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 beta₁-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 O₂ consumption, CO₂ production, tidal volume, or respiratory rate. Moreover, they did not influence perceived exertion. These results suggest that the arteriolar and bronchiolar beta₂-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 (Bevegard 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: beta₁ for the cardiac receptors and beta₂ for the arteriolar and bronchiolar receptors.

The beta₁-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; Ablåd et al., 1976; Reybrouck et al., 1977). It is possible, however, that the haemodynamic changes induced by beta₁-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 vaso-dilatation in exercising muscle by blocking the arteriolar beta₂-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 beta₁-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 broncho-dilatation that appears during exercise, by blocking the bronchiolar beta₂-receptors. On the other hand, a beta₁-selective blocker would not hinder this bronchodi-latation (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 vaso-dilatation and bronchodi-latation 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 beta1-selective and a non-selective beta-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, beta-blocker, placebo, beta-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 beta-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®), 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 O2 (Uras) and CO2 (Servomex OA 272) CO2 production (V CO2) and O2 consumption (V O2) were calculated and converted to STPD. Further respiratory rate (f) was measured and tidal volume (Vt) was calculated at BTPS. The arterial CO2 pressure (PaCO2) 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 (PvCO2) was determined indirectly via the rebreathing procedure according to the plateau method of Collier (1956). During this rebreathing procedure CO2 tension of respired gas was continuously recorded by means of a rapid infrared CO2 analyser (Capnograph Godart type MO). The PVCO2 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 (CvCO2 - CaCO2) was calculated by substituting PVCO2 and PA CO2 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 V CO2 by CvCO2 - CaCO2. The venoarterial O2 content
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difference was calculated by dividing the O₂ consumption by the cardiac output. An electrocardiogram was recorded every minute. The blood pressure was measured noninvasively with the Physiometrics SRII. 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 (Mastroapaolo 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 ± SEM. As the values appear to be divided normally, statistical analysis was carried out with Student’s t test for paired observations. The effects of the two beta-blockers were compared with each other and with the placebo period preceding the period with that particular beta-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 beta-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 CO₂ pressure (PvCO₂) increased during both types of beta-blockade, as did the venoarterial O₂ and CO₂ gradients. The arterial CO₂ pressure (PaCO₂) was slightly higher during treatment with metoprolol than during the placebo period. Neither beta-blocking agent caused significant differences in the O₂ consumption (Vo₂), CO₂ production (V̇co₂), tidal volume (Vt), 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>
<thead>
<tr>
<th>Table 1 Respiratory and haemodynamic parameters during exercise after 4 weeks placebo followed by 4 weeks beta-blockade (mean ± SEM, n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
</tr>
<tr>
<td>Systolic pressure (mmHg)</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
</tr>
<tr>
<td>Diastolic pressure (mmHg)</td>
</tr>
<tr>
<td>Total peripheral resistance (units)</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
</tr>
<tr>
<td>CaO₂ - ĊO₂ (ml/100 ml)</td>
</tr>
<tr>
<td>ĊO₂ - ĊO₂ (ml/100 ml)</td>
</tr>
<tr>
<td>Vo₂ (l/min)</td>
</tr>
<tr>
<td>V̇co₂ (l/min)</td>
</tr>
<tr>
<td>V̇t (l/min)</td>
</tr>
<tr>
<td>f (breaths/min)</td>
</tr>
</tbody>
</table>

P* Propranolol versus placebo.

P† Metoprolol versus placebo.

P‡ Metoprolol versus propranolol.

NS P > 0.10.
values of the propranolol and metoprolol periods. Neither beta-blocking agent significantly affected the exercise induced increase of the peak flow rate ($\Delta$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 $P_{\text{v}CO_2}$ after 6 months was lower and this tendency was also found in the venoarterial $CO_2$ and

![Fig. Changes of haemodynamic indices during exercise after 4 weeks of beta-blockade compared with placebo values.](image)

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Propranolol</th>
<th>$P^*$</th>
<th>Placebo</th>
<th>Metoprolol</th>
<th>$P^+$</th>
<th>$P^$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFR at rest (l/min)</td>
<td>563 ± 21</td>
<td>540 ± 20</td>
<td>&lt; 0.05</td>
<td>558 ± 16</td>
<td>557 ± 16</td>
<td>NS§</td>
<td>NS</td>
</tr>
<tr>
<td>PFR during exercise (l/min)</td>
<td>592 ± 18</td>
<td>568 ± 20</td>
<td>&lt; 0.05</td>
<td>581 ± 18</td>
<td>574 ± 15</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>$\Delta$PFR (l/min)</td>
<td>29 ± 7</td>
<td>28 ± 10</td>
<td>NS</td>
<td>23 ± 4</td>
<td>18 ± 6</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>P exercise versus rest</td>
<td>&lt; 0.01</td>
<td>&lt; 0.05</td>
<td></td>
<td>&lt; 0.001</td>
<td>&lt; 0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$P^*$ 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 ± SEM, n = 8)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Propranolol</th>
<th>Placebo</th>
<th>Metoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPE</td>
<td>12.0 ± 0.5</td>
<td>12.0 ± 0.6</td>
<td>11.5 ± 0.8</td>
<td>12.0 ± 0.6</td>
</tr>
<tr>
<td>Heart rate</td>
<td>121 ± 4</td>
<td>90 ± 2</td>
<td>118 ± 3</td>
<td>89 ± 2</td>
</tr>
<tr>
<td>14 Minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPE</td>
<td>13.4 ± 0.4</td>
<td>13.8 ± 0.4</td>
<td>12.5 ± 0.4</td>
<td>13.1 ± 0.3</td>
</tr>
<tr>
<td>Heart rate</td>
<td>134 ± 4</td>
<td>97 ± 3</td>
<td>131 ± 4</td>
<td>95 ± 2</td>
</tr>
</tbody>
</table>

Neither beta-blocking agent significantly affected the exercise induced increase of the peak flow rate ($\Delta$PFR).
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Table 4 Respiratory and haemodynamic indices during exercise after 4 weeks and 6 months of treatment with metoprolol compared with placebo values (mean ± SEM, n = 5)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>4 Weeks</th>
<th>P*</th>
<th>6 Months</th>
<th>P†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output (l/min)</td>
<td>13.4 ± 1.0</td>
<td>11.2 ± 0.9</td>
<td>&lt; 0.02</td>
<td>12.2 ± 0.8</td>
<td>&lt; 0.05</td>
<td>0.05 &lt; P &lt; 0.1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>128 ± 7</td>
<td>93 ± 3</td>
<td>&lt; 0.01</td>
<td>95 ± 2</td>
<td>&lt; 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>106 ± 10</td>
<td>122 ± 12</td>
<td>NS</td>
<td>127 ± 9</td>
<td>&lt; 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>130 ± 4</td>
<td>112 ± 3</td>
<td>&lt; 0.01</td>
<td>116 ± 1</td>
<td>&lt; 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Total peripheral resistance (units)</td>
<td>9.9 ± 0.5</td>
<td>10.1 ± 0.6</td>
<td>NS</td>
<td>9.7 ± 0.6</td>
<td>0.05 &lt; P &lt; 0.1</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pco₂ (mmHg)</td>
<td>64 ± 2</td>
<td>71 ± 2</td>
<td>&lt; 0.01</td>
<td>67 ± 1</td>
<td>0.05 &lt; P &lt; 0.1</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pco₂ (mmHg)</td>
<td>35 ± 2</td>
<td>38 ± 2</td>
<td>&lt; 0.05</td>
<td>36 ± 2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Caco – CaCO₂ (ml/100 ml)</td>
<td>11.9 ± 0.7</td>
<td>13.2 ± 0.8</td>
<td>&lt; 0.05</td>
<td>12.6 ± 0.5</td>
<td>&lt; 0.05</td>
<td>0.05 &lt; P &lt; 0.1</td>
</tr>
<tr>
<td>Cao – CaO₂ (ml/100 ml)</td>
<td>11.7 ± 0.5</td>
<td>13.4 ± 0.3</td>
<td>&lt; 0.05</td>
<td>12.6 ± 0.5</td>
<td>NS</td>
<td>0.05 &lt; P &lt; 0.1</td>
</tr>
</tbody>
</table>

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 reduced the blood pressure during exercise (Davidson et al., 1976).

Increased sympathetic activity plays an important role in the adaptation of the circulation during exercise (Bevegard and Shephard, 1967). In other parts of the body such as the ‘non-active’ muscles a reflex vasoconstriction appears (Bevegard 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 (ΔPFR) 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 bronchial 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 bronchial 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.

Metoprolol was kindly provided by Astra Pharamaceutica Holland as Seloken (= Betaloc = Beloc) tablets.

References


Haynes, R. L., Ingram, R. H., Jr., and McFadden, E. R., Jr. (1976). An assessment of the pulmonary response to exercise in asthma and an analysis of the factors influencing...
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it. American Review of Respiratory Disease, 114, 739-752.


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