Low-dose propranolol for the protection of the left ventricle from ischaemic damage

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ABSTRACT Global myocardial ischaemia improves intracardiac operating conditions but damages the myocardium. Propranolol should reduce this damage but may impair postoperative myocardial contractility. An assessment of its protective effect during 90 minutes of normothermic ischaemia in canine hearts has been made. The early and late changes of contractility caused by low-dose propranolol were also recorded. A comparison of cardiac isovolumic contractile force, velocity, and compliance was made in three groups of dogs given 30 μg/kg of propranolol with or without 90 minutes of cardiac ischaemia, or cardiac ischaemia without propranolol. Contractile force and velocity were significantly reduced by the propranolol, but recovered fully after 90 minutes. Ischaemia without propranolol reduced force and velocity of contraction significantly more than ischaemia with propranolol. Propranolol thus reduces operative ischaemic damage without itself impairing postoperative function.

There is an immediate need for a perfect method of intraoperative myocardial preservation,1 but this has not yet been achieved, and it is likely that there will have to be a compromise between allowing easy working conditions and minimising ischaemic myocardial damage. Propranolol lowers myocardial oxygen demands, but it does so by reduction of myocardial contractility which could prejudice postoperative recovery.

Myocardial ischaemia results in the release of catecholamines systemically and within the myocardium,2,3 increasing the myocardial oxygen requirements and mobilising free fatty acids4 which may further damage the myocardium.5–7 Catecholamines increase myocardial tension and rate as well as increasing the afterload, all of which increase the oxygen requirements8–9 and thus worsen the damage from myocardial oxygen demand exceeding supply.6 The arrhythmias and alterations of blood supply provoked by catecholamines lead to a progressive deterioration (fig 1).

The development of beta-adrenergic antagonists10 has allowed beta-blockade to be used for the benefit of patients with angina,11 thyrotoxicosis,12 and hypertension.13 The pain of angina is reduced14 and ST segment elevation15–17 and arrhythmias18 are diminished. Myocardial oxygenation is improved19 20 so that ischaemic injury is lessened.21

The potentially useful protection of the myocardium by propranolol during surgical global ischaemia has been investigated22 but not by functional evaluation, though the reduction by means of propranolol of operative mortality in hypertrophied ventricles has been reported.23

This study, therefore, was designed to assess this protection. Isovolumic ventricular function tests were used for accurate measurement of ventricular compliance. From these results and the intraventricular pressures, tension and velocity of contraction were calculated—these parameters are the main determinants of myocardial oxygen consumption and are preferable as indices of function to estimations of work or power.24 25 The heart was left in situ in preference to the more stable isolated cross-perfused preparation26–28 because beta-blockers modify the effects of stimuli arriving via both nerves and the bloodstream which must thus remain in continuity with the heart in any preparation to evaluate their effect.

Functional assessment of the protection afforded
Myocardial protection with propranolol

ISCHAEMIA

Release of catecholamines

Raised FFA concentrations

Increased oxygen requirements

Damage to myocardial microvasculature

Alterations in myocardial blood flow

Arrhythmias

Further ischaemia

Myocardial damage

Worsened function

Fig 1 The part played by catecholamines in the vicious cycle of ischaemia of the myocardium.

by propranolol may be obscured by the negative inotropic effect. Therefore, a series of experiments with propranolol but without ischaemia was devised. We determined the initial effect of these small doses, the risk of impaired ventricular function after operation, and the need for caution in using low-dose propranolol during operations.

Methods

Experimental plan

Three groups of dogs, randomly allotted, were used. In group 1 the hearts underwent 90 minutes of continuous perfusion with the animal on cardiopulmonary bypass. After a control ventricular function test propranolol was given and the measurements repeated after 10 and 90 minutes. In group 2, after a control ventricular function test, 90 minutes of ischaemia were followed by a period of cardiac reperfusion until maximal recovery, and then a second ventricular function test was carried out. In group 3, the procedure was a control test, an injection of propranolol, a second test, and then 90 minutes of ischaemia followed by a third test, after maximal recovery of function with perfusion. We could thus determine the effect of propranolol on function in groups 1 and 3, and the degree of recovery of function with time in group 1, as well as the degree of protection from ischaemia in groups 2 and 3.

Procedure

Mongrel dogs of either sex, weighing 14-34 kg, premedicated with 1-4 mg of droperidol and 25-100 μg of fentanyl were anaesthetised with 30-40 mg/kg of pentobarbitone and ventilated mechanically with a 60/40 N₂O/O₂ mixture. The heart was exposed through a median sternotomy, heparin 3 mg/kg was given intravenously, and the femoral arteries were cannulated for perfusion and pressure monitoring. The venae cavae and the right ventricle were cannulated via the right atrium, the cavae snared and the blood drained to a “Temptrol” Q100 bubble oxygenator (Bentley Lab Inc, Ilford, Essex) to start cardiopulmonary bypass. The ascending aorta was cannulated for pressure monitoring and coronary perfusion from a separate low-flow pump to maintain a constant coronary perfusion pressure of 13 kPa. The aorta was cross-clamped. The coronary blood flow was measured with a flow probe (Ormed Engineering, Welwyn Garden City, Herts) in the right ventricular cannula which collected blood from the coronary sinus only. After the heart had been fibrillated the left atrium was opened behind the interatrial groove and a purse-string suture was placed in the free edge of the mitral valve to retain a flange-mounted balloon (Durex, London Rubber Company) of over 50 ml capacity which was connected to a pressure transducer (Bell and Howell Ltd). Fluid was added to the balloon from a graduated syringe to raise the intraventricular pressure to 0-65 kPa (5 mmHg) before defibrillating the heart by direct current. Electrocardiograph (ECG) and pacing leads and a temperature probe were attached to the heart. The plan of the preparation is seen in fig 2. The recordings—on a Devices M-19 eight-channel recorder (Ormed Engineering)—were of cardiac perfusion pressure, ECG, intraventricular pressure on 0-34 kPa (0-250 mmHg) and 0-3-5 kPa (0-25 mmHg) ranges and differentiated against time (dp/dt), and of cardiac temperature, systemic pressure, and coronary flow.

When the preparation was stable, an initial ventricular function test was done by putting 2-5 ml
increments of fluid into the balloon, recording traces of a few beats at each increment, over the range end-diastolic pressure (EDP) 0 - 1·3 kPa (10 mmHg). In groups 1 and 3, 30 µg/kg of propranolol was given, and the ventricular function test repeated after 10 minutes. Then the hearts of groups 2 and 3 were exposed to 90 minutes of ischaemia by stopping the pump to the ascending aorta. The ischaemic hearts were reperfused until function had recovered maximally, and final ventricular function tests were done in all groups. The left ventricles were dissected free and their weights and displacement volumes measured. For each ventricular function test the values for peak systolic pressure, wall stress (Pr/2h, where P = peak systolic pressure r = internal radius and h = wall thickness), rate of rise of pressure and intraventricular volume were plotted mathematically against end-diastolic pressure, and the values at EDP 1·3 kPa (10 mmHg) taken from the resultant regression formulae. The values of the “post-propranolol” or “final” readings for each were expressed as percentages of the “initial” values, to eliminate innate differences between individual hearts. The “group value” for the changes in these indices of contractile force, velocity, and compliance,
Myocardial protection with propranolol

Table 1  Effect of propranolol on ventricular function 10 minutes after a dose of 30 μg/kg. Ventricular function before and after propranolol in groups 1 and 3, expressed as percentages of initial values

<table>
<thead>
<tr>
<th></th>
<th>Diastolic compliance</th>
<th>Peak systolic pressure</th>
<th>Peak systolic stress</th>
<th>Peak velocity (dp/dt)</th>
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<tr>
<td></td>
<td>Mean (Standard error)</td>
<td>Mean (Standard error)</td>
<td>Mean (Standard error)</td>
<td>Mean (Standard error)</td>
</tr>
<tr>
<td>Initial</td>
<td>100 (10-18)</td>
<td>100 (7-69)</td>
<td>100 (69-4)</td>
<td>100 (9-64)</td>
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<tr>
<td>Post-propranolol</td>
<td>103.2 (11-16)</td>
<td>&lt;0.0005</td>
<td>&lt;0.005</td>
<td>&lt;0.0005</td>
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<tr>
<td>p value</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
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n = 24

Table 2  Recovery from the effects of propranolol. Ventricular function before and 90 minutes after propranolol with cardiopulmonary bypass and continuous myocardial perfusion in group 1, expressed as percentage of initial values

<table>
<thead>
<tr>
<th></th>
<th>Compliance</th>
<th>Peak systolic pressure</th>
<th>Peak systolic stress (pr/2h)</th>
<th>Peak velocity (dp/dt)</th>
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<tr>
<td></td>
<td>Mean (Standard error)</td>
<td>Mean (Standard error)</td>
<td>Mean (Standard error)</td>
<td>Mean (Standard error)</td>
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<tr>
<td>Initial value</td>
<td>100 (10.08)</td>
<td>100 (8.34)</td>
<td>100 (10.31)</td>
<td>100 (8.77)</td>
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<tr>
<td>Final value</td>
<td>150.95 (17.83)</td>
<td>106.97 (10.87)</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>p value</td>
<td>&lt;0.01</td>
<td>ns</td>
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n = 11

and the standard error of the group, could thus be calculated. The significance of differences between the groups was shown with Student’s t test.

Results

NEGATIVE INOTROPIC ACTION OF 30 μG/KG PROPRANOLOL
Table 1 shows that the negative inotropic action of propranolol is present even in low dosage. Peak systolic pressure and rate of rise of pressure (dp/dt) both decreased significantly 10 minutes after propranolol. Compliance was unaffected.

RECOVERY OF MYOCARDIAL CONTRACTILITY AFTER PROPRANOLOL
Table 2 shows that after 90 minutes of cardiopulmonary bypass there is no evidence of the negative inotropic action of propranolol in doses of 30 μg/kg suggested for myocardial protection against ischaemia. Representative tracings are shown in fig 3.

CONTRACTILE FORCE AFTER ISCHAEMIA
Table 3 shows that the hearts continuously perfused (group 1) had undiminished (118.73%) peak systolic pressure after 90 minutes, the hearts made ischaemic after propranolol (group 2) had reduced (73%) systolic force, but do not significantly differ from the perfused controls, whereas those made ischaemic without previous propranolol (group 2) had significantly lower levels (36.09%) Propranolol gave significant protection from ischaemia (p < 0.02).

CONTRACTILE VELOCITY AFTER ISCHAEMIA (table 4)
Compared with the non-ischaemic controls (145% of initial value), the ischaemic hearts after propranolol were not significantly worse, whereas the unprotected ischaemic hearts were significantly less rapid in contraction (34.1%) and very significantly worse than ischaemic hearts after propranolol in this respect (p < 0.0005).

VENTRICULAR COMPLIANCE (table 5)
The volume in the ventricles at the end-diastolic pressure of 10 mmHg was rather higher than initially in all the groups, but there was no significant difference between them.

Discussion

We find that the negative inotropic action of beta-blockade with propranolol is present even in low dosage, but myocardial function recovers completely in 90 minutes, and there is significant protection from ischaemia. The indictment of the use of propranolol in cardiac surgery does not seem to apply if the dose is low, although after long-term beta blockade the persistence of the drug and the persistent haemodynamic effects may cause concern. Where ventricular function is adequate, it is unwise to
Fig 3  Traces from a non-ischaemic heart given propranolol, illustrating early depression of function with recovery before 90 minutes. Abbreviations as in previous figure.
Table 3  Peak systolic pressure at EDP 10 mmHg after 90 minutes of ischaemia expressed as percentages of initial values

<table>
<thead>
<tr>
<th></th>
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<th>Mean</th>
<th>Standard error</th>
<th>p values of difference between groups A and B</th>
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<td></td>
<td></td>
<td>A group = 1</td>
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<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td>B group =</td>
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<tr>
<td>After propranolol + 90 minutes of perfusion</td>
<td>11</td>
<td>118.73</td>
<td>27.76</td>
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<tr>
<td>90 minutes of ischaemia without propranolol</td>
<td>13</td>
<td>36.09</td>
<td>5.82</td>
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<td>Group 3</td>
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<tr>
<td>90 minutes of ischaemia after propranolol</td>
<td>16</td>
<td>73.05</td>
<td>12.35</td>
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Table 4  Contractile velocity after ischaemia (dp/dt at end-diastolic pressure 10 mmHg expressed as percentage of initial values)

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<td>B group =</td>
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<tr>
<td>Group 1</td>
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<td>90 minutes of perfusion after propranolol</td>
<td>11</td>
<td>145.36</td>
<td>57.27</td>
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<tr>
<td>90 minutes of ischaemia without propranolol</td>
<td>13</td>
<td>34.1</td>
<td>5.80</td>
<td>&lt; 0.005</td>
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<td>Group 3</td>
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<tr>
<td>90 minutes of ischaemia after propranolol</td>
<td>16</td>
<td>68.8</td>
<td>12.21</td>
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Table 5  Ventricular diastolic compliance after ischaemia. Intraventricular volume at end-diastolic pressure 10 mmHg expressed as percentage of initial values

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<th>Mean</th>
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<th>p values of difference between groups A and B</th>
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<td>A group = 1</td>
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<td>B group =</td>
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<tr>
<td>Group 1</td>
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<tr>
<td>90 minutes of perfusion after propranolol</td>
<td>11</td>
<td>164.3</td>
<td>8.85</td>
<td>&lt; 0.025 &lt; 0.05</td>
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<tr>
<td>90 minutes of ischaemia without propranolol</td>
<td>13</td>
<td>105.11</td>
<td>47.25</td>
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<td>Group 3</td>
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<tr>
<td>90 minutes of ischaemia after propranolol</td>
<td>16</td>
<td>115.18</td>
<td>51.43</td>
<td>3</td>
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withdraw the protection of beta-blockade before operation for ischaemic heart disease. In 150 cases of aortic valve replacement in hypertrophied hearts where propranolol was used there was no death and no case of “stone heart”.\(^{23}\) In our study we have confirmed the protective effect of propranolol suggested by these and other authors,\(^{15-19 41-43}\) against ischaemic damage from aortic cross-clamping.

Although beta-adrenoreceptor blocking drugs have a membrane—stabilising “quinidine-like” effect,\(^{29}\) this plays little part in their protective action,\(^{29 43}\) unlike corticosteroids in which membrane stabilisation is important in myocardial protection.\(^{44}\) It is the blockade of beta-receptors which protects the heart. The changes of myocardial necrosis after cerebral damage are mediated by catecholamines\(^{45-49}\) and are minimised by propranolol;\(^{50}\) similarly arrhythmias after acute myocardial infarction\(^{51}\) are suppressed by beta-blockade.\(^{5,18}\) Ischaemia is worsened by beta-adrenergic stimulation which hastens metabolic, structural, and haemodynamic deterioration. Catecholamine levels are raised during cardiopulmonary bypass,\(^{52-58}\) worsening the effects of inadequate myocardial protection and increasing the likelihood of the low-output syndrome.\(^{54 55}\)

At operation, myocardial energy demands in excess of supply\(^{59}\) reduce the high-energy nucleotides\(^{57 58}\) which may be insufficient for recovery on reperfusion.\(^{59}\) The end result may be the stone
Beta-blockade reduces myocardial energy demands and will therefore conserve adenosine triphosphate. Ventricular fibrillation increases myocardial energy demand and impairs supply, and is provoked by hypothermia which is important for myocardial preservation. Beta-blockade diminishes ventricular fibrillation time and is thus a logical and effective adjunct to hypothermia.

All these energy-sparing activities of beta-blockers may be augmented by the inherent negative inotropic qualities of the propranolol group of drugs.

During the reperfusion period, the supply of energy is enhanced by beta-blocking drugs, which reduce inequalities of myocardial blood-flow distribution and limit microvascular injury during ischaemia. The glucose extraction of the myocardium is increased and there is a peripheral antilipolytic action which reduces the rise in free fatty acids (FFA) usually associated with myocardial ischaemia and beta-adrenergic stimulation.

High concentrations of FFA depress contractility and lead to arrhythmias.

There is thus much theoretical rationale for the use of beta-blockade to minimise intraoperative ischaemic damage; we have confirmed this promise and have shown that though low-dose propranolol has a temporary effect on the heart during operation it does not impair postoperative contractility.

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