Effects of propranolol and metoprolol on haemodynamic and respiratory indices and on perceived exertion during exercise in hypertensive patients

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SUMMARY A double blind cross-over trial of the non-selective beta-blocker propranolol and the β_1 -selective blocker metoprolol was carried out in 8 hypertensive patients. At the end of each 4-week period of treatment haemodynamic and respiratory indices and perceived exertion were studied during moderate exercise. Both beta-blockers resulted in reduced heart rate, cardiac output, and blood pressure, whereas the stroke volume increased. Total peripheral resistance did not change. During exercise the expiratory peak flow rate equally increased in every period. However, the peak flow rate at rest, as well as during exercise, was reduced by propranolol, while metoprolol had no such influence. Neither of the beta-blockers changed O_2 consumption, CO_2 production, tidal volume, or respiratory rate. Moreover, they did not influence perceived exertion. These results suggest that the arteriolar and bronchiolar β_2 -receptors do not play a major role in the alteration of circulation and ventilation during exercise. As far as their practical use as antihypertensive agents is concerned, this study shows no advantage in the use of either of these beta-blockers.

During muscular exercise the plasma catecholamine concentration increases as a result of the increased activity of the sympathetic nervous system and the adrenal medulla (Vendsalu, 1960; Davies *et al.*, 1974; Galbo *et al.*, 1975). This increased adrenergic activity plays an important role in the adaptation of the circulatory system to exercise (Bevegård and Shephard, 1967). Adrenergic effects are mediated by stimulation of different kinds of receptors, which were nominated alpha- and beta-receptors by Ahlquist in 1948. Later the beta-receptors were divided by Lands *et al.* (1967) into two subgroups: β_1 for the cardiac receptors and β_2 for the arteriolar and bronchiolar receptors.

The β_1 -selective blockers, as well as the non-selective beta-blockers, reduce the heart rate, the cardiac output, and the blood pressure during exercise (Cumming and Carr, 1967; Johnsson *et al.*, 1969; Ablad *et al.*, 1976; Reybrouck *et al.*, 1977). It is possible, however, that the haemodynamic changes induced by β_1 -selective and non-

selective beta-blockers differ during exercise. For example, a non-selective beta-blocker, such as propranolol, could be expected to diminish the vasodilatation in exercising muscle by blockading the arteriolar β_2 -receptors. This would then affect the blood pressure. On the other hand, a much smaller effect on the peripheral resistance would be expected from a β_1 -selective blocker such as metoprolol (Johnsson, 1975; van Herwaarden *et al.*, 1977).

Moreover, it might be possible for a non-selective beta-blocker to partly inhibit the bronchodilatation that appears during exercise, by blockading the bronchiolar β_2 -receptors. On the other hand, a β_1 -selective blocker would not hinder this bronchodilatation (Johnsson *et al.*, 1975b; Tivenius, 1976).

During treatment with propranolol some patients complain of fatigue, muscle weakness, and worsening claudication (Kellaway, 1976; Zacharias, 1976). These side effects in theory may be related to vasodilatation and bronchodilatation during exercise. If the two types of beta-blockers indeed produce

different effects in this respect, it might be expected that exercise is tolerated better during metoprolol treatment.

For testing these suppositions we investigated the effects of a β_1 -selective and a non-selective β -blocker on haemodynamic and respiratory indices and on perceived exertion during exercise in hypertensive patients. During this study only non-invasive methods were used, in order to avoid stressful stimuli.

Patients

The study included 8 men with untreated essential hypertension, without demonstrable cardiac or pulmonary disease. The initial diastolic blood pressure, measured in the supine position after 15 minutes' bed rest, ranged from 100 to 120 mmHg (mean: 107 mmHg). The average age was 34 years (range 22 to 47). The mean values for height and weight were 1.76 m (range 1.64 to 1.82) and 76 kg (range 62 to 92), respectively. All patients were within 15 per cent of their ideal body weight.

Methods

DESIGN OF STUDY

Propranolol (80 mg thrice daily) and metoprolol (100 mg thrice daily) were compared with each other and with placebo in a double blind cross-over study. In these doses these drugs are considered to be equipotent in reducing heart rate during rest and exercise (Johnsson *et al.*, 1975a; Bengtsson, 1976). There were 4 consecutive periods of medication, each lasting 4 weeks: placebo, β -blocker, placebo, β -blocker. The effective agents were given in randomised order. At the end of each 4-week period the same set of investigations (see below) were performed. After this cross-over study 7 patients continued treatment with a β -blocker in the same dose: 5 preferred metoprolol and 2 propranolol. After 6 months of treatment these investigations were repeated.

The investigations were carried out in a room with a constant temperature of 19°C, starting at 9 am, two hours after ingestion of the morning dose. The patients were asked to take a light breakfast without coffee and to abstain from smoking. To begin with, blood pressure and heart rate were measured after 15 minutes' bed rest. Next, the effects of an adrenaline infusion on blood pressure, heart rate, and blood flow in the forearm were measured. The results of this part of the investigation are published separately (van Herwaarden *et al.*, 1977). The exercise test started at 10.30 am, a good half hour after stopping the adrenaline infusion. During moderate exercise

haemodynamic and respiratory studies were performed.

EXERCISE TEST

Exercise was performed in the sitting position on a bicycle ergometer (Lode^R), with a pedalling frequency of 60 cycles per minute. Before the start of the cross-over study we checked that the load of 1.5 W/kg bodyweight did represent a 'moderate' state of exercise. For this study 'moderate exercise' was arbitrarily defined as exercise with a heart rate below 150 beats per minute. The load of 1.5 W/kg was too heavy for 1 of our 8 patients and for him a load of 1 W/kg bodyweight was chosen. This load was built up within 2 minutes by increments of 0.5 W/kg and then it was maintained during 13 minutes. Measurements were performed during steady state exercise.

RESPIRATORY AND HAEMODYNAMIC INDICES

The expiratory peak flow rate (maximal value of 3 observations) was measured before and after 6 minutes of exercise with the aid of a Wright peak flow meter. After 7 minutes of exercise expired gas was collected in a Douglas bag for 2 minutes. After analysis of CO₂ (Uras) and O₂ (Servomex OA 272) CO₂ production ($\dot{V}CO_2$) and O₂ consumption ($\dot{V}O_2$) were calculated and converted to STPD. Further respiratory rate (f) was measured and tidal volume (V_t) was calculated at BTPS. The arterial CO₂ pressure (P_aCO_2) was determined indirectly using the formula of Bohr for physiological dead space, in which values for the dead space were substituted according to the data of Asmussen and Nielsen (1956). The mixed venous CO₂ pressure ($P_{\bar{v}}CO_2$) was determined indirectly via the re-breathing procedure according to the plateau method of Collier (1956). During this re-breathing procedure CO₂ tension of respired gas was continuously recorded by means of a rapid infrared CO₂ analyser (Capnograph Godart type MO). The $P_{\bar{v}}CO_2$ was calculated from the plateau CO₂ tension after correction for the alveolar-arterial CO₂ pressure difference according to Jones *et al.* (1972). The venoarterial CO₂ content difference ($C_{\bar{v}}CO_2 - C_aCO_2$) was calculated by substituting $P_{\bar{v}}CO_2$ and P_aCO_2 in the computer programme for CO₂ dissociation according to Godfrey (1970). In this computer programme the following values for arterial blood of healthy subjects during moderate exercise were assumed: haemoglobin 15 g/dl; O₂ saturation 0.95; pH 7.4, and base-excess -2.5 mmol/l (Barr *et al.*, 1964; Doll *et al.*, 1966).

The cardiac output was determined by employing Fick's principle for CO₂ and dividing $\dot{V}CO_2$ by $C_{\bar{v}}CO_2 - C_aCO_2$. The venoarterial O₂ content

difference was calculated by dividing the O_2 consumption by the cardiac output. An electrocardiogram was recorded every minute. The blood pressure was measured noninvasively with the Physio-metrics SR11. This device detects Korotkoff sounds by a microphone, which is placed under a rigid cuff. The low frequency vibrations (16 to 33 Hz) of the sounds are used as signals and recorded on a circular graduated disc. Similar techniques have been proved to produce reliable blood pressure recordings during submaximal exercise (Mastropaolo *et al.*, 1964; Sime *et al.*, 1975; own observations). The recorded blood pressure was the mean of two measurements after 7 and 9 minutes of exercise. The mean arterial pressure was calculated by addition of one-third of the pulse pressure to the diastolic pressure. The total peripheral resistance was calculated by dividing the mean arterial pressure by the cardiac output and was expressed in arbitrary units.

PERCEIVED EXERTION

For rating of perceived exertion the scale described by Borg (1970) was used. This R.P.E. scale consists of 15 grades from 6 to 20. Every second number is accompanied by descriptive words as follows: 7: very very light, 9: very light, 11: fairly light, 13: moderately hard, 15: hard, 17: very hard, and 19: very very hard. The scores and descriptions were printed on a chart. After 4 and 14 minutes of exercise the patients were asked to indicate their score of the perceived exertion.

STATISTICS

All results are presented as mean $\pm$ SEM. As the values appeared to be divided normally, statistical analysis was carried out with Student's *t* test for

paired observations. The effects of the two β -blockers were compared with each other and with the placebo period preceding the period with that particular β -blocker.

Results

CROSS-OVER STUDY PROPRANOLOL VERSUS METOPROLOL

The data of the four periods are presented in Tables 1, 2, and 3. No significant differences were found between the values recorded in the two placebo periods. Propranolol and metoprolol equally reduced the blood pressure, heart rate, and cardiac output during exercise (Table 1). The stroke volume increased during β -blockade, while peripheral resistance did not change. These haemodynamic changes in relation to the placebo values are graphically presented in the Fig. Systolic pressure appears to decrease more during propranolol medication than during metoprolol treatment. The mixed venous CO_2 pressure ($P_{\bar{v}CO_2}$) increased during both types of β -blockade, as did the venoarterial O_2 and CO_2 gradients. The arterial CO_2 pressure (P_aCO_2) was slightly higher during treatment with metoprolol than during the placebo period. Neither β -blocking agent caused significant differences in the O_2 consumption ($\dot{V}O_2$), CO_2 production ($\dot{V}CO_2$), tidal volume (V_t), and respiratory rate (*f*) (Table 1).

The expiratory peak flow rate was in every period higher during exercise than at rest (Table 2). Propranolol decreased expiratory peak flow rate at rest as well as during exercise. Metoprolol did not influence the peak flow rate. However, no statistically significant differences were found between the

Table 1 Respiratory and haemodynamic parameters during exercise after 4 weeks placebo followed by 4 weeks β -blockade (mean $\pm$ SEM, *n* = 8)

	Placebo	Propranolol	P*	Placebo	Metoprolol	P†	P‡
Cardiac output (l/min)	13.4 $\pm$ 0.7	11.4 $\pm$ 0.6	< 0.005	13.8 $\pm$ 0.7	11.7 $\pm$ 0.6	< 0.001	NS
Heart rate (beats/min)	130 $\pm$ 5	95 $\pm$ 3	< 0.001	127 $\pm$ 4	94 $\pm$ 2	< 0.001	NS
Stroke volume (ml)	105 $\pm$ 7	121 $\pm$ 7	< 0.001	110 $\pm$ 6	125 $\pm$ 8	< 0.05	NS
Systolic pressure (mmHg)	204 $\pm$ 4	161 $\pm$ 5	< 0.001	197 $\pm$ 5	168 $\pm$ 5	< 0.001	0.05 < P < 0.1
Mean arterial pressure (mmHg)	132 $\pm$ 1	113 $\pm$ 2	< 0.001	130 $\pm$ 3	113 $\pm$ 2	< 0.001	NS
Diastolic pressure (mmHg)	97 $\pm$ 2	89 $\pm$ 2	< 0.02	96 $\pm$ 3	86 $\pm$ 2	< 0.01	NS
Total peripheral resistance (units)	10.1 $\pm$ 0.6	10.1 $\pm$ 0.5	NS	9.5 $\pm$ 0.4	9.8 $\pm$ 0.4	NS	NS
$P_{\bar{v}CO_2}$ (mmHg)	66 $\pm$ 1	72 $\pm$ 1	< 0.001	65 $\pm$ 1	72 $\pm$ 1	< 0.001	NS
P_aCO_2 (mmHg)	37 $\pm$ 2	38 $\pm$ 1	NS	36 $\pm$ 2	39 $\pm$ 1	< 0.05	NS
$\dot{V}CO_2 - \dot{V}CO_2$ (ml/100 ml)	11.8 $\pm$ 0.5	13.6 $\pm$ 0.5	< 0.001	11.8 $\pm$ 0.5	13.4 $\pm$ 0.3	< 0.001	NS
$\dot{V}O_2 - \dot{V}O_2$ (ml/100 ml)	12.1 $\pm$ 0.4	14.3 $\pm$ 0.8	< 0.005	12.0 $\pm$ 0.3	13.9 $\pm$ 0.4	< 0.005	NS
$\dot{V}O_2$ (l/min)	1.62 $\pm$ 0.10	1.63 $\pm$ 0.13	NS	1.65 $\pm$ 0.08	1.63 $\pm$ 0.10	NS	NS
$\dot{V}CO_2$ (l/min)	1.58 $\pm$ 0.11	1.54 $\pm$ 0.10	NS	1.64 $\pm$ 0.10	1.57 $\pm$ 0.10	NS	NS
V_t (l)	2.2 $\pm$ 0.2	2.4 $\pm$ 0.2	NS	2.6 $\pm$ 0.3	2.4 $\pm$ 0.2	NS	NS
<i>f</i> (breaths/min)	21 $\pm$ 3	19 $\pm$ 2	NS	20 $\pm$ 3	19 $\pm$ 2	NS	NS

P* Propranolol versus placebo.

P† Metoprolol versus placebo.

P‡ Metoprolol versus propranolol.

NS P > 0.10.

Fig. Changes of haemodynamic indices during exercise after 4 weeks of beta-blockade compared with placebo values.

values of the propranolol and metoprolol periods. Neither beta-blocking agent significantly affected the exercise induced increase of the peak flow rate (Δ PFR).

Ratings of perceived exertion after 4 and 14 minutes of exercise and the simultaneously recorded heart rates are presented in Table 3. Heart rate was clearly decreased during beta-blockade ($P < 0.001$). Neither propranolol nor metoprolol influenced significantly the RPE scores (sign-test).

OBSERVATIONS AFTER 6 MONTHS OF BETA-BLOCKADE

The haemodynamic indices after 6 months of metoprolol medication were comparable with those measured after 4 weeks of metoprolol treatment (Table 4). The cardiac output after 6 months was possibly slightly higher than after 4 weeks of treatment.

The P_{vCO_2} after 6 months was lower and this tendency was also found in the venoarterial CO_2 and

Table 2 Expiratory peak flow rate (PFR) at rest and during exercise after 4 weeks placebo followed by 4 weeks beta-blockade (mean $\pm$ SEM, n = 8)

	Placebo	Propranolol	P*	Placebo	Metoprolol	P†	P‡
PFR at rest (l/min)	563 $\pm$ 21	540 $\pm$ 20	< 0.05	558 $\pm$ 16	557 $\pm$ 16	NS§	NS
PFR during exercise (l/min)	592 $\pm$ 18	568 $\pm$ 20	< 0.05	581 $\pm$ 18	574 $\pm$ 15	NS	NS
Δ PFR (l/min)	29 $\pm$ 7	28 $\pm$ 10	NS	23 $\pm$ 4	18 $\pm$ 6	NS	NS
P exercise versus rest	< 0.01	< 0.05		< 0.001	< 0.05		

P* Placebo versus propranolol.

P† Placebo versus metoprolol.

P‡ Metoprolol versus propranolol.

§ P > 0.10.

Table 3 Ratings of perceived exertion (RPE) and heart rate at 4 and 14 minutes of exercise after 4 weeks placebo followed by 4 weeks beta-blockade (mean $\pm$ SEM, n = 8)

	Placebo	Propranolol	Placebo	Metoprolol
4 Minutes				
RPE	12.0 $\pm$ 0.5	12.0 $\pm$ 0.6	11.5 $\pm$ 0.8	12.0 $\pm$ 0.6
Heart rate	121 $\pm$ 4	90 $\pm$ 2	118 $\pm$ 3	89 $\pm$ 2
14 Minutes				
RPE	13.4 $\pm$ 0.4	13.8 $\pm$ 0.4	12.5 $\pm$ 0.4	13.1 $\pm$ 0.3
Heart rate	134 $\pm$ 4	97 $\pm$ 3	131 $\pm$ 4	95 $\pm$ 2

Table 4 Respiratory and haemodynamic indices during exercise after 4 weeks and 6 months of treatment with metoprolol compared with placebo values (mean $\pm$ SEM, $n = 5$)

	Placebo	4 Weeks	P*	6 Months	P†	P‡
Cardiac output (l/min)	13.4 $\pm$ 1.0	11.2 $\pm$ 0.9	< 0.02	12.2 $\pm$ 0.8	< 0.05	0.05 < P < 0.1
Heart rate (beats/min)	128 $\pm$ 7	93 $\pm$ 3	< 0.01	95 $\pm$ 2	< 0.01	NS
Stroke volume (ml)	106 $\pm$ 10	122 $\pm$ 12	NS	127 $\pm$ 9	< 0.02	NS
Mean arterial pressure (mmHg)	130 $\pm$ 4	112 $\pm$ 3	< 0.01	116 $\pm$ 1	< 0.01	NS
Total peripheral resistance (units)	9.9 $\pm$ 0.5	10.1 $\pm$ 0.6	NS	9.7 $\pm$ 0.6	NS	NS
PvCO ₂ (mmHg)	64 $\pm$ 2	71 $\pm$ 2	< 0.01	67 $\pm$ 1	0.05 < P < 0.1	< 0.05
PaCO ₂ (mmHg)	35 $\pm$ 2	38 $\pm$ 2	< 0.05	36 $\pm$ 2	NS	NS
CvCO ₂ - CaCO ₂ (ml/100 ml)	11.9 $\pm$ 0.7	13.2 $\pm$ 0.8	< 0.05	12.6 $\pm$ 0.5	< 0.05	0.05 < P < 0.1
CaO ₂ - CvO ₂ (ml/100 ml)	11.7 $\pm$ 0.5	13.4 $\pm$ 0.3	< 0.05	12.6 $\pm$ 0.05	NS	0.05 < P < 0.1

P* Metoprolol versus placebo.

P† Metoprolol versus placebo.

P‡ Metoprolol 4 weeks versus metoprolol 6 months.

NS P > 0.10.

O₂ differences. The other respiratory indices and the RPE scores were not changed after 6 months of treatment with metoprolol. The measurements in the two patients after 6 months of propranolol treatment showed results comparable with those after 4 weeks of treatment. These values from only two patients are not compiled statistically.

Discussion

The doses of the two beta-blockers used in this study induced the same reduction in heart rate during exercise. This finding is in agreement with previous results (Johnsson *et al.*, 1975a; Davidson *et al.*, 1976). The drugs were given during a four-week period, which is sufficiently long for evaluation of the anti-hypertensive effect of beta-blockers (Zacharias and Cowen, 1970; Hansson *et al.*, 1974). Our results are in agreement with another study which showed that propranolol and metoprolol equally reduce the blood pressure during exercise (Davidson *et al.*, 1976).

Increased sympathetic activity plays an important role in the adaptation of the circulation during exercise (Bevegård and Shephard, 1967). Beta-blockers decrease the heart rate and cardiac output during exercise. The beta₁-selective metoprolol induced the same changes in heart rate, cardiac output, and stroke volume as the non-selective beta-blocker propranolol. This could be expected, because metoprolol and propranolol both block the cardiac adrenoreceptors. However, the remarkable finding was that both beta-blockers equally reduced the blood pressure. Apparently, there was no difference in the effect of the two drugs on the peripheral resistance which, during exercise, showed no change from the normal.

During exercise total peripheral resistance decreases by vasodilatation in active muscles, and this is induced by a local mechanism (Bevegård and

Shephard, 1967). In other parts of the body such as the 'non-active' muscles a reflex vasoconstriction appears (Bevegård and Shephard, 1967). It was not clear how far vascular beta₂-receptors figured in the vascular adaptation during exercise.

It has been established that propranolol blocks the vascular beta₂-receptors for circulating catecholamines, whereas metoprolol has a much less pronounced effect (Johnsson, 1975; van Herwaarden *et al.*, 1977). The fact that neither the beta₁-selective metoprolol nor the non-selective propranolol influenced the total peripheral resistance shows that stimulation of the vascular beta₂-receptors does not play an important part in the adaptation of the circulation during steady-state exercise.

During exercise bronchodilatation occurs; this may be induced by the increased sympathetic tone (Lefcoe, 1969). A consequence of this is the increase in the expiratory peak flow rate (Δ PF_R) during exercise as recorded in this study. Propranolol decreased the peak flow rate at rest and during exercise, while metoprolol had hardly any influence. Analogous results were published after administration of propranolol and the beta₁-selective practolol (Kumana *et al.*, 1974). These observations are probably related to the fact that metoprolol has a much less pronounced affinity for the bronchiolar beta₂-receptors than propranolol (Johnsson *et al.*, 1975b; Tivenius, 1976). However, the propranolol induced reduction of peak flow rate does not seem of functional significance because ventilation was not influenced; after all, asthmatic patients ventilate during exercise with a smaller tidal volume and faster respiratory rate (Haynes *et al.*, 1976). The increase of the expiratory peak flow rate during exercise was not influenced by propranolol or by metoprolol. Therefore, it seems probable that this bronchodilatation during moderate exercise is not mediated via stimulation of the bronchiolar beta₂-receptors, but via some other mechanism.

The O₂ consumption and the CO₂ production were not influenced by beta-blocking agents. There was an increase in venoarterial O₂ and CO₂ difference, associated with decreased cardiac output and decreased blood flow through the body. The blood is used more intensively as a transport medium during beta-blockade. It is not surprising that propranolol may cause a worsening of claudication (Zacharias, 1976) in patients with peripheral atherosclerosis as a result of sluggish blood flow. Since metoprolol and propranolol both equally influence the circulation during exercise, this adverse effect could be expected also during metoprolol treatment.

Other side effects such as fatigue and muscle weakness (Kellaway, 1976; Zacharias, 1976) may be associated with this decreased blood flow in muscle tissue.

The heart rate during exercise is often used as a measure for the relative load (Holmgren, 1956). Borg (1970) has so chosen the scores of his RPE scale that these multiplied by 10 represent the heart rate. This relation was seen also in our patients during the placebo periods, but was lacking during beta-blockade (Table 3). Both beta-blockers did not influence the RPE scores. This suggests that this moderate exercise was not perceived as being heavier during beta-blockade. On the other hand, this observation supports the idea that other factors besides heart rate influence perceived exertion (Ekblom and Goldbarg, 1971; Noble *et al.*, 1973). In any case the relation between heart rate and perceived exertion appears to be disturbed by beta-blockade (Ekblom and Goldbarg, 1971).

The results after a half year of treatment with metoprolol were not essentially different from those after 4 weeks of medication. Only the cardiac output showed a tendency to return to the initial value of the placebo period. This effect of long-term beta-blocker medication is well known (Tarazi and Dustan, 1972; Atterhög *et al.*, 1977). However, there was no decrease in the total peripheral resistance even after 6 months. Thus it may be that the antihypertensive effect is still caused by a decrease in cardiac output.

As far as their practical use is concerned, this study suggests no advantage for one or the other of these beta-blocking drugs. The investigations of the haemodynamic effects of adrenaline however argue in favour of the use of beta₁-selective blockers rather than non-selective beta-blockers in the treatment of hypertensive patients (van Herwaarden *et al.*, 1977). From a physiological point of view this study does not suggest an important role for the vascular and bronchiolar beta₂-adrenoreceptors in the adaptation of circulation and ventilation to steady state exercise.

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