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ACUTE HAEMODYNAMIC EFFECTS OF METOPROLOL IN HYPERTENSIVE PATIENTS

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1 The acute haemodynamic effects of metoprolol (0.15 mg/kg body weight) intravenously were studied at rest and during exercise, in a recumbent position in five patients with arterial hypertension of WHO Stage 1 or 2.

2 Significant decreases in heart rate, cardiac output and arterial blood pressures, both at rest and during exercise, were seen. There were no changes in the calculated stroke volume or systemic vascular resistance.

3 The apparent absence of any relative preponderance of the α-adrenoceptors after acute β-adrenoceptor blockade with metoprolol warrants further studies on metoprolol in arterial hypertension.

Introduction

Studies in animals and man have shown that metoprolol is a potent β-adrenoceptor blocker acting mainly on β_1-adrenoceptors and devoid of intrinsic sympathomimetic activity (Åblad, Borg, Carlsson, Ek, Johnsson, Malmfors & Regårdh, 1975; Johnsson, 1975; Stenberg, Wasir, Amery, Sannerstedt & Werkö, 1975). Theoretically, by using drugs of this type, which in therapeutic doses are devoid of any pronounced effect on β_2-adrenoceptors located in, for example, peripheral blood vessels and the bronchi, an increase in peripheral vascular tone reciprocal to a relative preponderance of the α-adrenoceptors could be avoided. They should, therefore, be safer than non-selective β-adrenoceptor blockers for routine use in arterial hypertension. Also, the risk of side-effects from the bronchial tree should be reduced.

Hence, it appeared to be of importance to evaluate the acute haemodynamic effects of metoprolol in arterial hypertension. In the present study, the haemodynamic responses to an intravenous injection of metoprolol were studied in five young patients with early, uncomplicated arterial hypertension.

Methods

Five inpatients, four men and one woman aged 23-38 years, took part in the study after having given their informed consent (Table 1). All patients had uncomplicated arterial hypertension of WHO Stage 1 (3 cases) or 2 (2 cases) (WHO, 1962). Three patients were previously untreated, one had received medical treatment for some time several years previously, and one man had been off treatment for 2 weeks before the study after having received a β-adrenoceptor blocker plus hydrallazine for a couple of weeks.

The test protocol was identical to that used in a previous study in normotensive men (Stenberg *et al*, 1975), and the techniques used for obtaining and analyzing the haemodynamic data have also previously been described in detail (Sannerstedt, 1966).

In brief, the patients were brought to the catheterization laboratory after an overnight fast. Polyethylene catheters were inserted percutaneously under local anaesthesia into the brachial artery and an antecubital vein. The tip of the venous catheter was placed, under fluoroscopic control, in the upper part of the right atrium or superior vena cava. The intra-arterial blood pressure was recorded on an Ultralette Recorder via a Statham P23Db strain gauge transducer, the zero level being at 5 cm below the sternal angle. The mean arterial blood pressure was obtained by electrical integration. Cardiac output was measured using a dye dilution technique with bromsulphalein as the indicator and with intermittent sampling of arterial blood. Oxygen consumption was determined by collection of expired air in a Douglas bag with subsequent gas analyses. All measurements were made with the subjects in a recumbent position. The arterial blood pressure

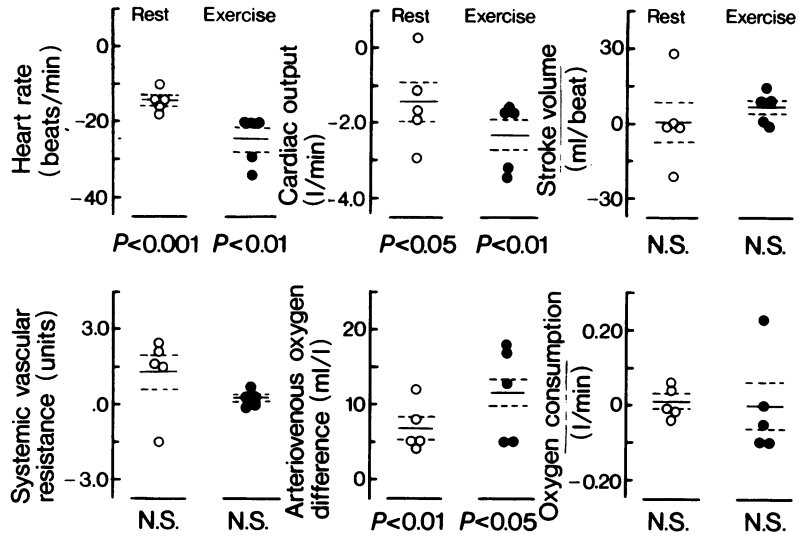

Figure 1 Changes in haemodynamic functions after administration of metoprolol i.v. to five hypertensive patients studied at rest and during exercise in the supine position. The means ± s.e. mean, and probabilities of paired differences are shown; N.S. = non-significant.

was recorded immediately before and after each dye dilution procedure, and the average of the two values was used for further analysis. The systemic vascular resistance was calculated by dividing the mean brachial arterial blood pressure by the cardiac output and expressed in arbitrary units. The arteriovenous oxygen difference in ml/litre was calculated by using the indirect Fick formula.

After insertion of the catheters, the subjects were allowed to rest for 30 to 40 min before the first measurements at rest were made. These were followed by exercise in the supine position at a standardized work load of 100 and 65 watts/min for the men and the woman, respectively, on an electrically braked, variable-load bicycle ergometer (Elema-Schönander AB, Sweden). The cardiac output was determined during the last minute of the 10 min period of exercise.

After cessation of the exercise the subjects rested for about 45 min before a new set of resting determinations were obtained. Thereafter, metoprolol was slowly injected intravenously in a dose of 0.15 mg/kg body weight (8.5-14.5 mg). Fifteen minutes after the completion of the injection the procedure described above was repeated. No side-effects of the drug were observed in any subject during or after the study.

The results were statistically evaluated for paired differences using Student's *t*-test. No consistent differences were found in the figures from the two determinations at rest before the drug was given, indicating that the subjects had returned to a basal or almost basal state, when the resting determination after the first exercise period was made. Accordingly, the second determination at rest has been used for calculating the paired differences.

Results

Mean values of haemodynamic findings at rest and during exercise before and after intravenous administration of metoprolol are given in Table 1, and individual differences are illustrated in Figures 1 and 2.

The heart rate (Figure 1) was lower in each patient after administration of metoprolol, both at rest and during exercise. The average decreases of 14 beats/min (18%) at rest, and 25 beats/min (18%) during exercise were statistically significant ($P < 0.001$ and $P < 0.01$, respectively). Concomitant to the fall in heart rate the cardiac output also decreased significantly both at rest and during exercise, resulting in an unchanged stroke volume in both situations. The decreases in cardiac output amounted to 1.5 (16%; $P < 0.05$), and 2.3 (14%; $P < 0.01$) litres/min, respectively, at rest and during exercise.

There were significant drops in the systolic, mean and diastolic arterial blood pressures, both at

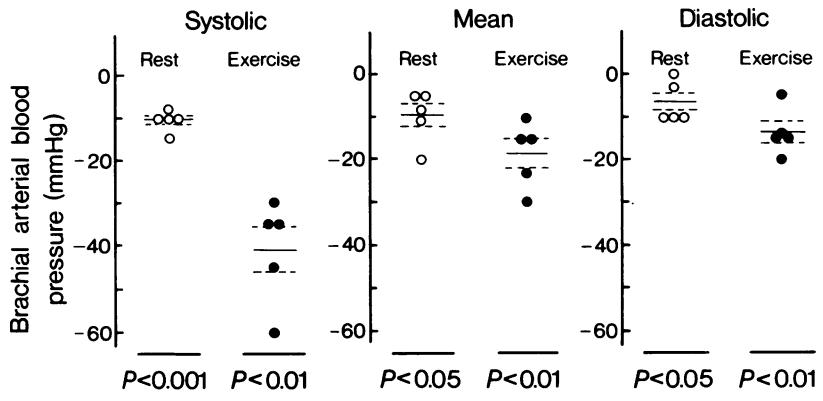

Figure 2 Changes in intra-arterial blood pressure after administration of metoprolol i.v. to five hypertensive patients studied at rest and during exercise in the supine position. The means ± s.e. mean, and probabilities of paired differences are shown.

rest and during exercise (Figure 2). The average decreases were 11/7; 10 and 41/14; 19 mm Hg, respectively, at rest and during exercise. The corresponding percentage decreases for the mean arterial blood pressure were 8% and 14%. The calculated systemic vascular resistance did not show any significant changes.

No changes in the total oxygen consumption were observed, either at rest or during exercise (Figure 1). Accordingly, the lowered total blood flow had to be compensated for by a greater arteriovenous oxygen difference, and significant increases of 7 (25%; $P < 0.01$), and 12 (15%; $P < 0.05$) ml/litre, respectively, at rest and during exercise were found.

Discussion

For technical reasons isoproterenol infusions, or a test of a similar kind, were not used in the present set-up to verify the degree of β-adrenoceptor blockade obtained by the injection of metoprolol. From extensive exercise tests in human subjects, however, it is known that metoprolol i.v. in doses of 5 to 20 mg has significant effects on the heart rate during exercise consistent with a β-adrenoceptor blocking effect (Johnsson, Regårdh & Sölvell, 1975). It may therefore be concluded that the changes observed after the injection of metoprolol were due to the β-adrenoceptor blocking properties of this compound.

Table 1 Mean ± s.e. mean haemodynamic findings at rest and during exercise in the supine position before and after intravenous administration of metoprolol (0.15 mg/kg body weight) to five hypertensive patients.

	Before metoprolol		*After metoprolol*		
	Rest	*Exercise*	*Rest*	*Rest*	*Exercise*
Brachial arterial blood pressure (mm Hg)					
systolic	154 ± 7	201 ± 14	151 ± 6	140 ± 6	160 ± 9
mean	115 ± 6	132 ± 10	114 ± 5	104 ± 6	113 ± 8
diastolic	91 ± 7	95 ± 8	89 ± 6	82 ± 6	81 ± 8
Heart rate (beats/min)	79 ± 4	134 ± 9	85 ± 6	71 ± 5	110 ± 6
Cardiac output (l/min)	9.0 ± 0.3	16.8 ± 0.9	8.7 ± 0.6	7.3 ± 0.5	14.4 ± 1.1
Stroke volume (ml/beat)	116 ± 9	128 ± 14	105 ± 11	105 ± 14	135 ± 15
Systemic vascular resistance (units)	12.9 ± 0.9	7.8 ± 0.9	13.3 ± 1.2	14.6 ± 1.6	8.0 ± 1.0
Arteriovenous oxygen difference (ml/l)	30 ± 1	76 ± 5	31 ± 3	38 ± 2	87 ± 6
Oxygen consumption (l/min)	0.26 ± 0.01	1.25 ± 0.06	0.27 ± 0.01	0.27 ± 0.02	1.24 ± 0.05

The present findings are in agreement with previous results in normotensive subjects (Stenberg *et al.*, 1975), and confirm metoprolol to be a potent β-adrenoceptor blocker also capable of producing substantial reductions of the heart rate and cardiac output in patients with early, uncomplicated arterial hypertension.

Of special interest is the absence of any compensatory increase of the systemic vascular resistance accompanying the decrease in cardiac output seen after metoprolol. This is in contrast to the findings with e.g. propranolol, which in a similar category of patients will cause an increase in the systemic vascular resistance, probably due to blockade of vascular β_2-adrenoceptors with an ensuing relative preponderance of the α-adrenoceptors (Sannerstedt, Julius & Conway, 1970). Accordingly, absence of a rise in systemic vascular resistance after β-adrenoceptor blockade would indicate selective blockade of β_1-adrenoceptors. However, it should be noted that in another study in untreated hypertensives comparing the effects of propranolol and practolol given intravenously, both drugs increased the systemic vascular resistance indicating that other factors than the presence or absence of cardioselectivity may be of importance (Savard, Tarazi & Dustan, 1971).

Although the negative chronotropic effect of metoprolol, leading to markedly reduced heart rates both at rest and during exercise, might have been expected to result in an increased stroke volume (Guyton, Jones & Coleman, 1973), the unchanged stroke volume at rest and the tendency to a higher stroke volume during exercise do not suggest any prominent negative inotropic effect of metoprolol in patients with early arterial hypertension.

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