Cardiovascular effects of prenalterol on rest and exercise haemodynamics in patients with chronic congestive cardiac failure

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SUMMARY The cardiovascular effects of the cardioselective beta, agonist prenalterol have been studied in nine patients with severe chronic congestive cardiac failure and in six patients with left ventricular dysfunction resulting from previous myocardial infarction. In the patients with cardiac failure intravenous prenalterol in a dosage of 1-5 μg/kg bodyweight increased the cardiac index from 1.8±0.1 to 2.1±0.1 l/min per m² and the left ventricular ejection fraction from 22±3 to 28±3%. There was a modest but significant increase in heart rate from 76±3 to 87±4 beats/min. Systemic vascular resistance fell from 2285±51 to 2041±534 dynes s⁻¹ cm⁻⁵. On exercise, the left ventricular filling pressure fell from 33±6 to 26±3 and both cardiac index and stroke index increased by 13% and 16%, respectively. There was no significant change in heart rate or systemic blood pressure. In the patients with left ventricular dysfunction, coronary sinus blood flow increased from 107±11 to 133±12 ml/min but the increase in myocardial oxygen consumption was small and not significant (11.6±1.2 and 14.5±1.9 ml/min). In all patients there was no evidence that prenalterol was arrhythmogenic.

There has been a resurgence of interest in the management of the patient with congestive cardiac failure. Vasodilator therapy has been shown to be effective in increasing cardiac output and reducing left ventricular filling pressure in patients with both acute and chronic cardiac failure. Inotropie drugs can also be of value in improving cardiac performance but side-effects can be troublesome. Isoprenaline is a potent beta-adrenoreceptor agonist but provokes tachycardia, can precipitate arrhythmias, and increases myocardial oxygen consumption. Dobutamine has been shown to have significant inotropic properties but in patients after open-heart surgery a chronotropic effect similar to that of isoprenaline was found. The endogenous catecholamine dopamine has been shown to be a useful inotropic agent and in addition dilates renal control and splanchnic vessels. As with isoprenaline, however, it may provoke ventricular arrhythmias, and in addition it has alpha-adrenergic effects. A combination of vasodilator therapy and inotropic agents has also been shown to be of value. Prenalterol (S-(−)-1-(4-hydroxyphenoxy)-3-iso-propylamino propanol-2 hydrochloride) is a new selective beta-adrenoreceptor agonist which has been described as having potent inotropic effects with little chronotropic action. Johnsson et al. have reported that, in human volunteers, prenalterol when administered either orally or intravenously produced an increase in myocardial contractility with little or no increase in heart rate. Ariniego et al. have confirmed these findings in patients with acute myocardial infarction and in addition suggested that prenalterol was a useful antidote to the unwanted cardiac effects of beta-adrenoreceptor blocking drugs. Hutton et al. studied the haemodynamic effects in patients with coronary heart disease using both invasive and non-invasive methods and concluded that prenalterol enhanced the contractile state of the myocardium without altering heart rate. Reiz and Friedman have reported that prenalterol is of value in improving the haemodynamic status of hypotensive patients with Gram-negative septic shock. Prenalterol appears to be effective both orally and parenterally and could well be of value in the management of the patient with acute and chronic cardiac failure.

The object of this study was to determine the effects of intravenously administered prenalterol on...
coronary haemodynamics in patients with left ventricular dysfunction and the effects on rest and exercise haemodynamics in a further group of patients with low output cardiac failure.

Patients and methods

CARDIAC FAILURE PATIENTS
Nine male patients, mean age 51±3 years (range 45 to 65 years), with severe chronic cardiac failure were studied. All patients were in sinus rhythm and were classified as functional class III (New York Heart Association). Six patients had coronary heart disease and three had idiopathic congestive cardiomyopathy. The clinical diagnosis of left ventricular dysfunction was confirmed by cardiac catheterisation and selective coronary angiography in all patients. Cardiac glycosides were withdrawn for seven days before the study and vasodilator therapy was withdrawn 48 hours before the study, but the patients' regular diuretic therapy was continued. Approval for this study was obtained from the Ethical Committee of the Glasgow Royal Infirmary and informed consent was obtained from each patient.

A Swan-Ganz catheter was inserted percutaneously into a peripheral vein for measurement of cardiac output, pulmonary pressure, and pulmonary capillary wedge pressure. Cardiac output was measured using the thermodilution technique (Instrumentation Laboratories 701). All cardiac outputs were measured in triplicate and the mean of the results was used. Pressures were recorded using an Elromatic transducer and recorded on a Mingograph 81 recorder. Blood pressure was obtained by sphygmomanometry. Heart rate was recorded continuously by means of a telemetered electrocardiogram using a modified V5 chest lead electrode. Measurements were made at rest and during dynamic exercise. Upright exercise was performed on a mechanically braked bicycle ergometer at an individually predetermined "load" which was near maximal, usually within the range 25 to 50 watts, and which could be continued for three minutes.

Radionuclide angiography was performed after in vivo labelling of red blood cells with 20 mCi of technetium 99m pyrophosphate. After reaching equilibrium, electrocardiographically gated blood pool scintigrams were obtained in the left anterior oblique projection which provided optimal septal separation of right and left ventricular activity, using an Ohio Nuclear Series 100 Gamma Camera, interfaced to a Varian 620L computer. Left atrial activity was excluded using a 10° caudal tilt. Image data were stored in list mode with simultaneous acquisition of electrocardiogram and time. The computer was used to reconstruct 16 frames per cardiac cycle and the end-diastolic frame displayed. After background correction the left ventricular edge was identified for each frame using a thresholding technique validated in our laboratory.

Control haemodynamic data were obtained at rest and during exercise. Radionuclide angiography for technical reasons could only be performed at rest. Prenal terol was then infused intravenously over a 30 minute period using a calibrated infusion pump, in a dosage of 1.5 μg/kg bodyweight, and the above measurements repeated both at rest and during exercise. Continuous electrocardiographic monitoring was maintained after the completion of the study for a period of 12 hours while the patients were observed in a coronary care unit.

CARDIAC ISCHAEMIC PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION
Six male patients with a mean age of 47±4 (37 to 59 years), who had sustained a previous myocardial infarction and had angiographic evidence of regional wall abnormality, were studied at the time of cardiac catheterisation. All drug treatment was discontinued over the 48 hours before the study.

Systemic blood pressure was obtained from an intra-arterial catheter placed in the ascending aorta via the femoral artery. Pulmonary pressure, pulmonary capillary wedge pressure, and cardiac output were measured as described above. A 7F double thermistor catheter (Wilton-Webster) was introduced into a left median antecubital vein and advanced into the proximal 1 to 2 cm of the coronary sinus. The catheter tip was not moved during the course of the study. Coronary sinus blood flow was measured using a continuous infusion thermodilution technique using a constant infusion of a 0.9% saline solution at 60 ml/min for 30 seconds. The reproducibility of coronary sinus blood flow measurements using this technique is 3±2% and in this study relative effects were assessed with each patient acting as his own control. Simultaneous blood samples were obtained from the aorta and the coronary sinus and were assayed for oxygen content using an Instrumentation Laboratories Co-Oximeter 282.

Prenal terol was infused intravenously in a dosage of 1.5 mg in 50 ml of dextrose over a 30 minute period using a calibrated infusion pump.

Statistical analysis in both studies was performed using Student's paired t test, a p value of <0.05 being considered significant. The results are expressed as the mean ± standard error of the mean.

Results

CALCULATED VARIABLES
Systemic vascular resistance (SVR) =
\[
\frac{\text{(MBP-RA) x 80 dynes s}^{\text{-1}} \text{ cm}^{\text{-5}}}{\text{CO}}
\]
Cardiovascular effects of prenalterol on rest and exercise

Table 1  Haemodynamic effects of prenalterol in patients with chronic cardiac failure

<table>
<thead>
<tr>
<th>Table 1 Haemodynamic effects of prenalterol in patients with chronic cardiac failure</th>
<th>Rest</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Prenalterol</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76±3</td>
<td>87±4*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>120±6</td>
<td>130±7†</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75±3</td>
<td>75±4</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>90±4</td>
<td>94±4</td>
</tr>
<tr>
<td>Cardiac index (l/min per m²)</td>
<td>1.8±0.1</td>
<td>2.1±0.1†</td>
</tr>
<tr>
<td>Stroke index (ml/m²)</td>
<td>24±2</td>
<td>24±2</td>
</tr>
<tr>
<td>Pulmonary capillary wedge (mmHg)</td>
<td>19±2</td>
<td>17±2</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>22±3</td>
<td>28±3†</td>
</tr>
<tr>
<td>Stroke work index (g m/m²)</td>
<td>23±4</td>
<td>25±3</td>
</tr>
<tr>
<td>Systemic vascular resistance (dynes s⁻¹ cm⁻²)</td>
<td>2285±193</td>
<td>2041±201*</td>
</tr>
</tbody>
</table>

Results are mean ± SEM of nine patients  *p<0.05  †p<0.02  ‡p<0.005.

where MBP is mean blood pressure (mmHg), RA is mean right atrial pressure (mmHg), CO is cardiac output (l/min).

Stroke work index (SWI)=(MBP-LVEDP)×SI×0.0136 g/min per m²

where LVEDP is left ventricular end-diastolic pressure (mmHg) and SI is stroke index (ml/m²).

CARDIAC FAILURE GROUP
The detailed haemodynamic results are shown in Table 1.

At rest, prenalterol produced significant increases in cardiac index from 1.8±0.1 to 2.1±0.1 l/min per m² (p<0.02) and in left ventricular ejection fraction from 22±3 to 28±3% (p<0.02) (Fig. 1). There was a modest but significant increase in heart rate from 76±3 to 87±4 beats/min (p<0.005) and in systolic blood pressure from 120±6 to 130±7 mmHg (p<0.02) (Fig. 2). Systemic vascular resistance fell from 2285±511 to 2041±534 dynes s⁻¹ cm⁻² (p<0.05).

On exercise, left ventricular filling pressure fell from 33±6 to 26±3 mmHg (p<0.05) and both cardiac index and stroke volume increased by 13% and 16%, respectively. Systemic vascular resistance fell from 1733±134 to 1414±184 dynes s⁻¹ cm⁻² (p<0.05). There was no significant change in heart rate or systemic blood pressure (Fig. 3). All patients tolerated the drug well and did not complain of palpitation or angina pectoris. No evidence of significant ventricular extrasystoles was found on the continuous recording electrocardiogram.

Fig. 1  The effects on cardiac index and stroke index at rest, after the intravenous administration of prenalterol in a dosage of 1.5 µg/kg bodyweight.

Fig. 2  The effects on heart rate, left ventricular filling pressure, and blood pressure after intravenous administration of prenalterol. The bars indicate mean blood pressure, at rest.

Fig. 3  The effects on heart rate, left ventricular filling pressure, and blood pressure during dynamic exercise, after intravenous administration of prenalterol. The bars indicate mean blood pressure.
CARDIAC ISCHAEMIC PATIENTS WITH LEFT VENTRICULAR DYSFUNCTION
The detailed haemodynamic findings are shown in Table 2. In these patients with left ventricular regional wall abnormalities, prenalterol increased cardiac index from 3.1±0.2 to 3.6±0.3 l/min per m² (p<0.02). There was a modest but significant increase in heart rate from 74±4 to 90±6 beats/min (p<0.005). There were no significant changes in systemic blood pressure or in left ventricular filling pressure.

Table 2  Haemodynamic effects of prenalterol in patients with left ventricular dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Prenalterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>74±4</td>
<td>90±6</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>115±7</td>
<td>116±2</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>71±4</td>
<td>73±2</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>87±6</td>
<td>88±3</td>
</tr>
<tr>
<td>Cardiac index (l/min per m²)</td>
<td>3.1±0.2</td>
<td>3.6±0.3†</td>
</tr>
<tr>
<td>Stroke index (ml/m²)</td>
<td>42±4</td>
<td>41±4</td>
</tr>
<tr>
<td>Pulmonary capillary wedge (mmHg)</td>
<td>9±1</td>
<td>7±1</td>
</tr>
<tr>
<td>Coronary sinus blood flow (ml/min)</td>
<td>107±4</td>
<td>133±12*</td>
</tr>
<tr>
<td>Myocardial oxygen consumption (ml/min)</td>
<td>11.6±1.2</td>
<td>14.5±2</td>
</tr>
</tbody>
</table>

Results are mean ±SEM of six patients.
* p<0.05  † p<0.02  ‡ p<0.005.

sure. Coronary sinus blood flow increased from 107±11 to 133±12 ml/min (p<0.05) but with an associated but not significant increase in myocardial oxygen consumption from 11.6±1.2 to 14.5±1.9 ml/min (Fig. 4).

Discussion
This study has shown that prenalterol enhances the cardiac performance of patients with congestive cardiac failure both at rest and during dynamic exercise as reflected by significant increases in cardiac output and left ventricular ejection fraction. The reduction in left ventricular filling pressure appears to be secondary to a positive inotropic action, but there was a modest but significant fall in systemic vascular resistance suggesting that a degree of peripheral vasodilatation might be contributing to the improvement in ventricular performance. The increase in systolic blood pressure with a decrease in systemic vascular resistance again suggests that the principal action of prenalterol is to increase myocardial contractility. In addition there was a slight but significant increase in heart rate at rest, indicating a chronotropic response mediated through the beta1 cardiac receptors.

In the presence of coronary artery obstruction, inotropic agents which increase myocardial oxygen consumption have to be used with caution.19 None of the patients with cardiac failure experienced angina pectoris, and in the patients with left ventricular dysfunction, who all had a history of angina pectoris, prenalterol did not provoke cardiac pain. In the latter group, though there was an increase in myocardial oxygen consumption, there appeared to be a greater increase in coronary blood flow. In our previous study with patients who had recently sustained an acute myocardial infarction the administration of prenalterol did not provoke angina pectoris.16 This has been confirmed by Ariniego et al.15 with prenalterol and by Gillespie et al.20 with dobutamine in patients with acute myocardial infarction.

No evidence of ventricular arrhythmias nor indeed of increased ventricular extrasystoles was found in this study but Kirlin and Pitt21 have reported that ventricular tachycardia occurred in two out of nine patients with severe low output cardiac failure after the intravenous administration of prenalterol. It should be noted that these patients were having frequent ventricular extrasystoles before the start of the study and all were receiving concomitant digitalis therapy which suggests that the combination of prenalterol and digoxin may induce ventricular arrhythmias.

The only oral inotropic agents used in clinical practice are the cardiac glycosides which have a narrow toxic therapeutic ratio, and hence toxicity, including ventricular arrhythmias, is not uncommon and has been reported in as high a percentage as 20% of a hospital population.22 There is considerable controversy about the efficacy of digitalis as an inotropic agent in the patient with cardiac failure who is in sinus rhythm. Goldstein et al.,23 in patients with acute myocardial infarction and cardiac failure, found little improvement after intravenous digoxin, as did Hodges et al.24 Arnold et al.25 and Murray et al.26 have reported that both intravenous and chronic oral digoxin therapy have a
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modest but definite positive inotropic effect in patients with chronic congestive cardiac failure, particularly during dynamic exercise. There thus appears to be a place for new oral inotropic agents in the management of patients with chronic congestive cardiac failure.

Prenalterol has been shown to be effective orally in both normal volunteers and patients with congestive cardiac failure where an increase in cardiac output and reduction in left ventricular filling pressure were found with an improvement in functional exercise capacity.\(^{27}\) It therefore seems appropriate to evaluate the haemodynamic effects of oral prenalterol in chronic congestive cardiac failure over a prolonged period, though Braunwald has raised the possibility that prolonged administration of a beta-adrenergic agonist might lead to alteration of haemodynamic responses, a consequence of “down-regulation” of the beta receptor.\(^{28}\)

This study has shown that intravenous prenalterol improves cardiac performance in patients with chronic congestive cardiac failure, and a placebo-controlled trial of oral prenalterol in such patients appears indicated.

References


Requests for reprints to Dr I Hutton, University Department of Medical Cardiology, Royal Infirmary, Glasgow G4 0SF.
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