Acute Effects of Oral Pirbuterol on Myocardial Oxygen Metabolism and Systemic Hemodynamics in Chronic Congestive Heart Failure

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SUMMARY Pirbuterol hydrochloride, an orally effective β-adrenergic agonist, improves hemodynamic abnormalities in patients with congestive heart failure, but its effects on myocardial oxygen consumption (MVO₂) and coronary blood flow have not been characterized. We studied the effects of 20–30 mg of oral pirbuterol on myocardial metabolic and hemodynamic parameters in 12 patients (six with coronary artery disease) with chronic CHF refractory to standard medical therapy. Pirbuterol induced an increase in cardiac index (1.7 ± 0.1 to 2.3 ± 0.2 l/min/m², p < 0.05) and a fall in systemic vascular resistance (1884 ± 118 to 1391 ± 69 dyn·sec·cm⁻⁴, p < 0.01) 2 hours after administration. Pulmonary capillary wedge pressure fell from 27 ± 2 to 23 ± 2 mm Hg (p < 0.001) at the time of peak hemodynamic response. Mean arterial, pulmonary arterial and right atrial pressures did not change. Heart rate remained constant. Arterial–coronary sinus oxygen content difference narrowed (from 12.9 ± 4.0 to 11.1 ± 0.3 vol%, p < 0.05), while no significant change occurred in MVO₂. Myocardial oxygen extraction ratio and myocardial lactate extraction ratio did not change, and no patient developed angina or electrocardiographic evidence of myocardial ischemia. Patients with coronary artery disease had hemodynamic and myocardial metabolic responses similar to those without coronary artery disease.

Pirbuterol effects substantial acute hemodynamic improvement in patients with chronic congestive heart failure without increasing requirements for coronary blood flow or myocardial oxygen delivery and without provoking myocardial ischemia.

PIRUTEROL HYDROCHLORIDE,* an orally effective β-adrenergic agonist, has prominent bronchodilator and inotropic and vasodilator effects in experimental animals. Clinical studies in patients with congestive heart failure indicate that pirbuterol consistently increases cardiac output and decreases left ventricular filling pressure and systemic vascular resistance without apparent chronotropic effects. However, the effects of pirbuterol on myocardial oxygen demand and coronary blood flow in the patient with heart failure are unknown. Because the value of this agent in patients with heart failure and coronary artery disease would be limited if the drug’s salutary hemodynamic effects were associated with large increases in myocardial oxygen demand and significant myocardial ischemia, we studied the effects of oral pirbuterol on myocardial metabolism, coronary blood flow, and systemic and pulmonary hemodynamics in 12 patients with advanced congestive heart failure. The results indicate that oral pirbuterol therapy can effect substantial improvement in cardiac function without an increase in myocardial oxygen demand and suggest that it can be used safely in patients with coronary artery disease and congestive heart failure.

Material and Methods

Fourteen patients with chronic congestive heart failure gave informed consent for this study under a protocol approved by the Human Subjects Committee of the Peter Bent Brigham Hospital. To be eligible for the study, patients had to demonstrate continuing symptoms of congestive heart failure (fatigue, dyspnea, orthopnea) in New York Heart Association functional classes III or IV after intensive medical therapy consisting of salt restriction, digitalis glycosides and diuretics. In addition, objective evidence of left ventricular dysfunction (left ventricular ejection fraction <40%) was required from a recent contrast left ventriculogram or radionuclide ventriculogram. Patients with myocardial infarction or unstable angina pectoris within the preceding 30 days, systolic blood pressure consistently below 90 mm Hg, symptomatic ventricular arrhythmias, operable valvular or congenital heart disease or severe diseases of other organ systems were not included in the study.

Patients were studied in the Cardiac Catheterization Laboratory at the Peter Bent Brigham Hospital in the postabsorptive state. Local anesthesia was produced by subcutaneous infiltration of 2% lidocaine; because of the patients’ familiarity with cardiac

* [2-hydroxymethyl-3-hydroxy-6,1-hydroxy-2-terti-butylamine].

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catheterization procedures, sedative medications were not administered, except to two patients who received diazepam (5 mg) and diphenhydramine (50 mg) orally immediately before the procedure. Diuretics and vasodilators were withheld for at least 12 hours before the study, but chronic digoxin administration was not interrupted. Using either the brachial or femoral approach, a double-lumen balloon-tip catheter (Hancock Laboratories) was positioned in the pulmonary artery such that pulmonary artery occlusive (pulmonary capillary wedge) pressures could be measured through the end hole while right atrial pressure was recorded from the proximal catheter port without catheter manipulation. Coronary sinus catheterization was successful in eight patients with a specially designed #8F thermodilution coronary sinus flow catheter (Wilton-Webster Instruments). Its position in the coronary sinus was verified initially by injection of 2–5 ml of angiographic contrast medium. The fluoroscopic position of the radiopaque thermonsters on the coronary sinus flow catheter was noted in reference to the lateral borders of vertebrae in the anteroposterior projection and was verified at intervals throughout the procedure. A small plastic catheter was inserted percutaneously into either the femoral or brachial artery for arterial pressure monitoring and blood sampling. All pressures were measured through standard fluid-filled catheters connected to Statham P50 Micron transducers without intervening tubing and were recorded on an Electronics for Medicine VR-12 recorder. Coronary sinus flow was measured by thermodilution and calculated as previously described.6

Hemodynamic measurements (systemic arterial, pulmonary arterial, pulmonary capillary wedge and right atrial pressures; coronary sinus blood flow; and cardiac output by the Fick method) and 12-lead ECGs were obtained at 15 minutes and immediately before and 30, 60, 90, 120, 150 and 180 minutes after oral administration of 20–30 mg of pirbuterol hydrochloride (supplied in capsule form by Pfizer Central Research). Arterial and coronary sinus blood samples were obtained simultaneously for determination of oxygen content, using a fuel-cell method (Lex-O2-Con, Lexington Instruments) and for measurement of lactate concentration (by the method of Marbach and Weil6 at 60, 90, 120, 150 and 180 minutes after pirbuterol administration.

The following hemodynamic parameters were calculated from pressure and cardiac output data by standard formulas:8

\[ \text{SVR} = (\frac{\text{MAP} - \text{RAP}}{80/\text{CO}}) \times 80/\text{CO}; \]
\[ \text{PVR} = (\frac{\text{PAP} - \text{PCW}}{80/\text{CO}}) \]
\[ \text{LVSWI} = \frac{\text{SI} \times (\text{MAP} - \text{PCW})}{0.0136}, \]

where SVR and PVR are systemic and pulmonary vascular resistances (dyn·sec·cm⁻⁵); MAP, RAP, PAP and PCW are mean arterial, right atrial, pulmonary arterial and pulmonary capillary wedge pressures (mm Hg); CO is cardiac output (l/min); LVSWI is left ventricular stroke work index (g·m·m²), and SI is stroke index (ml/m² body surface area). Coronary sinus blood flow (CBF, ml/min) was calculated as

\[ \text{CBF} = (1.17 \times 38.2) \left[ \frac{\text{T}_B - \text{T}_I}{\text{T}_B - \text{T}_M} - 1 \right], \]

where \( T_B \), \( T_I \) and \( T_M \) are the temperatures (°C) of blood, indicator and blood-indicator mixture measured by the catheter-mounted thermistors, 1.17 is a constant accounting for the specific heat and density of both blood and indicator and 38.2 ml/min is the injection rate of the indicator (5% dextrose in water).8

Myocardial oxygen and lactate extraction ratios were calculated as \( \text{ART} \left( \frac{\text{O}_2 - \text{CS} \left[ \text{O}_2 \right]}{\text{ART} \left[ \text{O}_2 \right]} \right) \) and \( \text{ART} \left( \frac{\text{lac} - \text{CS} \left[ \text{lac} \right]}{\text{ART} \left[ \text{lac} \right]} \right) \), respectively, where ART and CS represent arterial and coronary sinus sources of blood, \( \text{O}_2 \) is the measured content of oxygen (vol%) and [lac] is the concentration of lactate (mEq/l). Myocardial oxygen consumption (ml/min) was calculated as \( \text{MO}_{2} = \text{CBF} \times (\text{ART} \left[ \text{O}_2 \right] - \text{CS} \left[ \text{O}_2 \right]) \) where \( \text{VO}_{2} \) is myocardial oxygen consumption of the myocardium drained by the CS (predominantly the left ventricle) and CBF, ART, CS and \( \text{O}_2 \) are as defined above.

The arithmetic mean of the two pretreatment values (15 minutes before and immediately before drug administration) was used as the control value for each hemodynamic parameter. Statistical analyses involving multiple comparisons of post-treatment measurements to control values were performed by analysis of variance while comparisons of control data to peak hemodynamic responses were performed using the t test for paired comparisons. A p value < 0.05 was required for statistical significance. All group data in this report are presented as the mean ± SEM.

Results

Results are reported for the 12 patients who had a detectable pirbuterol blood level (≥ 2 ng/ml) 2 hours after oral dosing. The mean age of the patients was 56.8 years (range 39–71 years). All were male. Congestive heart failure had required treatment for 9–192 months (average 54.8 months) before the study. Six were in New York Heart Association functional class III and six were in class IV at the time of the study. A recent left ventricular ejection fraction averaged 21%. Six patients had coronary artery disease (documented by prior coronary angiography demonstrating ≥ 70% stenosis of at least two coronary arteries or by previous transmural myocardial infarction, or both). Six patients had heart disease of other etiologies that caused congestive cardiomyopathy; prior coronary angiography in each of these patients revealed no significant stenosis. Four patients had undergone previous cardiac surgery, two for coronary bypass grafting with associated aortic and/or mitral valve replacement and two for aortic valve replacement alone. Five patients remained symptomatic after treatment with nitrates or other vasodilators. Of the six with coronary artery disease, two had reproducible angina pectoris with mild exertion. Clinical data and serum digoxin levels at the time of study are presented in table 1.

The hemodynamic and myocardial metabolic responses were the same for patients with and without coronary artery disease. Group data are presented in figures 1–3 and individual changes in cardiac index
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Table 1. Clinical Characteristics of Patient Population

<table>
<thead>
<tr>
<th>Pt</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>Duration of congestive heart failure (months)</th>
<th>Ejection fraction</th>
<th>NYHA class</th>
<th>Digoxin level (ng/ml)</th>
<th>Rhythm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-vessel CAD; s/p inferior and anterior MI</td>
<td>61</td>
<td>25</td>
<td>0.29(R)</td>
<td>III</td>
<td>1.1</td>
<td>SR</td>
</tr>
<tr>
<td>2</td>
<td>s/p anterior MI</td>
<td>50</td>
<td>16</td>
<td>0.08(R)</td>
<td>IV</td>
<td>1.3</td>
<td>SR</td>
</tr>
<tr>
<td>3</td>
<td>3-vessel CAD, s/p anterior MI</td>
<td>66</td>
<td>36</td>
<td>0.15(A)</td>
<td>III</td>
<td>1.8</td>
<td>SR</td>
</tr>
<tr>
<td>4</td>
<td>3-vessel CAD, s/p CABG and MVR for mitral regurgitation</td>
<td>62</td>
<td>100</td>
<td>0.24(R)</td>
<td>IV</td>
<td>2.4</td>
<td>AF</td>
</tr>
<tr>
<td>5</td>
<td>3-vessel CAD; s/p CABG, MVR for mitral regurgitation, AVR for aortic stenosis</td>
<td>63</td>
<td>28</td>
<td>0.27(R)</td>
<td>IV</td>
<td>1.2</td>
<td>SR</td>
</tr>
<tr>
<td>6</td>
<td>s/p inferior and anterior MI</td>
<td>52</td>
<td>24</td>
<td>0.07(R)</td>
<td>IV</td>
<td>1.3</td>
<td>SR</td>
</tr>
<tr>
<td>7</td>
<td>Viral cardiomyopathy</td>
<td>39</td>
<td>13</td>
<td>0.15(A)</td>
<td>III</td>
<td>1.5</td>
<td>SR</td>
</tr>
<tr>
<td>8</td>
<td>Alcoholic cardiomyopathy</td>
<td>54</td>
<td>9</td>
<td>0.12(A)</td>
<td>IV</td>
<td>0.4</td>
<td>SR</td>
</tr>
<tr>
<td>9</td>
<td>Congestive cardiomyopathy secondary to aortic regurgitation, s/p AVR</td>
<td>68</td>
<td>84</td>
<td>0.12(R)</td>
<td>III</td>
<td>1.6</td>
<td>SR</td>
</tr>
<tr>
<td>10</td>
<td>Congestive cardiomyopathy secondary to aortic regurgitation, s/p AVR</td>
<td>54</td>
<td>70</td>
<td>0.39(R)</td>
<td>III</td>
<td>0.8</td>
<td>AF</td>
</tr>
<tr>
<td>11</td>
<td>Chronic mitral regurgitation</td>
<td>71</td>
<td>192</td>
<td>0.32(A)</td>
<td>III</td>
<td>2.3</td>
<td>AF</td>
</tr>
<tr>
<td>12</td>
<td>Congestive cardiomyopathy secondary to hypertensive cardiovascular disease</td>
<td>41</td>
<td>60</td>
<td>0.26(R)</td>
<td>IV</td>
<td>4.1</td>
<td>AF</td>
</tr>
</tbody>
</table>

Abbreviations: NYHA class = New York Heart Association functional classification; CAD = coronary artery disease; s/p = status post; MI = myocardial infarction; R = radionuclide ventriculogram; A = contrast angiogram; SR = sinus rhythm; CABG = coronary artery bypass graft; MVR = mitral valve replacement; AVR = aortic valve replacement; AF = atrial fibrillation.

and PCW pressure are presented in table 2. The only clinical developments within 6 hours of therapy that were possibly adverse effects were mild exacerbation of preexisting tremor in one patient and nausea in one patient. No patient developed angina pectoris or new ischemic electrocardiographic changes during pirbuterol therapy.

Effects on Systemic Hemodynamics

Mean arterial blood pressure was 86 ± 4 mm Hg in the basal state and did not change significantly at any time during the period of observation. Similarly, heart rate was not altered from its control value of 85 ± 6 beats/min. Cardiac output rose in each patient after pirbuterol administration. The resting cardiac index was markedly depressed (1.7 ± 0.1 l/min/m²) and peaked at 2.3 ± 0.2 l/min/m² 2 hours after oral pirbuterol (35% increase, p < 0.01). Furthermore, a statistically significant increase in cardiac index was found at each measurement point 90–180 minutes after oral pirbuterol. The peak cardiac index 2 hours after pirbuterol was accompanied by a 19% fall in the systemic arterial–mixed venous oxygen difference, from 7.5 ± 0.4 to 6.1 ± 0.3 vol% (p < 0.01). Calculated left ventricular stroke work index was markedly depressed in the control state (16.9 ± 1.8 g-m/m²) and tended to rise after pirbuterol administration, although these changes were not significant by analysis of variance. Systemic vascular resistance was initially elevated (1884 ± 118 dyn-sec-cm⁻⁴) and fell by 26%, to 1391 ± 69 dyn-sec-cm⁻⁴ (p < 0.01) at 120 minutes after therapy. Pulmonary vascular resistance was not significantly changed from its control value of 389 ± 67 dyn-sec-cm⁻⁴ at any measurement point. Cardiac index, systemic vascular resistance and left ventricular stroke work index at control and post-pirbuterol measurement points are presented in figure 1.

The pretreatment mean PCW pressure was substantially elevated (27 ± 2 mm Hg). Although most patients had decreases in PCW pressure of 5–7 mm Hg after pirbuterol administration, the times at which these decreases occurred varied widely and there was no significant change for the group as a whole at any single measurement point. Similarly, mean pulmonary arterial and right atrial pressures were also elevated (43 ± 4 and 11 ± 2 mm Hg, respectively) compatible with severe cardiac failure; neither changed significantly after pirbuterol administration. Because of the known variability in the time between oral dosing and peak hemodynamic effect, 4 PCW pressure, cardiac index and left ventricular stroke work index were further analyzed with regard to the apparent peak hemodynamic response to pirbuterol. PCW pressure fell significantly, from 27 ± 2 to 23 ± 2 mm Hg (p < 0.001) when data were analyzed in this fashion. Cardiac index at the time of
peak hemodynamic response was 47% higher than control (1.7 ± 0.1 vs 2.5 ± 0.2 l/min/m² for control and peak response, respectively, *p < 0.001). Individual patients demonstrated maximum increases in cardiac index at 60 minutes (one patient), 90 minutes (four patients), 120 minutes (two patients), 150 minutes (four patients) and 180 minutes (one patient) after pirbuterol. Left ventricular stroke work index also increased significantly from control values compared with values at the time of maximum increase in cardiac index (16.9 ± 1.8 to 23.8 ± 3.4 g-m/m², **p < 0.001). Figure 2 presents control and peak response
data for cardiac index, PCW pressure and left ventricular stroke work index.

Effects on Myocardial Oxygen Metabolism

Arterial–coronary sinus oxygen difference fell significantly, from 12.9 ± 0.5 to 11.1 ± 0.3 vol% (14% decrease) at 150 minutes after pirbuterol administration (p < 0.05). Coronary sinus blood flow was not significantly changed from its control value of 187 ± 23 ml/min at any measurement point. Calculated myocardial oxygen consumption tended to fall but was not changed significantly from its control value of 24 ± 3 ml/min at any time during the measurement protocol. The myocardial oxygen extraction ratio was not altered from its control value of 0.81 ± 0.03 after pirbuterol and similarly, the lactate extraction ratio was not significantly changed at any observation point from the control value of 0.43 ± 0.12. Changes in coronary sinus blood flow, arterial–coronary sinus oxygen difference and MVO₂ are presented in figure 3.

Discussion

The primary purpose of this study was to investigate the acute effects of oral pirbuterol on myocardial oxygen metabolism in the heart failure patient in order to assess possible risks of the agent in patients with coronary artery disease. This seemed particularly important because a β-adrenergic agonist that stimulates cardiac contractility might be expected to increase myocardial oxygen demand. Our interest in this topic was heightened by the recent demonstration in our laboratory that amrinone, an agent with both inotropic and vasodilator properties, can actually effect a net decrease in myocardial oxygen demand while exerting favorable overall hemodynamic effects in the patient with heart failure due to ischemic heart disease; such an effect may be mediated by diminution of cardiac volumes and thus of left ventricular wall stress, a major determinant of myocardial oxygen demand.

Although pirbuterol was initially found to be a β₂-adrenergic agonist in experimental studies and although a sustained β₂ effect is also found in humans with asthma, some stimulation of β₁ receptors is likely to occur, especially at higher concentrations. In fact, for most β₁ and β₂ "selective" β-adrenergic drugs, the selectivity is only relative. Whether cardiac β₁-receptor stimulation plays a major role in mediating pirbuterol's favorable hemodynamic effects in congestive heart failure is not known; the agent might be primarily active through β₂-receptor-mediated vasodilation of sufficient magnitude to achieve reduction in afterload and an increase in cardiac output. The relative importance of vasodilator and inotropic actions in cardiac failure will probably remain unknown until an i.v. preparation of pirbuterol is available for acute testing of its effects on indexes of cardiac contractility in man, or until more detailed animal experiments (preferably in conscious, unsedated animals) are performed.

Our data indicate that 20–30 mg of pirbuterol given orally to patients with severe and chronic congestive heart failure is not associated with an augmentation of myocardial oxygen demand (fig. 3). In fact, the observed narrowing of arterial–coronary sinus oxygen difference after pirbuterol administration in-
indicates a tendency toward diminution rather than augmentation of myocardial oxygen requirements. The stable lactate extraction ratio during the study period indicates that overall cardiac metabolism was maintained in an aerobic state after pirbuterol. No patient in our study developed clinical or electrocardiographic evidence of myocardial ischemia.

Our findings suggest that oral pirbuterol may be used in patients with coronary artery disease who have severe congestive heart failure on the basis of prior infarction and/or ischemic cardiomyopathy, without danger of major augmentation of myocardial oxygen requirements, and imply that exacerbation of myocardial ischemia should not occur as a result of pirbuterol therapy. Our study confirms the findings of earlier investigators that oral pirbuterol therapy is not associated with acute changes in mean arterial blood pressure or heart rate, and that the drug is well tolerated acutely by patients with symptoms of congestive heart failure refractory to digitalis and diuretic treatment.

The specific changes in systemic hemodynamics after a single oral dose of 20-30 mg of pirbuterol in our 12 patients with severe heart failure are qualitatively similar to those previously reported. Although percent changes in cardiac index were higher in these reports (average increase of 51% compared with 35% in our study), this may be because in these early studies, a comparison of peak hemodynamic responses for individual patients to control values was performed rather than an examination of group data as a function of time after drug administration (fig. 1). Our analysis of cardiac index data for changes observed at peak hemodynamic response (fig. 2) indicates a greater percent increase in cardiac index (47%) when results are expressed in this fashion; a modest (4 mm Hg) fall in PCW pressure similar to that seen by the previous group is also apparent, as well as a significant rise (41%) in left ventricular stroke work index.

Too few patients were studied to perform the multiple subgroup analyses necessary to determine whether pirbuterol's efficacy varies with certain clinical characteristics of congestive heart failure. Our data (tables 1 and 2) indicate that cardiac index increases substantially in patients with or without coronary artery disease (e.g., patients 3 and 10) and in those with severely depressed ejection fraction (e.g., patients...
3 and 9), and that absence of coronary disease with a higher left ventricular ejection fraction does not necessarily predict a marked hemodynamic response (e.g., patient 11). Further studies are needed to determine if any hemodynamic or clinical parameters will predict which patients with CHF are most likely to respond to pirbuterol.

Our studies, as well as those of Awan et al., and Sharma et al., suggest that the increases in cardiac output after pirbuterol administration are equivalent to those reported with prazosin and perhaps slightly less than those with hydralazine, although protocol differences in studies of orally active drugs do not allow exact comparisons of drug potency. We observed more dramatic increases in cardiac output with intravenously administered amrinone. Although amrinone is active when given orally, hemodynamic characterization of these effects is incomplete, so it is difficult to compare its oral potency to that of pirbuterol and the vasodilators. Although attenuation of pirbuterol's effects on noninvasively measured left ventricular ejection fraction after chronic oral therapy has been demonstrated, data are not available to determine whether these changes are accompanied by attenuation of the drug's effects on cardiac output and other hemodynamic parameters similar to those observed with chronic prazosin therapy. Our study does not predict whether pirbuterol will be efficacious in the management of chronic heart failure.

In summary, pirbuterol hydrochloride is an orally active β-adrenergic agonist that effects substantial hemodynamic improvement in patients with chronic severe congestive heart failure refractory to digitalis and diuretic therapy. Cardiac output increased and systemic vascular resistance decreased without significant changes in heart rate or arterial blood pressure. This improvement in cardiac performance was not accompanied by an increased requirement for coronary blood flow, myocardial oxygen delivery or myocardial oxygen extraction. Our findings suggest that chronic trials of pirbuterol therapy for congestive heart failure may safely include patients with ischemic heart disease.

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