Effect of timolol maleate on pacing induced myocardial ischaemia

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SUMMARY The effects of timolol maleate administered intravenously on coronary and systemic haemodynamics, myocardial metabolism, and plasma catecholamine concentrations were assessed in 10 patients with confirmed coronary artery disease. Rapid atrial pacing to the onset of angina was performed in all patients. Timolol reduced cardiac output at rest and during pacing and reduced resting heart rate but did not affect arterial blood pressure. Left ventricular stroke work index fell during pacing. Coronary sinus blood flow was unchanged, but pulmonary artery diastolic pressure rose after timolol. The drug produced clinical improvement in nine of the 10 patients with prolongation of the mean pacing time to angina. There was evidence of improved myocardial metabolism with a change from production to extraction of lactate: Arterial noradrenaline concentrations at rest rose after timolol.

In these patients with coronary artery disease timolol produced an increased tolerance to atrial pacing stress, which appears to be due to a combination of effects including reduced myocardial contractility and decreased lipolysis.

The symptomatic benefits of beta adrenergic blocking agents in angina pectoris have resulted in their widespread use in patients with coronary artery disease. This beneficial role in the treatment of myocardial ischaemia has variously been attributed to the reduction of exercise induced increase in heart rate and systolic blood pressure, the reduction of myocardial contractility, the redistribution of coronary blood flows, and an effect on metabolic factors. There is considerable variance in published reports as to the relative importance of these mechanisms. More recently, these agents have been advocated in the treatment of survivors of myocardial infarction.

Timolol maleate is a non-selective beta adrenergic blocking agent which has been shown to reduce mortality and reinfarction in patients surviving acute myocardial infarction, and to reduce infarct size when given within four hours of the onset of chest pain. It is effective in the treatment of angina pectoris. Like other such agents, however, its precise mode of action has not been defined. This study examines the effect of acute timolol administration on haemodynamic and metabolic changes and circulating catecholamine concentrations in 10 patients with confirmed coronary heart disease.

Patients and methods

Ten patients with confirmed coronary artery disease and stable angina pectoris were studied. All had symptoms in the New York Heart Association function class II or III. Table 1 gives the details of individual patients. The patients had received no cardioactive drugs for at least 48 hours before the study and for 72 hours in the case of beta adrenergic blocking agents. None had renal or hepatic disease or clinical or radiological evidence of heart failure. Studies were performed after food and without premedication, and all patients were studied during normal sinus rhythm. In all cases written informed consent was obtained before the study, approval for the study having been obtained from the hospital ethical committee.

A Swan Ganz thermodilution catheter was positioned in the pulmonary artery for measurement of cardiac output and right atrial and pulmonary artery pressures. A thermodilution catheter (Wilton-Webster Laboratory) was placed in the mid-
Effect of timolol on myocardial ischaemia

Table 1 Clinical characteristics of 10 patients with coronary artery disease

<table>
<thead>
<tr>
<th>Case No</th>
<th>Age (yr)</th>
<th>NYHA class</th>
<th>NYHA</th>
<th>Coronary artery with luminal stenosis &gt;75%</th>
<th>Left ventricular function</th>
<th>LVEF (%)</th>
<th>LVEDP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64 M</td>
<td>II</td>
<td>LAD</td>
<td>Minor anterior wall hypokinesia</td>
<td></td>
<td>70</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>64 M</td>
<td>III</td>
<td>LAD, Cx, RCA</td>
<td>Anterior wall dyskinesia, inferior wall hypokinesia</td>
<td></td>
<td>53</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>46 M</td>
<td>III</td>
<td>LAD, Cx</td>
<td>Normal</td>
<td></td>
<td>72</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>63 M</td>
<td>III</td>
<td>LAD, Cx, RCA</td>
<td>Anterior and inferior wall hypokinesia</td>
<td></td>
<td>48</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>54 M</td>
<td>II</td>
<td>LAD</td>
<td>Anteroapical dyskinesia</td>
<td></td>
<td>58</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>49 M</td>
<td>III</td>
<td>LAD, Cx, RCA</td>
<td>Normal</td>
<td></td>
<td>72</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>56 M</td>
<td>II</td>
<td>LAD</td>
<td>Normal</td>
<td></td>
<td>69</td>
<td>4</td>
</tr>
<tr>
<td>8</td>
<td>52 M</td>
<td>II</td>
<td>LAD</td>
<td>Anterior wall hypokinesia</td>
<td></td>
<td>64</td>
<td>4</td>
</tr>
<tr>
<td>9</td>
<td>54 M</td>
<td>II</td>
<td>LAD</td>
<td>Normal</td>
<td></td>
<td>72</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>58 M</td>
<td>III</td>
<td>LAD, Cx, RCA</td>
<td>Anterior and inferior wall hypokinesia</td>
<td></td>
<td>50</td>
<td>12</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; LAD, left anterior descending; Cx, circumflex; RCA, right coronary artery; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end diastolic pressure.

portion of the coronary sinus, its position confirmed by the injection of radio-opaque dye. This allowed measurement of coronary sinus blood flow by the continuous thermodilution method and also sampling of coronary venous blood. Arterial pressure was monitored and blood samples obtained through a 19 gauge needle positioned in the femoral artery. All pressures were measured with reference to the mid-chest and were recorded with an electrocardiogram on a Mingograph 82 recorder (Siemens). No heparin was given, and the catheters were flushed with saline.

After placement of the catheters the patients were permitted to rest for 20 minutes, and control haemodynamic measurements were then obtained. At the same time blood samples were withdrawn from the coronary sinus and femoral artery for later biochemical analysis. Atrial pacing was then started and the rate rapidly increased to 85% of maximum predicted heart rate for the individual patient. At the time of onset of angina, haemodynamic measurements were repeated and blood samples withdrawn before atrial pacing was stopped.

After a rest period of 20 minutes timolol maleate 2 mg was given intravenously over 10 minutes. After a further 20 minutes rest haemodynamic measurements and blood sampling were repeated. Atrial pacing was then restarted at the same rate as in the control period. At an equivalent time to that at which angina occurred during control, pacing measurements were repeated and then pacing continued to the onset of angina.

Arterial and coronary sinus blood samples were assayed for whole blood lactate, glucose, plasma free fatty acids, and noradrenaline. Whole blood oxygen and haemoglobin concentrations were measured using a radiometer OSM2 haemoximeter. Myocardial extraction ratios for each substrate were derived by dividing the arterial-coronary sinus difference by the arterial level expressed as a percentage.

STATISTICAL ANALYSIS
The data at rest and during pacing before and after timolol administration were compared with Student's t test for paired data. Values are expressed as mean (SEM).

Results

PACING TIME TO ANGINA
All 10 patients experienced typical angina pectoris during control atrial pacing. After the administration of timolol the pacing time to angina was prolonged in nine patients and remained unchanged in one (Figure). The mean (SEM) pacing time to angina for the group increased from 199 (96) to 389 (75) s (p<0.01).

Figure: Effect of timolol (2 mg intravenously) on pacing time to angina in 10 patients with coronary artery disease. Mean (SEM) values before timolol 199 (96) s; after timolol 389 (75) s (p<0.01).
HAEMODYNAMIC RESPONSES

After timolol administration heart rate fell at rest from 71.3 (2.6) to 64.6 (1.5) beats/minute (Table 2). No change in either systolic, diastolic, or mean arterial blood pressure occurred either at rest or during pacing with the drug. Right atrial pressure also remained unchanged. Pulmonary artery diastolic pressure, an indirect measurement of left ventricular end diastolic pressure, showed a small but significant rise at rest with the drug. There were no changes in the pacing values of this variable. Cardiac output fell significantly with the drug both at rest (6.2 (0.4) to 5.3 (0.4) l/min, p<0.02) and during atrial pacing (6.7 (0.4) to 5.6 (0.3) l/min, p<0.001). While a similar trend was seen in stroke volume only the pacing value was significantly less after the drug (p<0.001). Although the expected increase in coronary sinus blood flow was seen between resting values and those at peak pacing, neither the resting nor pacing values were significantly changed by timolol. Similarly, coronary vascular resistance remained unchanged.

Total systemic vascular resistance rose both at rest (15.4 (1) to 18.1 (1.5) units, p<0.05) and during pacing (16.3 (1.2) to 18.7 (1.4) units, p<0.01). Stroke work index showed a small but insignificant fall at rest after timolol but fell significantly during pacing (32.5 (2.8) to 26.6 (2.6) g m per m², p<0.01). Owing to the effect of heart rate, the rate pressure product fell significantly at rest but not during pacing (p<0.02).

METABOLIC RESPONSES

No significant change was seen in arterial lactate concentration after timolol, but the myocardial extraction ratio of lactate during pacing was significantly improved after the drug (−26 (16) to 7.3 (7.7)%, P<0.05) (Table 3). The arterial concentration of free fatty acids showed a trend towards reduction after the drug, although neither the resting nor pacing values were significantly different. A similar trend was seen for myocardial extraction of free fatty acids. Again, no significant changes in glucose arterial concentration or extraction ratios occurred. The coronary sinus oxygen

Table 2  Haemodynamic responses before and after timolol administration at rest and during atrial pacing in 10 patients. Values are mean (SEM)

<table>
<thead>
<tr>
<th></th>
<th>Before (control)</th>
<th>Pacing</th>
<th>After</th>
<th>Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>71.3 (2.6)</td>
<td>64.6 (1.5)**</td>
<td>139 (2.3)</td>
<td>144 (0.5)***</td>
</tr>
<tr>
<td>Arterial blood pressure (mm Hg):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>144.7 (8)</td>
<td></td>
<td>144.5 (8)</td>
<td>141.6</td>
</tr>
<tr>
<td>Diastolic</td>
<td>72.4 (3)</td>
<td></td>
<td>73.7 (4)</td>
<td>89 (3)</td>
</tr>
<tr>
<td>Pulmonary artery diastolic pressure (mm Hg)</td>
<td>6.2 (1)</td>
<td>6.7 (0.4)</td>
<td>7.6 (1)**</td>
<td>13.4 (2)</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>3.7 (0.6)</td>
<td>4.2 (0.6)</td>
<td>3.6 (0.6)</td>
<td>4.6 (0.7)</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>6.2 (0.4)</td>
<td></td>
<td>5.3 (0.4)**</td>
<td>5.6 (0.3)**</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>87 (5.5)</td>
<td>48 (3)</td>
<td>83 (5)</td>
<td>41 (2.4)**</td>
</tr>
<tr>
<td>Coronary sinus blood flow (ml/min)</td>
<td>143 (13)</td>
<td>226.7 (17)</td>
<td>143.9 (12)</td>
<td>209 (12.9)</td>
</tr>
<tr>
<td>Mean right atrial pressure (mm Hg)</td>
<td>7.7 (1.5)*</td>
<td>18.1 (1.5)**</td>
<td>18.7 (1.4)***</td>
<td></td>
</tr>
<tr>
<td>Coronary vascular resistance (units)</td>
<td>6.1 (0.4)</td>
<td>6.7 (0.4)</td>
<td>5.3 (0.4)**</td>
<td>5.6 (0.3)**</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>6.2 (0.4)</td>
<td></td>
<td>5.3 (0.4)**</td>
<td>5.6 (0.3)**</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>87 (5.5)</td>
<td>48 (3)</td>
<td>83 (5)</td>
<td>41 (2.4)**</td>
</tr>
<tr>
<td>Rate pressure product (mm Hg beats/min)</td>
<td>10.3 (0.7)</td>
<td>20.2 (0.8)</td>
<td>9.4 (0.6)**</td>
<td>19.6 (0.8)</td>
</tr>
</tbody>
</table>

Significance of changes with respect to control values: *p<0.05, **p<0.02, ***p<0.01, ****p<0.001.
saturation rose significantly at rest after the drug (p<0.02), but no change was seen during pacing. Myocardial oxygen consumption fell slightly after the drug, but the small changes were not significant.

CATECHOLAMINE RESPONSE
The resting arterial noradrenaline concentration showed a rise after timolol from 241.2±58 to 357.8±98 ng/l (1425±5 (342±8) to 2114±6 (579±2) pmol/l) (p<0.05). A similar but insignificant trend occurred during atrial pacing after the drug.

Discussion
Timolol maleate is a non-selective beta adrenergic blocking agent of proved efficacy in the treatment of angina pectoris11,18 and mild to moderate hypertension19 and in reducing mortality after myocardial infarction.6 Although similar in its properties to propranolol, except for its lack of membrane stabilising activity, it is less negatively inotropic than propranolol in a dose that produces equipotent beta adrenergic blockade.20 This study shows that in a group of patients with confirmed coronary artery disease, timolol increased tolerance to atrial pacing and improved myocardial metabolism. Such improvement could theoretically have been due to several effects attributable to beta blockade—namely, reduced myocardial oxygen consumption secondary to haemodynamic effects, changes in myocardial perfusion, or direct metabolic effects of the drug.

The rate pressure product is a sensitive index of the level of myocardial oxygen consumption.21 Whereas timolol reduced this at rest owing to a fall in heart rate, the pacing values for rate pressure product at the onset of angina were similar before and after the drug. Similarly, neither resting nor pacing values of arterial blood pressure were significantly changed. The other major determinants of myocardial oxygen demand are contractility and left ventricular wall tension.22 Although the study design did not allow direct measurement of these indices, cardiac output fell after timolol by approximately 16% with a significant fall in stroke volume on pacing (p<0.001). These changes suggest a reduction in myocardial contractility. Such interpretation is open to criticism, especially in the face of a rise in systemic vascular resistance. This rise, however, was more likely to have been due to the baroreceptor reflex response to the fall in cardiac output rather than to blockade of vascular beta₂ receptors,23 since a similar response has been shown for the beta₂ selective receptor blockers metoprolol and atenolol.

Despite the fall in resting heart rate, probable reduction in contractility both at rest and during pacing, and fall in left ventricular stroke work index on pacing myocardial oxygen consumption did not fall significantly in these patients after timolol. A small trend towards reduced oxygen consumption was seen, and this together with increased coronary sinus oxygen saturation at rest, despite unchanged coronary sinus blood flow, could be interpreted as indicating reduced oxygen demand. Similar studies with other beta adrenergic blocking agents5,24 have, however, failed to show reduced myocardial oxygen consumption despite improvement in symptoms and myocardial metabolism. It is likely that the benefits of decreased contractility are partially counterbalanced by the increase in left ventricular volume that occurs with these agents. This is supported by the small but significant rise in left ventricular filling pressure that occurred at rest after timolol.

No change in global coronary perfusion was seen after timolol. Although redistribution of blood flow to ischaemic areas of the myocardium has been suggested as a mode of action of beta blocking agents,5 this study did not include examination of such possible effects.

Beta blocking agents can partially inhibit both peripheral25 and myocardial26 lipolysis, lessen the inhibitory effect of fatty acids on myocardial pyruvate metabolism, and cause a preferential shift to metabolism of other substrates such as lactate.27 Such an effect has been suggested to contribute to the efficacy of propranolol6 and atenolol23 in the relief of angina. In this study, however, timolol caused a small but statistically insignificant fall in arterial concentration and myocardial extraction of free fatty acids. The extent of this fall is unlikely to completely explain the improvement in lactate metabolism but cannot be discounted as having made some contribution to the overall effect of the drug.

The resting plasma noradrenaline concentrations in these patients were similar to those previously described in ischaemic heart disease.28 A small rise in the arterial noradrenaline concentration was seen after timolol both at rest and during pacing, although the pacing values did not reach statistical significance. A similar increase in plasma noradrenaline has been described after propranolol both in ischaemic29 and hypertensive30 patients and is probably the result of activation of the sympathoadrenal system by the decrease in cardiac output after beta blockade. Any potentially deleterious effect of this rise, such as increased lipolysis, appears to have been prevented by timolol.

The negative chronotropic effect of timolol maleate, as with other beta adrenergic blocking agents, is of prime importance in the prevention of exercise induced angina pectoris. In this atrial pacing study benefits other than that due to heart rate reduction were seen after the administration of intravenous timolol. The improvement in myocardial metabolism...
at an equivalent pacing time appears to be due to the combined effects of reduced contractility and decreased lipolysis brought about by the drug. The broad profile of this non-selective beta adrenergic blocking agent emphasises its role in the treatment of myocardial ischaemia in its various clinical situations.

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References


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