearm tissue) as well as during the cold pressor test (1 min) applied before and during prazosin infusion in 15 normotensive subjects (NT) and 18 patients with essential hypertension (EHT).

TABLE 1. Intra-arterial mean blood pressure, heart rate, forearm blood flow, and plasma adrenaline and noradrenaline concentrations measured under basal conditions and after a 10 min intra-arterial infusion of prazosin (0.5 μg min⁻¹ 100 ml⁻¹ of forearm tissue) as well as during the cold pressor test (1 min) applied before and during prazosin infusion in 15 normotensive subjects (NT) and 18 patients with essential hypertension (EHT).

Mean values ± SEM are shown. Significance (Student’s t-test) for differences between NT and EHT: *P < 0.01; **P < 0.001.

<table>
<thead>
<tr>
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<th>Basal conditions</th>
<th>Cold pressor test</th>
<th>Prazosin infusion</th>
<th>Cold pressor test during prazosin</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>NT</td>
<td>EHT</td>
<td>NT</td>
<td>EHT</td>
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<tr>
<td>Forearm blood flow (ml min⁻¹ 100 ml⁻¹ of tissue)</td>
<td>2.9 ± 0.4</td>
<td>4.3 ± 0.4***</td>
<td>1.9 ± 0.3</td>
<td>2.4 ± 0.4***</td>
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<tr>
<td>Plasma adrenaline (nmol/l)</td>
<td>0.08 ± 0.02</td>
<td>2.0 ± 0.02**</td>
<td>0.15 ± 0.02</td>
<td>0.33 ± 0.07**</td>
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<tr>
<td>Plasma noradrenaline (nmol/l)</td>
<td>1.65 ± 0.12</td>
<td>1.71 ± 0.14</td>
<td>2.04 ± 0.17</td>
<td>2.32 ± 0.12</td>
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<tr>
<td>Mean blood pressure (mmHg, intra-arterial)</td>
<td>83 ± 2</td>
<td>118 ± 3***</td>
<td>102 ± 3</td>
<td>146 ± 4***</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>60 ± 2</td>
<td>72 ± 3***</td>
<td>69 ± 3</td>
<td>84 ± 2***</td>
</tr>
</tbody>
</table>

those with EHT in whom sitting diastolic pressure (Korotkoff phase V) was repeatedly ≥100 mmHg were included. All NT subjects were selected on a basis of non-familiarity with laboratory procedures and none of them was taking any medication; their sitting diastolic pressure was <90 mmHg. Informed consent was obtained from all participants.

Study protocol

Investigations started at 08.00 hours with the subjects in a fasting state and having refrained from smoking for the last 12 h. The left brachial artery and a right antecubital vein were cannulated. After a 30 min rest venous blood was drawn for the estimation of plasma adrenaline and noradrenaline concentrations as well as plasma renin activity by radioenzymatic [8, 9] and radioimmunological [10] methods. Forearm blood flow was measured by venous occlusion plethysmography [11], a mercury in silastic strain gauge being used [7]. After basal flow measurement the cold pressor test [12] was performed by immersing the right hand in ice-water, containing equal parts of ice and water (0–2°C), for 1 min. Immediately afterwards venous blood was drawn for the estimation of plasma adrenaline and noradrenaline concentrations. Forearm blood flow was measured throughout this procedure and the mean of the three curves with the lowest flow used for analysis. Thirty minutes later, after forearm blood flow, blood pressure and heart rate had returned to control values, the selective α₁-adrenoceptor postsynaptic blocking agent prazosin [13] was infused (0.5 μg min⁻¹ 100 ml⁻¹ of forearm tissue), a dose known to produce maximal dilatation without causing systemic effects [7], for 11 min and forearm blood flow measured from minute 9 to minute 10. From minute 10 to minute 11 of prazosin infusion the cold pressor test procedure was repeated as described before. Intra-arterial blood pressure and pulse rate, as derived from the pulse curve, were continuously monitored except during the cold pressor test on prazosin, because its infusion interfered with intra-arterial blood pressure recording.

Results

Under basal conditions intra-arterial mean blood pressure was 118 ± SEM 3 in EHT and 83 ± 2 in NT (P < 0.001) (Table 1). Heart rate and forearm blood flow values were higher in EHT (P < 0.01). Plasma adrenaline concentrations were also higher (P < 0.01) in EHT compared with NT although there was some overlap between the two groups. In contrast, plasma noradrenaline concentrations were not significantly different in EHT and NT groups.

During the cold pressor test mean blood pressure and heart rate rose in both groups (P < 0.001), paralleled by an increase in plasma adrenaline (P < 0.001) and noradrenaline (P < 0.01). Starting from a higher basal level, the stimulated plasma adrenaline concentrations were higher (P < 0.01) in EHT. The percentage increase in plasma adrenaline correlated positively with the rise in mean blood pressure (r = 0.514; P < 0.05). Forearm blood flow fell
in both groups \( (P < 0.001) \), somewhat more pronouncedly in EHT.

Infusion of prazosin produced an increase in forearm blood flow in both groups \( (P < 0.001) \), which was greater in EHT than in NT \( (P < 0.001) \). In EHT but not in NT the increase in prazosin-induced forearm blood flow correlated with the resting plasma adrenaline concentrations \( (r = 0.710; P < 0.001) \). Cold pressor test during the infusion of prazosin induced a similar rise in plasma adrenaline and noradrenaline concentrations to that observed before prazosin. When the cold pressor test was repeated during prazosin infusion forearm blood flow increased similarly in EHT and NT groups \( (P < 0.05 \) for both).

**Discussion**

Cold pressor stimulation evoked a marked increase in sympathetic activity, as reflected by increases in plasma catecholamines, blood pressure and heart rate and by the decrease in forearm blood flow as a result of vasoconstriction in EHT. These changes paralleled those observed in NT subjects. Higher values for resting and stimulated plasma adrenaline concentrations, blood pressure and heart rate as well as the more pronounced decrease in forearm blood flow during the cold pressor test strongly suggest sympathetic overactivity in patients with essential hypertension. An enhanced \( \alpha \)-adrenoceptor-mediated vasoconstrictor component seems to contribute to this sympathetic overactivity since postsynaptic \( \alpha \)-receptor blockade with prazosin increased forearm blood flow to a greater extent in EHT than in NT subjects.

Although plasma adrenaline concentrations were doubled after the cold pressor test noradrenaline concentrations rose only by about half of the initial value, which is in agreement with data published by others [14]. Thus the cold pressor test, which causes considerable discomfort and pain, appears predominantly to stimulate the sympatho-adrenal activity and hence differs from the physical exercise test where augmentation of plasma noradrenaline occurs \([6, 9, 14]\). As the half-life of noradrenaline is 1–2 min \([15]\) junctional noradrenaline release may not be adequately reflected by the plasma concentrations unless sympathetic stimulation lasts for at least 4 min. The 1 min duration of the cold pressor test may therefore be too short to produce 'steady-state' noradrenaline concentrations. This to some extent might account for the apparent discrepancy between the increase in plasma noradrenaline levels and the powerful sympatho-neural response to the cold pressor test as demonstrated by the marked vasoconstriction and the rise in blood pressure. The increase in heart rate is more likely to be due to vagal withdrawal.

The reversal of the cold pressor-induced reduction in forearm blood flow observed during prazosin infusion probably is due to an increase in flow secondary to the rise in blood pressure. Whether in the presence of \( \alpha \)-adrenoceptor blockade unopposed \( \beta \)-adrenoceptor-mediated vasodilatation contributes to this effect remains uncertain, but appears a less likely proposition since \( \beta \)-adrenoceptor function, if anything, is blunted in EHT \([6, 16]\).

Plasma adrenaline rather than noradrenaline concentrations were elevated at rest as well as during sympathetic stimulation and the stimulated increase in plasma adrenaline correlated with the rise in blood pressure. This suggests that plasma adrenaline is a suitable marker for sympathetic overactivity in patients with EHT. The correlation between plasma adrenaline and the response of forearm blood flow to postsynaptic \( \alpha \)-receptor blockade with prazosin suggests that plasma adrenaline reflects an enhanced \( \alpha \)-adrenoceptor-mediated vasoconstrictor component.

Alternatively, it has been suggested that adrenaline could facilitate neurotransmitter release from sympathetic nerve endings by activating presynaptic \( \beta \)-adrenoceptors \([17, 18]\). Thus circulating elevated adrenaline concentrations might actively contribute to vasoconstriction and thereby to the elevation of blood pressure in patients with EHT.

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**References**


Adrenaline and α-receptor-mediated vasoconstriction


