Renin-suppressive potency of various beta-adrenergic blocking agents at supine rest and during upright exercise

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Summary
1. Renin responses to different types of beta-adrenergic blocking agents were compared in eight normal volunteers at supine rest and during moderate upright exercise.
2. Comparable beta-adrenergic blockade was achieved with equipotent cardiodeceleratory doses of 100 mg of propranolol, 400 mg of practolol, 100 mg of oxprenolol, 10 mg of timolol, 5 mg of pindolol or 100 mg of ICI 66082.
3. All beta-blocking agents tested significantly and markedly reduced plasma renin activity during upright exercise. Renin suppression was not related to either $\beta_1$- or $\beta_2$-type receptor blocking action.
4. Renin levels at rest were generally reduced by the blocking drugs, but these responses did not reach significance for oxprenolol and pindolol. With both these drugs, lesser suppressibility of basal renin may be due to their inherent sympathomimetic activity.
5. The results suggest that different types of beta-blocking agents suppress plasma renin activity and therefore that they all may lower blood pressure through reduction of angiotensin vasoconstriction.

Key words: beta-blockade, hypertension, ICI 66082, oxprenolol, pindolol, practolol, propranolol, renin.

Introduction
The anti-hypertensive effectiveness of the beta-adrenergic blocking drug propranolol was found to correlate with the pretreatment plasma renin activity and with the degree of drug-induced renin suppression (Bühler, Laragh, Baer, Vaughan & Brunner, 1972). Hence, in patients with essential hypertension, propranolol controls blood pressure in three-quarters of the group with high and two-thirds of the category with normal plasma renin activity. In contrast, monotherapy with propranolol proved ineffective in low-renin patients (Bühler, Laragh, Vaughan, Brunner, Gavras & Baer, 1973). These renin-related responses tally with results in which propranolol was also found to control pressure in 50–60% of the average hypertensive population (Zacharias, Cowen, Prestt, Vickers & Wall, 1972).

Comparable anti-hypertensive results have also been reported with other types of beta-adrenergic blocking agents which differ in features such as degree of intrinsic sympathomimetic activity, predominance of $\beta_1$- or $\beta_2$-receptor blocking action, or haemodynamic response patterns.

The question thus arises whether an anti-renin mechanism may represent the common denominator of the blood pressure-lowering effects observed with beta-blocking agents other than propranolol. In order to test and compare the renin-suppressive capacity of different beta-blocking agents, heart rate and plasma renin activity were measured in normal subjects at supine rest and during moderate upright exercise. During exercise, heart rate is predominantly controlled by the beta-adrenoceptor activity (Robinson, Epstein, Beiser & Braunwald, 1966). With equipotent pulse-slowing doses, all beta-blocking agents tested reduced plasma renin activity. Accordingly, they may all lower pressure by reducing angiotensin vasoconstriction.

Subjects and methods
Eight normotensive male volunteers, aged 22–28 years, were studied at weekly intervals between 09.00 and 14.00 hours. After 30 min supine bed rest,
TABLE 1. Comparison of beta-blocking agent-induced changes of heart rate and renin activity at rest and during exercise

Mean values ± sem are shown. Comparisons by paired t-test: *P < 0.05 or less; studies in eight normal subjects.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Propranolol (100 mg)</th>
<th>Practolol (400 mg)</th>
<th>Optrenolol (100 mg)</th>
<th>Pindolol (5 mg)</th>
<th>Timolol (10 mg)</th>
<th>ICI 66082 (100 mg)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
<td>Exercise</td>
<td>Rest</td>
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<tr>
<td>Pulse (beats/min)</td>
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<td></td>
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<td></td>
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<tr>
<td>Before</td>
<td>67 ± 4</td>
<td>148 ± 6</td>
<td>65 ± 4</td>
<td>143 ± 5</td>
<td>69 ± 4</td>
<td>140 ± 4</td>
<td>63 ± 3</td>
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<tr>
<td></td>
<td>65 ± 5</td>
<td>143 ± 4</td>
<td>64 ± 4</td>
<td>144 ± 6</td>
<td>63 ± 3</td>
<td>144 ± 6</td>
<td>63 ± 3</td>
</tr>
<tr>
<td>During</td>
<td>66 ± 4</td>
<td>146 ± 6</td>
<td>61 ± 4</td>
<td>115* ± 4</td>
<td>69 ± 3</td>
<td>113* ± 3</td>
<td>67 ± 2</td>
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<tr>
<td></td>
<td>64 ± 5</td>
<td>116 ± 4</td>
<td>63 ± 3</td>
<td>112* ± 2</td>
<td>63 ± 3</td>
<td>113* ± 3</td>
<td>67 ± 2</td>
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<tr>
<td>Plasma renin activity (ng h⁻¹ ml⁻¹)</td>
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<td></td>
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<tr>
<td>Before</td>
<td>2.7 ± 0.6</td>
<td>7.9 ± 1.2</td>
<td>2.6 ± 0.4</td>
<td>7.3 ± 0.2</td>
<td>2.8 ± 0.4</td>
<td>5.7 ± 0.2</td>
<td>3.0 ± 0.2</td>
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<tr>
<td></td>
<td>2.6 ± 0.4</td>
<td>7.0 ± 1.1</td>
<td>2.6 ± 0.4</td>
<td>7.0 ± 1.0</td>
<td>2.7 ± 0.4</td>
<td>5.0 ± 0.2</td>
<td>2.3 ± 0.3</td>
</tr>
<tr>
<td>During</td>
<td>2.0* ± 0.4</td>
<td>3.7* ± 1.1</td>
<td>2.0* ± 0.4</td>
<td>3.0* ± 0.5</td>
<td>2.0* ± 0.4</td>
<td>3.0* ± 0.5</td>
<td>2.0* ± 0.3</td>
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<td></td>
<td>2.0* ± 0.4</td>
<td>3.8* ± 0.5</td>
<td>2.0* ± 0.4</td>
<td>3.8* ± 0.5</td>
<td>2.0* ± 0.4</td>
<td>3.8* ± 0.5</td>
<td>2.0* ± 0.3</td>
</tr>
</tbody>
</table>
Renin-suppressive potency of beta-blocking drugs

Heart rates were measured and blood samples were taken for the determination of plasma renin activity via an antecubital intravenous cannula. Subjects were then exercised in the upright position on an electrically-braked ergometer bicycle (Elema-Schönander EM 370). Heart rates were measured every 5 min by electrocardiogram. Inter-individual differences in physical work capacity were corrected by adjusting work load, 100–150 W being used. In order to obtain values for renin under steady-state conditions exercise was extended to 30 min, at the end of which period measurements of heart rates and renin were repeated. The same procedures were repeated 2 h after random oral administration of a single dose of beta-adrenergic blocking agent or placebo.

Drugs were given in equipotent doses, i.e. doses ascertained in preceding studies to produce the same reduction in exercise tachycardia. These were: 100 mg of propranolol, 400 mg of practolol, 100 mg of oxprenolol, 10 mg of timolol, 5 mg of pindolol or 100 mg of ICI 66082.

Blood samples were processed for measurement of plasma renin activity, the radioimmunoassay method of Sealey, Gerten-Banes & Laragh (1972) being used. To reduce methodological variability, all samples obtained in studies with a particular drug were simultaneously assayed; the intra-assay coefficient of variability was 9% (Bühler, Patel & Marbet, 1974).

Analysis of statistical significance of differences in heart rate and renin was determined by Student’s paired t-test, and for the comparison of effects produced by different blocking agents an analysis of variance (F-test) was applied.

Results

The results are summarized in Table 1. In all control experiments repeated before administration of beta-adrenergic blocking agents, heart rates and renin activities were similar at rest, and both rose significantly during ergometry; the slopes of the increases in both heart rate and renin did not differ significantly between these groups of experiments. The average increase in heart rate was 80 ± 2 beats/min and in renin 3.8 ± 0.4 ng h⁻¹ ml⁻¹ (± SEM). After administration of a placebo, resting as well as exercise-stimulated heart rates and renin remained practically unchanged.

Effects of beta-adrenergic blocking drugs on heart rates

Resting heart rates were hardly affected by six of the seven drugs; only timolol significantly reduced control heart rates. Reductions in exercise tachycardia elicited by the beta-adrenergic blocking drugs were not significantly different, thus allowing better comparison of the drugs’ renin-suppressing activity.

Effects of beta-adrenergic blocking drugs on plasma renin activity

Resting renin levels were lowered by all the drugs, but this response did not reach significance with oxprenolol and pindolol. Analysis of variance, however, did not show significant differences between the blocking drugs with regard to their effects, but this still does not exclude slight quantitative differences. Upright-stimulated renin levels were consistently and significantly reduced by all beta-adrenergic blocking drugs. These responses did not differ significantly when the drugs were compared with each other. Upright renin was reduced by 54% with practolol, 49% with propranolol, 47% with ICI 66082, 46% with oxprenolol, 36% with pindolol and 30% with timolol.

Discussion

All beta-adrenergic blocking agents included in this comparison significantly suppressed upright plasma renin activity by 30–54% in normotensive subjects. Resting recumbent values were also generally reduced, but these responses did not reach significance for oxprenolol and pindolol. This subtly lesser suppressibility of basal renin perhaps may be due to the drugs’ intrinsic sympathomimetic action (Barret & Carter, 1970), since the other compounds tested have little or no agonist activity (Imhof, 1975).

Our results compare favourably with some reports in which beta-adrenergic blocking agents other than propranolol, such as pindolol (Johnston, Anavekar, Chua & Louis, 1973), and ICI 66082 (Åberg, 1974), were also found to decrease renin; the failure of renin to respond to the same drugs observed by others remains unexplained (Stokes, Weber & Thornell, 1974; Amery, Billiet & Fagard, 1974).

Renin was equally reduced by β₁-receptor antagonists and by the more cardioselective com-
pounds practolol and ICI 66082 when given in equipotent β₁-receptor-antagonizing doses. Accordingly, renin inhibition is not specific for either β₁- or β₂-type blocking agents, and therefore an anti-renin mechanism could also play a role in the anti-hypertensive effects observed with cardio-selective beta-adrenergic blocking agents as well (Leishman, Thirkettle, Allen & Dixon, 1970; Amery, Billiet, Joossens, Meekers, Reybrouck & van Mieghem, 1973).

Variable haemodynamic responses have been demonstrated with the drugs studied. Some, such as practolol (Tarazi, Savard, Dustan & Bravo, 1972), oxprenolol (Wilson, Watson, Peel, Lanley & Turner, 1968) and timolol (Franciosa, Freis & Conway, 1973), were found to cause little change in cardiac output, whereas marked reductions were observed with propranolol (Tarazi & Dustan, 1972) or ICI 66082 (Amery et al., 1973). Accordingly, there seems to be a dissociation between cardio-dynamic responses to these drugs, on the one hand, and the observed consistency in renin suppression, as well as the known similarity in anti-hypertensive effectiveness, on the other.

The degree of renin suppression in normal subjects found in this study was consistently less than the 80% average reduction in renin observed in high renin, and the 60% renin suppression found in normal renin hypertension patients with propranolol (Bühler et al., 1972). This greater suppressibility of renin in high and particularly in normal renin essential hypertensions further suggests the presence of relatively increased adrenergic nerve activity. In these patients, elevated renin and blood pressure can be returned to normal by beta-adrenoceptor blockade.

Acknowledgment

This work has been supported by the Swiss National Fund (no. 3.719.72).

References
