Influence of selective and non-selective β-adrenoreceptor blockade on the haemodynamic effect of adrenaline during combined antihypertensive drug therapy


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Summary
1. Haemodynamic effects of adrenaline were studied in 27 hypertensive patients, successively during treatment with propranolol and metoprolol. In 12 patients β-adrenoreceptor blockade was combined with diuretics and in 15 patients the blockade was combined with vasodilators.

2. During propranolol adrenaline caused a marked pressor effect: there was a considerable rise in systolic as well as in diastolic blood pressure and a marked fall in heart rate. During metoprolol there was only a slight rise in blood pressure and an increase in heart rate.

3. Forearm blood flow was decreased by adrenaline during propranolol and was increased during metoprolol. Calculated vascular resistance showed opposite changes.

4. Results were essentially the same when β-adrenoreceptor blockade was combined with diuretics or with vasodilators and did not differ from previous results obtained in patients treated by blockade alone.

5. If adrenaline infusion can be considered as a model for acute stress, our results seem to favour a selective β₁-adrenoreceptor blocking agent over a non-selective one, even when the blocker is combined with a diuretic or a vasodilator.

Key words: adrenaline, β-adrenoreceptor blockade, haemodynamics, metoprolol, propranolol.

Introduction
In recent years β₁-adrenoreceptor selective blocking agents have proved to reduce blood pressure and heart rate in hypertensive patients to the same degree as non-selective blocking agents (Bengtsson, 1976).

For β₁-adrenoreceptor selectivity much attention has been paid to the relative degree of blockade of the cardiac receptors and the pulmonary receptors. However, another aspect of selectivity may be clinically important, i.e. the effect on muscle blood flow. In the heart β₁-receptors are dominant, whereas β₂- and α-receptors dominate in the blood vessels of skeletal muscles. Adrenaline stimulates both α and β-receptors. In the blood vessels of skeletal muscles β-receptor stimulation causes vasodilatation, whereas α-receptor stimulation causes vasoconstriction.

Previous studies showed that infusion of adrenaline during propranolol has a pronounced pressor effect, probably because the vasodilatation mediated by β₂-receptors is blocked. This pressor effect was absent when adrenaline was administered during metoprolol (Johnsson, 1975; Van Herwaarden, Binkhorst, Fennis & van 't Laar, 1977).

The aim of this study was to investigate whether these effects of adrenaline were the same, when, in the antihypertensive regimen, diuretics and vasodilators were added to the β-receptor blockade.

Methods
The study was done in two groups of hypertensive patients, who had given their informed consent.

Group 1 comprised 12 patients, mean age 35
years (range 20–50 years). All had long-standing essential hypertension. Mean blood pressure before treatment was (mean ± sd) 177/112 ± 31/12 mmHg and, after 29 ± 17 months of treatment: 145/97 ± 15/8 mmHg. The mean dose of propranolol amounted to 233 ± 80 mg daily. All patients used chlorthalidone (73 ± 29 mg daily).

Group 2 consisted of 15 patients, mean age 38 years (range 25–50 years). All had long-standing hypertension, 12 essential and three of renal origin. Blood pressure before treatment was 189/120 ± 31/18 mmHg and, after 45 ± 13 months of treatment: 141/93 ± 11/5 mmHg. The mean dose of propranolol amounted to 288 ± 95 mg daily; 11 patients used chlorthalidone, two frusemide. All patients used vasodilators: 11 hydralazine (125 ± 49 mg daily), three oral diazoxide (100–300 mg daily) and one minoxidil (60 mg daily).

After the first adrenaline-infusion experiment in all patients propranolol was substituted by an equipotent dose of metoprolol: 100 mg of metoprolol for each 80 mg of propranolol. The other medications were continued in the same dose. After a period of 1–3 months on metoprolol the second test was performed.

The tests were carried out in a room with a constant temperature, between 09.00 and 12.00 hours. Before the test the patients had a light breakfast without coffee and abstained from smoking.

After 20 min of rest in the supine position blood pressure and heart rate were measured every 2 min. When five readings were completed the intravenous infusion of adrenaline was started. The infusion rate was increased stepwise to 8 μg/min in 4 min, and then this dose was sustained for 6 min. The last two readings during the infusion were used for statistical analysis. After adrenaline was stopped measurements were continued for 8 min. The last three values were used for analysis. Forearm blood flow was measured (up to a maximum of 10 times) before, during the highest dose of adrenaline and after stopping the infusion.

The measurements were done with the arm elevated obliquely in an arm support. Blood pressure was measured with the Arteriosonde 1217, heart rate was recorded with an electrocardiograph, forearm blood flow was measured with a mercury strain-gauge plethysmograph. Mean arterial pressure (MAP) was calculated as the sum of the diastolic and 1/3 of the pulse pressure. Forearm vascular resistance was calculated by dividing MAP through flow and was expressed in arbitrary units.

Statistical analysis

For each group and each variable a two-way analysis-of-variance model (fixed effects, unequal cell frequencies) was postulated, the first factor being 'patients' and the second the 'periods of measurement' (before, during and after propranolol or metoprolol). Estimates of main effects and their standard errors were computed accordingly. Multiple comparisons were carried out with Scheffe's (1959) S-method. In each analysis, both factors and their interaction contributed highly significantly (P < 0.001) to the explanation of variance, implying a (rather large) variation in reactions between patients.

Results

Table 1 shows the haemodynamic values before, during and after infusion of adrenaline. It should be noted that the blood pressures listed were lower than those obtained by conventional sphygmomanometry, both because of the elevated position of the arm and because Arteriosonde was used.

In group 1 adrenaline induced a rise of systolic blood pressure of 30 and 11 mmHg respectively during treatment with propranolol and metoprolol. Diastolic blood pressure increased during propranolol and hardly changed during metoprolol. Adrenaline caused a marked reduction in heart rate during propranolol (lowest heart rate recorded: 29 beats/min) and an increase during metoprolol. The forearm blood flow was decreased significantly by adrenaline during treatment with propranolol and the calculated vascular resistance increased considerably. During metoprolol, however, blood flow increased and vascular resistance decreased. The difference in reaction was also manifested by signs such as cold acra and pallor in the propranolol group.

In group 2 adrenaline caused also an increase of systolic and diastolic blood pressures during propranolol, 31 and 18 mmHg respectively, whereas during metoprolol adrenaline caused only a modest increase of systolic (10 mmHg) and diastolic (5 mmHg) pressures. Heart rate decreased again during propranolol and increased during metoprolol. During propranolol adrenaline caused a reduction in flow and during metoprolol a significant increase. The rise in vascular resistance during propranolol was again striking compared with the lack of change during metoprolol.
**TABLE 1. Haemodynamic effects of adrenaline infusion during propranolol and metoprolol in two groups of hypertensive patients**

For details see the text. Mean values ± se are given before, during and after adrenaline. P₁, Difference between ‘before’ and ‘during’; P₂, difference between propranolol and metoprolol during adrenaline. *P < 0.001; N.S., P > 0.05.

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<tr>
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<th>Propranolol</th>
<th>Metoprolol</th>
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<tr>
<td></td>
<td>Before</td>
<td>During</td>
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<tr>
<td>Systolic arterial blood pressure (mmHg)</td>
<td>125 ± 0.7</td>
<td>122 ± 1.1</td>
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<tr>
<td>Diastolic arterial blood pressure (mmHg)</td>
<td>86 ± 0.5</td>
<td>84 ± 0.7</td>
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<td>Mean arterial blood pressure (mmHg)</td>
<td>99 ± 0.4</td>
<td>97 ± 0.6</td>
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<td>Heart rate (beats/min)</td>
<td>55 ± 0.3</td>
<td>54 ± 0.3</td>
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<td>Blood flow (ml min⁻¹ 100 ml⁻¹)</td>
<td>3.9 ± 0.1</td>
<td>4.3 ± 0.1</td>
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<td>Vascular resistance (units)</td>
<td>38 ± 1.8</td>
<td>34 ± 1.8</td>
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**Discussion**

In previous studies great differences were found in the haemodynamic effects of an adrenaline infusion between propranolol- and metoprolol-treated subjects (Johnsson, 1975; van Herwaarden et al., 1977). These differences are a consequence of the fact that propranolol blocks the β₂-receptors, thereby leaving a dominating role for α-receptor stimulation, whereas during metoprolol β₂-receptor stimulation remains possible. So, during metoprolol the administration of adrenaline tends to decrease vascular resistance, whereas during propranolol vascular resistance increases considerably. This increase in resistance leads to a further rise in blood pressure. Bradycardia develops due to the stimulation of the baroreceptors.

In more severe hypertension, however, treatment with a combination of β-receptor blockers, diuretics and/or vasodilators is usual.

The results of the present study appear to be in full agreement with the previous ones in subjects treated with β-receptor-blocking agents alone. Even strong vasodilators did not prevent a pressor response to adrenaline during non-selective β-receptor blockade.

Admittedly, not all stress situations are comparable with adrenaline infusions. However, endogenous adrenaline release has also been shown to increase during modest emotional stress (Bonelli, Hörtnagel, Brücke, Magometschnig, Lochs & Kaik, 1979). Therefore the present results suggest that β₁-receptor selective blocking agents may be preferable, in order to avoid unwanted pressor reactions, even when the therapeutic regimen also comprises diuretics and strong vasodilators.

**Acknowledgments**

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**References**


