Haemodynamic long-term effects of β-receptor-blocking agents in hypertension: a comparison between alprenolol, atenolol, metoprolol and timolol

P. LUND-JOHANSEN AND O. J. OHM
Medical Department A, University of Bergen,
School of Medicine, Bergen, Norway

Summary
1. Oxygen consumption and central haemodynamics were recorded at rest and during exercise in fifty-one men with essential hypertension (W.H.O. stage I) and repeated after 1 year on a single drug: alprenolol (n = 10), atenolol (13) metoprolol (12) and timolol (16).
2. Mean arterial pressure was significantly reduced in all groups at rest (11–18%) and during exercise (5–11%). Heart rate was significantly reduced in all groups (20–28%) at rest and (17–26%) during exercise. Owing to increase in supine resting and exercise stroke volume in the alprenolol and atenolol group, cardiac index decreased less than heart rate—in contrast to the timolol group where cardiac index was decreased 26–32%. The calculated post-treatment total peripheral resistance was significantly increased at rest and during exercise in the timolol group. In the other groups the total peripheral resistance was significantly increased at rest when sitting, but not at rest when supine and during exercise.
3. It is concluded that the major haemodynamic changes induced in subjects with moderate and mild essential hypertension by these different β-receptor blockers are the same, but that minor differences exist with respect to effect upon stroke volume and total peripheral resistance.

Key words: alprenolol, atenolol, exercise, haemodynamics, hypertension, metoprolol, β-receptor blockade, timolol.

Introduction
The circulatory adjustments to long-term therapy with propranolol in hypertension are characterized by a gradual decrease in the total peripheral resistance and an increase in the initially reduced cardiac output (Tarazi & Dustan, 1972). Little is known about the long-term effects of the newer β-receptor blockers, but two studies on timolol have suggested that this drug induces less depression in cardiac output than propranolol (Franciosa, Freis & Conway, 1973; Franciosa & Freis, 1975).

Methods
The study includes fifty-one men, aged 20–58 years, with previously untreated essential hypertension (W.H.O. stage I). After informed consent was obtained the subjects were studied haemodynamically during strictly standardized conditions at rest, supine and sitting and during bicycling at 50, 100 and 150 W. Oxygen consumption (Douglas bag), intra-arterial pressure (brachial artery), heart rate (ECG) and cardiac output (Cardiogreen) were measured in duplicate in each situation (Lund-Johansen, 1967, 1970).

Without being divided into matched groups subjects were then treated with one drug for 11–12 months, and the haemodynamic study was repeated. The difference between the haemodynamic results during the first and second study was tested by Student's t-test.

Mean values for age, body surface area, pretreatment blood pressure and heart rate in the alprenolol (n = 10), atenolol (n = 13), timolol (n = 16) and metoprolol (n = 12) groups were: 37.1, 33.8, 47.4 and 47.8 years; 171/116, 163/103, 171/114 and 170/104 mmHg; 94, 86, 89 and 88 beats/min.

The β-receptor blockers were given as tablets at
07.00 and 17.00 hours (also on re-study day) and the total daily doses were: alprenolol, 1.6-3.2 mmol (400-800 mg); atenolol, 0.43-0.86 mmol (100-200 mg); timolol, 0.03-0.06 mmol (10-20 mg); metoprolol, 0.18-1.11 mmol (50-300 mg).

During the first 3 weeks a few temporary side-effects were seen: muscular fatigue (6), dizziness (2) and cold feet (1).

Results

Details of the four groups have been or will be published elsewhere (Lund-Johansen, 1974a, 1976a, b; P. Lund-Johansen & O. J. Ohm, unpublished observations).

Casual blood pressure and heart rate

Casual blood pressure and heart rate dropped in all subjects during treatment, the mean reductions in the alprenolol, atenolol, timolol and metoprolol groups being: 39/19, 28/16, 29/17 and 25/14 mmHg; 24, 23, 31 and 19 beats/min.

Haemodynamics (Table 1)

Oxygen consumption at rest did not change. The mean values for the pretreatment oxygen consumption at the 50, 100 and 150 W exercise levels were about 550, 750 and 1200 ml min⁻¹ m⁻². The post-treatment values tended to be higher, but the difference was significant only in the timolol group at 100 and 150 W.

The changes in systolic, diastolic and mean arterial pressure were rather similar. Mean arterial pressure was decreased significantly in all groups in all situations, the relative decrease in the alprenolol, atenolol, timolol and metoprolol groups being: 11, 17, 18 and 13% at rest supine, 7, 17, 17 and 11% at rest sitting and 6, 19, 14 and 9% at the 100 W exercise level.

Cardiac index was significantly lower after therapy in all four groups. The individual data showed that the post-treatment cardiac index was lower in all but three subjects. The decrease was greatest at rest sitting (23, 27, 32 and 24%) in the alprenolol, atenolol, timolol and metoprolol groups respectively, corresponding to reductions in cardiac output of 1.5, 1.7, 2.0 and 1.5 l/min. During exercise the reductions in cardiac output were 1.5, 3.0, 4.0 and 2.6 l/min respectively. As oxygen consumption was increased or remained unchanged, this implies an increase in the arteriovenous oxygen difference.

Post-treatment total peripheral resistance index tended to increase in most situations and was significantly increased in the sitting position (21, 9, 21 and 17% in the alprenolol, atenolol, timolol and metoprolol groups respectively). Timolol induced a significant increase in this index in all situations (13% at rest supine and about 20% during exercise).

Heart rate dropped in all subjects in all situations; this was most pronounced (about 28%) in the atenolol and timolol groups. Nine subjects on these drugs had heart rates of <48 beats/min at rest supine. The heart rate during exercise was much lower than normal.

The changes in systolic, diastolic and mean arterial pressure were rather similar. Mean arterial pressure was decreased significantly in all groups in all situations, the relative decrease in the alprenolol, atenolol, timolol and metoprolol groups being: 11, 17, 18 and 13% at rest supine, 7, 17, 17 and 11% at rest sitting and 6, 19, 14 and 9% at the 100 W exercise level.

Cardiac index was significantly lower after therapy in all four groups. The individual data showed that the post-treatment cardiac index was lower in all but three subjects. The decrease was greatest at rest sitting (23, 27, 32 and 24%) in the alprenolol, atenolol, timolol and metoprolol groups respectively, corresponding to reductions in cardiac output of 1.5, 1.7, 2.0 and 1.5 l/min. During exercise the reductions in cardiac output were 1.5, 3.0, 4.0 and 2.6 l/min respectively. As oxygen consumption was increased or remained unchanged, this implies an increase in the arteriovenous oxygen difference.

Post-treatment total peripheral resistance index tended to increase in most situations and was significantly increased in the sitting position (21, 9, 21 and 17% in the alprenolol, atenolol, timolol and metoprolol groups respectively). Timolol induced a significant increase in this index in all situations (13% at rest supine and about 20% during exercise).

Heart rate dropped in all subjects in all situations; this was most pronounced (about 28%) in the atenolol and timolol groups. Nine subjects on these drugs had heart rates of <48 beats/min at rest supine. The heart rate during exercise was much lower than normal.

In the alprenolol and atenolol groups the reductions in heart rate was partly compensated by

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Oxygen consumption (ml min⁻¹ m⁻²)</th>
<th>Heart rate (beats/min)</th>
<th>Cardiac index (l min⁻¹ m⁻²)</th>
<th>Stroke index (ml/m²)</th>
<th>Mean arterial pressure (mmHg)</th>
<th>Total peripheral resistance index (kPa s l⁻¹ m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprenolol</td>
<td>10 B</td>
<td>148 ± 13</td>
<td>83 ± 11</td>
<td>3.2 ± 0.5</td>
<td>38.9 ± 5.6</td>
<td>124 ± 15</td>
<td>313 ± 42</td>
</tr>
<tr>
<td>Atenolol</td>
<td>13 B</td>
<td>150 ± 21</td>
<td>79 ± 15</td>
<td>3.3 ± 0.9</td>
<td>41.1 ± 5.5</td>
<td>122 ± 7</td>
<td>315 ± 71</td>
</tr>
<tr>
<td>Timolol</td>
<td>16 B</td>
<td>145 ± 14</td>
<td>75 ± 9</td>
<td>3.1 ± 0.5</td>
<td>41.2 ± 5.4</td>
<td>127 ± 10</td>
<td>336 ± 51</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>12 B</td>
<td>150 ± 12</td>
<td>83 ± 14</td>
<td>3.2 ± 0.6</td>
<td>39.3 ± 6.5</td>
<td>125 ± 14</td>
<td>321 ± 65</td>
</tr>
</tbody>
</table>

TABLE 1. Haemodynamics at rest when sitting before (B) and during (D) therapy

Results are shown as mean values ± SD.
greater post-treatment stroke index at rest when supine and during exercise. At rest when sitting, however, the stroke index in all groups was practically unchanged and consequently the cardiac index was reduced in proportion to the heart rate.

Discussion

Only four of fifty-one subjects showed a reduction in casual diastolic arterial pressure of less than 10 mmHg and with this criterion almost all were therefore 'responders'. The pressure reduction was less with alprenolol than the three other drugs. Other groups have found a similar blood pressure reduction with a mean dose of 460 mg of alprenolol and 24 mg of timolol, but a greater reduction in heart rate at rest with timolol (Morgan, Sabto, Anavekar, Louis & Doyle, 1974).

The reduction in blood pressure and heart rate obtained by atenolol and timolol are similar to those reported by Hansson, Åberg, Karlberg & Westerlund (1975) and by Morgan et al. (1974).

The study of haemodynamic mechanisms demonstrated that in all four groups the blood pressure drop was associated with a pronounced decrease in heart rate and cardiac output at rest as well as during exercise. Reduced cardiac output on 'long-term' therapy with propranolol has been reported by others, after 4 weeks (Hansson, 1973), after 5 weeks (Franciosa et al., 1973), after 10 months (Frohlich, Tarazi, Dustan & Page, 1968) and after 20 months (Tarazi & Dustan, 1972).

The changes induced by atenolol resemble those reported in a short-term study by Amery, Billet, Joossens, Meekers, Reybrouck & van Mieghem (1973). It was not possible to confirm the observations by Franciosa et al. (1973) and Franciosa & Freis (1975), which suggest that there is no reduction in cardiac output with long-term use of timolol. In the last of these studies mean arterial pressure was reduced by only 6% and cardiac output decreased 5% (not significant) in spite of 40 mg of timolol daily.

The post-treatment total peripheral resistance index tended to be increased, but was significantly changed only in the timolol group. In this respect the long-term effects of the β-receptor blockers in essential hypertension differ from the long-term effects of the thiazide diuretics (Lund-Johansen 1970) and peripheral vasodilators like prazosin (Lund-Johansen, 1974b).

References


