Decrease in α-adrenoceptor-mediated vasoconstriction parallels the antihypertensive response to propranolol in patients with normal renin essential hypertension

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Summary

1. α₁-Adrenoceptor-mediated vasoconstriction was studied before and during propranolol therapy in eight normal renin essential hypertensive patients; four were known ‘responders’ and four, age-matched ‘non-responders’ to previous β-receptor blocker monotherapy. Plasma renin activity, plasma adrenaline and noradrenaline concentrations as well as forearm blood flow were measured before and during regional postjunctional α₁-adrenoceptor blockade with prazosin. All measurements were done on placebo and again after 6 weeks’ propranolol monotherapy (320 mg/day).

2. Propranolol reduced heart rate and plasma renin activity to the same extent in ‘responders’ and ‘non-responders’. Resting plasma adrenaline concentrations tended to be higher in ‘responders’ before propranolol; they remained unchanged in both groups on propranolol. Plasma noradrenaline concentrations were similar in both groups before and on propranolol.

3. Before propranolol forearm flow was not different in ‘responders’ and ‘non-responders’. Non-specific vasodilatation with sodium nitroprusside produced a similar increase in forearm flow before and after propranolol in both groups.

4. Prazosin-induced increments in forearm flow tended to be higher in ‘responders’ before propranolol. After propranolol the vasodilator effect of prazosin was attenuated in ‘responders’ but it remained unchanged in ‘non-responders’ (P < 0.01).

5. In patients with normal renin essential hypertension the antihypertensive response to propranolol monotherapy is paralleled by a decrease in postjunctional α₁-adrenoceptor-mediated vasoconstriction.

Key words: α₁-adrenoceptor, propranolol, vasoconstriction.

Introduction

Established essential hypertension is characterized by elevated total peripheral arteriolar resistance, which, besides adaptive structural vascular wall changes [1], is determined by the combined effects of the angiotensinergic [2, 3] and adrenergic vasoconstrictor systems [4–9] as shown by enhanced α-adrenoceptor-mediated vasoconstriction [10].

Chronic β-adrenoceptor blockade lowers high blood pressure by reducing peripheral resistance [11, 12] and hence ultimately has to interfere with adrenergic and/or angiotensinergic vasoconstrictor mechanisms [12, 13]. A direct relationship between the degree of renin reduction and the attendant fall in blood pressure has been demonstrated [12–14]. However, since reduction of the renin/angiotensin vasoconstrictor component does not seem to fully explain the antihypertensive mode of action of β-receptor blockers in all patients the question arises whether changes in α-adrenoceptor-mediated vasoconstriction contribute to the chronic β-receptor blocker response.

We therefore measured the effect of prazosin-induced postjunctional α₁-adrenoceptor blockade on forearm blood flow before and during chronic β-receptor blocker therapy in patients with normal renin essential hypertension.
Methods

Patients

Eight male patients with uncomplicated normal renin essential hypertension were selected. Four patients, aged 38 to 55 (mean 45.5) years, who, from previous therapeutic experience, were known to normalize their blood pressure (diastolic pressure < 95 mmHg) on β-blocker monotherapy, were classified as ‘responders’. Four patients, aged 38–54 (mean 47.5) years, who were known to be refractory to previous β-blocker monotherapy, were classified as ‘non-responders’. Antihypertensive treatment was withdrawn at least 6 weeks before the study; in all patients the sitting casual diastolic blood pressure (Korotkoff phase V) rose to > 100 mmHg. Informed consent was obtained from all patients.

Study protocol

Investigations started at 08:00 hours with the patient 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 [15] as well as plasma renin activity [16]. Subsequently forearm blood flow was measured by venous occlusion plethysmography [17] by using a mercury in silastic strain gauge as described elsewhere [10]. In brief, after basal flow values had been recorded, sodium nitroprusside (0.6 µg min⁻¹ 100 ml⁻¹ of forearm tissue) was infused into the brachial artery for 2 min in order to assess non-specific vasodilatation, and forearm blood flow measured from the first to the second minute. After forearm blood flow had returned to basal values, the selective postjunctional α₁-blocking agent prazosin [18] (0.5 µg min⁻¹ 100 ml⁻¹ of forearm tissue) was infused for 10 min. In preceding dose-finding studies the above doses of sodium nitroprusside and prazosin were found to produce a maximal dilating response without causing systemic effects. Intra-arterial blood pressure and heart rate were continuously monitored. All measurements were performed on placebo and repeated after 6 weeks of a monotherapy with the long-acting formulation of propranolol, 160 mg given twice daily at 07:00 and 19:00 hours.

Results

After 6 weeks of propranolol monotherapy systolic and diastolic blood pressures were normalized in ‘responders’ and remained unchanged in ‘non-responders’ (Table 1). Heart rate and plasma renin activity decreased to the same extent in both groups. Under basal conditions forearm flow was similar in ‘responders’ and ‘non-responders’; infusion of sodium nitroprusside produced a similar increase in forearm blood flow before as well as on propranolol in both groups of patients.

Before propranolol, forearm blood flow during infusion of prazosin tended to be higher in the ‘responders’. After 6 weeks of propranolol monotherapy the vasodilating response to prazosin was attenuated in ‘responders’ (P < 0.01), whereas it remained unchanged in ‘non-responders’. Resting plasma adrenaline concentrations measured before propranolol therapy tended to be higher in ‘responders’ than in ‘non-responders’. The values remained unchanged during propranolol therapy. Plasma noradrenaline concentrations were similar in ‘responders’ and ‘non-responders’ before propranolol; on propranolol there was a minor but non-significant increase in mean values in both groups.

Table 1. Intra-arterial mean blood pressure (MBP), heart rate (HR), plasma adrenaline (PA) and plasma noradrenaline (PNA) concentrations, plasma renin activity (PRA) and forearm blood flow (FAF) measured after a 2 min intra-arterial infusion of sodium nitroprusside (0-6 µg min⁻¹ 100 ml⁻¹ of forearm tissue) and a 10 min prazosin infusion (0.5 µg min⁻¹ 100 ml⁻¹ of forearm tissue) before and after 6 weeks of propranolol monotherapy (320 mg/day) in four ‘responders’ and four ‘non-responders’.

<table>
<thead>
<tr>
<th></th>
<th>MBP (mmHg)</th>
<th>HR (beats/min)</th>
<th>FAF (ml min⁻¹ 100 ml⁻¹ of tissue)</th>
<th>PA (nmol/l)</th>
<th>PNA (nmol/l)</th>
<th>PRA (nmol h⁻¹ 1⁻¹)</th>
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<td>Basal</td>
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<td>Prazosin</td>
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<td>Responders</td>
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<tr>
<td>Before propranolol</td>
<td>121 ± 2</td>
<td>68 ± 5</td>
<td>3.7 ± 0.5</td>
<td>21.0 ± 5.2</td>
<td>11.7 ± 3.2</td>
<td>0.25 ± 0.03</td>
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<tr>
<td>On propranolol</td>
<td>92 ± 6***</td>
<td>57 ± 1</td>
<td>2.0 ± 0.4</td>
<td>22.9 ± 5.0</td>
<td>5.0 ± 1.2**</td>
<td>0.27 ± 0.04</td>
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<td>Non-responders</td>
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<tr>
<td>Before propranolol</td>
<td>120 ± 4</td>
<td>74 ± 5</td>
<td>3.2 ± 1.0</td>
<td>17.4 ± 3.0</td>
<td>7.7 ± 2.0</td>
<td>0.16 ± 0.01</td>
</tr>
<tr>
<td>On propranolol</td>
<td>118 ± 3</td>
<td>61 ± 5</td>
<td>2.6 ± 0.4</td>
<td>18.0 ± 2.1</td>
<td>7.4 ± 0.7</td>
<td>0.16 ± 0.02</td>
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Mean values ± SEM are shown. Significance of results: **P < 0.01; ***P < 0.001 (Student’s t-test).
Discussion
In patients with normal renin essential hypertension the fall in blood pressure on propranolol is associated with a decrease in the postjunctional \( \alpha \)-adrenoceptor-mediated vasoconstriction, as expressed in a reduced vasodilating response to prazosin. The observation that ‘responders’ to propranolol monotherapy tended to have a higher resting plasma adrenaline and a greater prazosin-induced forearm blood flow before propranolol than ‘non-responders’ could, at least in part, explain the difference in the antihypertensive effect of propranolol in the two groups. This may indicate that in ‘responders’ to \( \beta \)-blocker monotherapy a predominant neurogenic component may contribute to the elevated peripheral vascular resistance, since it has been found that in patients with essential hypertension the decrease of neurogenic vasoconstriction may play a decisive role in determining the response to antihypertensive \( \beta \)-blocker monotherapy mechanisms which interfere with peripheral neurotransmission and/or neurotransmitter release may possibly be involved. Thus blockade of prejunctional \( \beta \)-receptors may result in an attenuation of their facilitatory effect on neurotransmitter release from the sympathetic nerve ending [19]. Alternatively, suppression of the renin–angiotensin system might result in an attenuation of angiotensin’s amplifying effect on \( \alpha \)-adrenoceptor stimulation [20, 21], e.g. through depression of its facilitatory effect on noradrenaline release. However, because of the similarity in observed renin suppression between ‘responders’ and ‘non-responders’, a greater attenuation of adrenergic facilitation in ‘responders’ could only be explained by a difference in the prejunctional response to angiotensin. Whether any of these peripheral vascular mechanisms or their combined attenuating effects on adrenergic facilitation may suffice in reducing the enhanced \( \alpha \)-adrenoceptor-mediated vasoconstrictor component remains still open.

Theoretically, response to prazosin may not necessarily be related to the \( \alpha \)-receptor but may be determined by events distal to the receptor. For example, different effects on intracellular calcium consequent to \( \beta \)-receptor blockade may play a decisive role [22].

Alteration of the baroreflex mechanism [23] is unlikely to be responsible for the difference in the antihypertensive effect of propranolol monotherapy in the two groups since \( \beta \)-receptor blockade per se does not greatly affect the baroreflex arc [24, 25], though ‘resetting’ of baroreceptors may have occurred, presumably secondarily to the fall in blood pressure, in the ‘responders’. Blockade of \( \beta \)-receptors in the central nervous system, leading to decreased peripheral impulse traffic [26] and attenuation of central, angiotensin-mediated adrenergic facilitation [27] has been suggested but such mechanisms are hardly compatible with the finding that plasma catecholamines remain unchanged or slightly increase on propranolol in both ‘responders’ and ‘non-responders’.

Structural changes in the vascular wall may influence responsiveness to \( \beta \)-blocker monotherapy yet the known duration of hypertension did not differ in this study. However, since non-specific vasodilatation with sodium nitroprusside was not different between the two groups structural vascular changes alone cannot be implicated in the lack of an antihypertensive effect in the ‘non-responders’.

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References


