Haemodynamic and metabolic effects of α-adrenoceptor blockade with phentolamine at rest and during forearm exercise

O. J. HARTLING AND J. TRAP-JENSEN
Department of Clinical Physiology, Glostrup Hospital, and Department of Clinical Physiology, Frederiksberg Hospital, Copenhagen, Denmark

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Summary
1. The pre- and post-junctional α-adrenoceptor blocking agent, phentolamine, was given by intravenous infusion to eight healthy volunteers during rest, forearm exercise and post-exercise.

2. Phentolamine produced a sustained increase in heart rate. The diastolic blood pressure decreased slightly whereas systolic and mean blood pressures remained unchanged. Phentolamine caused a marked increase in the forearm blood flow and a decrease in vascular resistance at rest and post-exercise, but did not influence the blood flow or vascular resistance in the exercising forearm.

3. There was a small increase in arterial blood glucose concentration, and a decrease in blood alanine concentration during drug infusion. Blood lactate was not affected by phentolamine. The arterial concentrations of free fatty acids and glycerol increased, and the concentration of triglycerides decreased during phentolamine infusion.

4. Forearm exchange of glucose, lactate, alanine, glycerol, free fatty acids, triglycerides and forearm oxygen consumption were not changed significantly.

5. These findings corroborate the concept that α-adrenoceptor induced vasoconstriction plays a subordinate role in exercising skeletal muscle. All of the metabolic findings might be explained as secondary to an increased noradrenaline release during phentolamine infusion.

Key words: alanine, adrenergic α-receptor blockade, blood pressure, exercise, fatty acids, glucose, glycerol, heart rate, forearm, lactate, oxygen consumption, phentolamine, triglycerides, vascular resistance.

Introduction
In peripheral blood vessels innervated by sympathetic neurons, stimulation of postjunctional α-adrenoceptors brings about contraction of the vascular smooth muscle cells. Conversely, α-adrenoceptor blocking agents produce peripheral vasodilatation through blockade of the vascular α-adrenoceptors. The vasodilatating effect of an α-adrenoceptor blocking agent may be expected to disappear when adrenergic vasoconstrictor activity recedes in an exercising muscle group.

Prazosin and phentolamine are competitive postjunctional α-adrenoceptor blocking drugs [1, 2]. Phentolamine also blocks prejunctional α-adrenoceptors, thus increasing the release of noradrenaline from sympathetic nerve endings [3]. Several studies have demonstrated the vasodilator effect of phentolamine [4–7]. A study on digital arteries in vitro showed that phentolamine competitively and phenoxybenzamine non-competitively antagonized the vasoconstriction induced by α-adrenoceptor stimulation with noradrenaline but phentolamine had no effect on the non-specific vasoconstrictor activity of barium chloride [8].

In the present study phentolamine was administered by intravenous infusion to young healthy subjects to assess its haemodynamic and metabolic effects at rest and during forearm exercise.

Methods
Subjects
The study involved eight healthy non-obese men. Median weight was 70 kg (range 60–79 kg),
median age 28 years (range 19-38 years). The subjects consented to participate in the study having been informed of its nature, purpose and possible risks. The study complied with the code of ethics of the Declaration of Helsinki. Some days before the investigation we tested each subject's working capacity on a springloaded hand ergometer [9] adjusted so that the work load could be performed for 10 min. On the same occasion, the subjects were familiarized with the laboratory surroundings and the techniques and personnel involved in the investigation.

Techniques

By the Seldinger technique a polyethylene catheter (inner diameter 0.61 mm) was inserted percutaneously in the right brachial artery at the level of the humeral intercondylar line and was advanced 5 cm upstream. A Teflon catheter was inserted into a deep cubital vein of the right arm, and was advanced 5 cm in the distal direction. The arterial catheter was kept patent by injecting small amounts of sodium chloride solution (154 mmol/l: saline). The venous catheter was infused with saline at a rate of 0.55 ml/min. Heparin was not used.

Forearm blood flow at rest was measured by means of venous occlusion strain-gauge plethysmography, with a collecting pressure of 50 mmHg, and during forearm exercise by the indicator-dilution technique after an intra-arterial bolus injection of $^{131}$I-labelled human albumin [10]. The bolus volume was 0.8 ml containing about 2 μCi of $^{131}$I-labelled albumin. To protect the thyroid gland from possible free $^{131}$I the subjects were given 100 mg of potassium iodide tablets thrice daily on the day before and on the day of the study. The forearm volume was determined by water displacement.

Intra-arterial blood pressure was continuously recorded, except when blood samples were collected, with an Elema-Schönander EMT 35 pressure transducer. ECG was continuously recorded on a direct writing recorder. Forearm vascular resistance was calculated by dividing the mean blood pressure by the blood flow.

Blood samples for the determination of oxygen saturation and substrate concentrations were collected simultaneously from the brachial artery and the deep vein. Blood oxygen saturation and haemoglobin concentration were determined spectrophotometrically, and packed cell volume was determined by centrifugation [11]. Blood glucose, lactate, alanine and glycerol were determined enzymatically in aliquots of arterial and venous blood. Samples were deproteinized in ice-cold perchloric acid immediately after collection [11-13]. Free fatty acids and triglycerides were determined in serum [11]. One minute before each blood sample was taken a wrist cuff was inflated to a suprasystolic pressure and was maintained at this level during the sampling and subsequent blood flow measurement to exclude the hand from the circulation.

Procedure

The subject arrived at the laboratory in the morning after an overnight fast and not having smoked for 12 h. The study was performed in an air-conditioned room maintained at 21 ± 1°C. After we had placed the intravascular catheters, the subject rested recumbently for half an hour. During a subsequent period of 30 min supine rest forearm blood flow was measured, and at the end of this period blood samples were collected. Then the subjects, remaining in the supine position, performed right forearm dynamic exercise for 10 min at a rate of 50 contractions/min (range of hand ergometer work load 1.0-1.3 W). During the last 4 min of exercise a wrist cuff was inflated to suprasystolic pressure. After a recovery period of 30 min a priming dose of 5 mg of phentolamine was given intravenously in the course of 2 min, followed by infusion at a rate of 0.44 mg/min during the rest of the study, that is 30 min rest, 10 min forearm exercise and 30 min recovery. Thus the total dose of phentolamine amounted to about 35 mg. In the control period and after the start of phentolamine infusion, blood samples were collected repeatedly at rest, during exercise and during recovery.

Statistical analysis

The significance of differences between paired observations was tested by Student’s t-test [14]. To compare time curves a two-way analysis of variance was employed with correction for correlated errors [14, 15]. Differences were considered to be significant if a 2P value below 0.05 was obtained, denoted as P<0.05.

Results

The intravenous infusion of phentolamine caused an increase in the heart rate throughout the study (Fig. 1). The mean blood pressure did not change significantly except at the end of the exercise period, where a slight fall in mean blood pressure occurred (Table I). Systolic blood pressure was unchanged by phentolamine, but there was a small decrease in diastolic blood pressure (Fig. 1).

During phentolamine infusion forearm blood flow increased at rest ($P<0.01$) and in the recovery...
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Arterial blood pressure, forearm blood flow, forearm vascular resistance and forearm exchange of substrates before and during phentolamine infusion.

Table 1. Group mean values ± SEM are presented. A negative value means a net release of the substrate. Significance of differences between values before and during phentolamine infusion: *P < 0.05; **P < 0.01.

<table>
<thead>
<tr>
<th></th>
<th>Rest</th>
<th>Exercise</th>
<th>Recovery (10 min)</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Before</td>
<td>87.1 ± 10.1</td>
<td>103.5 ± 9.93</td>
<td>84.4 ± 9.90</td>
<td>85.8 ± 8.17</td>
</tr>
<tr>
<td>During</td>
<td>85.6 ± 8.73</td>
<td>98.4 ± 11.2</td>
<td>82.1 ± 12.0</td>
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</tr>
<tr>
<td>Blood flow (ml min⁻¹ 100 ml⁻¹)</td>
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<td></td>
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</tr>
<tr>
<td>Before</td>
<td>4.05 ± 1.93</td>
<td>29.6 ± 5.18</td>
<td>9.13 ± 3.08</td>
<td>6.41 ± 2.53</td>
</tr>
<tr>
<td>During</td>
<td>7.64** ± 3.69</td>
<td>28.5 ± 4.32</td>
<td>9.95 ± 3.53</td>
<td>15.7 ± 7.04</td>
</tr>
<tr>
<td>Vascular resistance (g ml⁻¹ min 100 ml⁻¹)</td>
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<tr>
<td>Before</td>
<td>25.5 ± 11.0</td>
<td>3.52 ± 0.697</td>
<td>10.8 ± 5.90</td>
<td>15.7 ± 7.04</td>
</tr>
<tr>
<td>During</td>
<td>13.8** ± 7.26</td>
<td>3.46 ± 0.558</td>
<td>9.62 ± 4.89</td>
<td>9.14 ± 3.64</td>
</tr>
<tr>
<td>Oxygen uptake (ml min⁻¹ 100 ml⁻¹)</td>
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</tr>
<tr>
<td>Before</td>
<td>10.5 ± 4.10</td>
<td>154.9 ± 32.5</td>
<td>14.3 ± 8.15</td>
<td>1.59 ± 2.90</td>
</tr>
<tr>
<td>During</td>
<td>12.7 ± 4.20</td>
<td>147.9 ± 23.3</td>
<td>11.4 ± 4.40</td>
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</tr>
<tr>
<td>Glucose uptake (pmol min⁻¹ 100 ml⁻¹)</td>
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<td></td>
<td></td>
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<tr>
<td>Before</td>
<td>1.43 ± 0.80</td>
<td>10.2 ± 6.66</td>
<td>2.91 ± 2.63</td>
<td></td>
</tr>
<tr>
<td>During</td>
<td>1.44 ± 1.15</td>
<td>6.59 ± 3.11</td>
<td>2.83 ± 2.21</td>
<td></td>
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<tr>
<td>Lactate uptake (pmol min⁻¹ 100 ml⁻¹)</td>
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<tr>
<td>Before</td>
<td>-0.24 ± 0.23</td>
<td>-0.86 ± 0.36</td>
<td>-43.1 ± 12.4</td>
<td>-0.77 ± 0.19</td>
</tr>
<tr>
<td>During</td>
<td>-0.02 ± 0.012</td>
<td>-0.02 ± 0.013</td>
<td>-0.02 ± 0.015</td>
<td>-0.01 ± 0.033</td>
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<tr>
<td>Alanine uptake (pmol min⁻¹ 100 ml⁻¹)</td>
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<tr>
<td>Before</td>
<td>-0.02 ± 0.03</td>
<td>-0.171 ± 0.127</td>
<td>-0.134 ± 0.034</td>
<td>-0.03 ± 0.012</td>
</tr>
<tr>
<td>During</td>
<td>-0.02 ± 0.003</td>
<td>-0.139 ± 0.057</td>
<td>-0.143 ± 0.031</td>
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<tr>
<td>Glucose uptake (pmol min⁻¹ 100 ml⁻¹)</td>
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<tr>
<td>Before</td>
<td>0.30* ± 0.38</td>
<td>0.00 ± 1.27</td>
<td>0.18 ± 0.36</td>
<td>0.04 ± 0.27</td>
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<tr>
<td>During</td>
<td>0.38 ± 0.31</td>
<td>0.84 ± 1.89</td>
<td>0.30 ± 0.48</td>
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<tr>
<td>Triglyceride uptake (pmol min⁻¹ 100 ml⁻¹)</td>
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<tr>
<td>Before</td>
<td>0.29 ± 0.16</td>
<td>1.58 ± 2.46</td>
<td>0.25 ± 0.36</td>
<td>0.25 ± 0.27</td>
</tr>
<tr>
<td>During</td>
<td>0.08 ± 0.30</td>
<td>0.15 ± 1.49</td>
<td>0.27 ± 0.27</td>
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</table>
Effects of α-adrenoceptor blockade

The hypotensive effect of phentolamine is augmented when reflex cardiac activity is blocked with a β-adrenoceptor antagonist [24]. Likewise, combined blockade of α- and β-adrenoceptors with labetalol produced a clear-cut blood pressure reduction both in normal subjects and in hypertensive patients [10, 28].

Metabolic effects

There was a slight and persistent increase in blood glucose concentration during phentolamine infusion. This was not explained by a decrease in peripheral (forearm) glucose uptake. Although phentolamine might be expected to reduce blood glucose concentration, because insulin release from pancreatic islets is increased during α-adrenoceptor blockade [29–30], several studies have shown an unchanged blood glucose during intravenous phentolamine infusion [26, 27, 29, 30]. Also, Galbo et al. [25] found a significantly increased glucose concentration after exhaustive exercise during phentolamine infusion in healthy volunteers. Moreover, Ratzmann et al. [31] and Cerasi et al. [32] reported a lower carbohydrate tolerance in normal subjects during phentolamine infusion.

The increased blood glucose concentration can be explained by an increased hepatic glycogenolysis.
and gluconeogenesis induced by noradrenaline [3, 25, 26, 33]. Thus the finding of a decrease in blood alanine concentration during phentolamine infusion may reflect an increased gluconeogenesis, because alanine is quantitatively the most important gluconeogenic amino acid [34]. Forearm release of alanine during phentolamine was not changed, consonant with findings in isolated skeletal muscle [35].

The increased serum concentration of free fatty acids and glycerol, and the decreased concentration of triglycerides suggested an increased lipolysis. This agrees with previous results [25, 27, 29]. Human adipose tissue possesses both α- and β-adrenoceptors [25, 27, 29, 36, 37]. Stimulation of α-adrenoceptors inhibits and stimulation of β-adrenoceptors activates triglyceride lipase, but the α-adrenoceptors are less important than the β-adrenoceptors [37]. In isolated human fat cells phentolamine exerted no lipolytic effect when given alone, but when it was given together with noradrenaline there was a marked lipolysis [36]. Presumably, blockade of α-adrenoceptors by phentolamine renders the β-adrenoceptor-mediated lipolytic effect of noradrenaline unopposed. Therefore the lipolytic effect of phentolamine in vivo is probably indirect and due to noradrenaline released by phentolamine [3, 25, 26].

Acknowledgments

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References


Effects of α-adrenoceptor blockade


