Hemodynamic Effects of Oral Pirbuterol in Chronic Severe Congestive Heart Failure

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SUMMARY The achievement of satisfactory ambulatory therapy of severe chronic congestive heart failure may be helped by the development of safe and orally effective cardiotonic agents. Therefore, we evaluated by cardiac catheterization and limb plethysmography the temporal cardiocirculatory responses of the new ingestible \( \beta \) agonist pirbuterol in 10 coronary heart disease patients with severe congestive heart failure refractory to digitalis and diuretics. After a single oral dose of 0.4 mg/kg, ventricular dysfunction was considerably improved during 6 hours of hemodynamic monitoring. Cardiac index increased from a control of 1.71/min/m\(^2\) to 2.61/min/m\(^2\) \((p < 0.001)\) at 1 hour and to 2.41/min/m\(^2\) \((p < 0.005)\) at 3 hours and was 2.21/min/m\(^2\) \((p < 0.001)\) at 6 hours; left ventricular filling pressure decreased from a control of 24 mm Hg to 19 mm Hg \((p < 0.005)\) at 1 hour and to 18 mm Hg \((p < 0.005)\) at 3 hours and was 22 mm Hg \((p < 0.05)\) at 6 hours. Concomitantly, the peak increment in heart rate (6 beats/min) was minimal and without ectopy and mean arterial blood pressure decreased only 10 mm Hg. Total systemic vascular resistance declined by 887 dyn-sec-cm\(^{-5}\), forearm venodilation occurred and the rate-pressure product was unaltered. Thus, oral pirbuterol provides beneficial hemodynamic effects in patients with severe left ventricular dysfunction and appears potentially useful for long-term management of low-output congestive heart failure.

Methods

**Patient Population**

The study population (table 1) consisted of 10 patients with severe chronic congestive heart failure (mean ejection fraction 19\%). There were eight males and two females, with a mean age of 62 years. All patients had stable (more than 3 months) severe left ventricular dysfunction despite therapy with digoxin and diuretics. None of the patients had valvular heart disease. Seven patients had received systemic vasodilator agents, which were discontinued at least 2 weeks before evaluation. The etiology of chronic congestive heart failure was ischemic cardiomyopathy due to coronary disease, with documented myocardial infarction confirmed by previous left-heart catheterization and angiography in eight patients, and by characteristic electrocardiographic and nuclear scintigraphic criteria in the remaining two patients. To maintain a stable hemodynamic state during evaluation, the usual morning dose of diuretics was administered on the evening before study and the usual daily dose of digoxin was ingested on the morning of the study.

**Hemodynamics**

Systemic arterial pressure was measured directly through an intra-arterial Teflon catheter placed in a brachial artery. Right atrial, pulmonary artery and pulmonary artery wedge pressures were recorded with the Swan-Ganz catheter. Determinations of cardiac output by thermodilution were performed in triplicate (less than 10\% variation) with use of iced saline, and computations were done using a bedside computer (Santa Barbara Technology, Incorporated). Derived hemodynamic variables were calculated as follows: stroke work index \((SI) = SI = (\overline{AP} - LVFP) \times 0.0136\), where \(\overline{AP}\) = mean systemic arterial pressure and \(LVFP\) = left ventricular filling pressure (either mean pulmonary artery wedge or pulmonary artery diastolic pressure, the particular method used for this variable remaining constant throughout the study for each patient); total systemic vascular resistance \((TSVR) = 80 ( [\overline{AP} - RA]/CO)\), where 80 is a conversion factor (mm Hg to dyn-sec-cm\(^{-5}\)) and \(RA\) = mean right atrial pressure; and the
product of HR × SAP, where HR = heart rate and SAP = systolic systemic arterial pressure.

**Plethysmography**

Forearm plethysmography was performed in eight patients using a mercury-filled rubber strain gauge placed around the mid-forearm as previously described. Patients were studied in the supine position with the forearm elevated so that venous pressure in the arm approached zero; the hand vessels were isolated from the forearm by inflation of a wrist cuff to suprasystolic pressures. Forearm venous occlusion was rapidly achieved by inflation of a sphygmomanometer cuff wrapped around the upper arm and attached to a container of compressed air with a special pressure gauge preset at 30 mm Hg. Forearm blood flow was calculated from the change in forearm circumference during acute venous occlusion and was expressed as ml/100 g of tissue per minute. Intra-arterial pressure was obtained simultaneously from the indwelling brachial artery catheter placed in the opposite arm. Forearm vascular resistance was calculated as the ratio of mean arterial pressure to forearm blood flow expressed as mm Hg/ml/100 g/min. All values for forearm blood flow and forearm vascular resistance (less than 5% variation) represent the average of at least six determinations.

Forearm venous tone was also determined in the eight patients by the acute occlusion technique with an indwelling 19-gauge Teflon catheter or needle placed in a forearm vein immediately distal to the forearm strain gauge. The ratio of change in forearm venous pressure to the change in forearm volume (expressed in ml/mm Hg) that occurred during the initial 10 seconds after inflation of the upper-arm venous occlusion cuff to 30 mm Hg was measured to determine the pressure-volume relations of the capacitance bed. All venous tone determinations were performed in triplicate (less than 5% variation).

### TABLE 1. Pretreatment Characteristics of Patient Group

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Remote MI</th>
<th>NYHA class</th>
<th>LV ejection fraction</th>
<th>Daily therapy (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>M</td>
<td>Ant</td>
<td>IV</td>
<td>17</td>
<td>Dig, Fur 320, HD 400</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>Ant + Inf</td>
<td>IV</td>
<td>14</td>
<td>Dig, Fur 480, ISO 320</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>M</td>
<td>Ant</td>
<td>III</td>
<td>20</td>
<td>Dig, Fur 240</td>
</tr>
<tr>
<td>4</td>
<td>58</td>
<td>M</td>
<td>Ant</td>
<td>III</td>
<td>39</td>
<td>Dig, Fur 240, ISO 320</td>
</tr>
<tr>
<td>5</td>
<td>77</td>
<td>M</td>
<td>Ant + Inf</td>
<td>IV</td>
<td>15</td>
<td>Dig, Fur 240, ISO 160, HD 400</td>
</tr>
<tr>
<td>6</td>
<td>64</td>
<td>M</td>
<td>Ant + Inf</td>
<td>III</td>
<td>12</td>
<td>Dig, Fur 240, ISO 160, HD 400</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>M</td>
<td>Ant + Inf</td>
<td>III</td>
<td>21</td>
<td>Dig, Fur 80, ISO 240</td>
</tr>
<tr>
<td>8</td>
<td>63</td>
<td>M</td>
<td>Ant + Inf</td>
<td>IV</td>
<td>15</td>
<td>Dig, Fur 320</td>
</tr>
<tr>
<td>9</td>
<td>69</td>
<td>M</td>
<td>Ant</td>
<td>IV</td>
<td>14</td>
<td>Dig, Fur 120, HD 300</td>
</tr>
<tr>
<td>10</td>
<td>69</td>
<td>M</td>
<td>Ant + Inf</td>
<td>III</td>
<td>23</td>
<td>Dig, Fur 240</td>
</tr>
</tbody>
</table>

Abbreviations: Ant = anterior; Dig = digoxin, 0.25 mg; Fur = furosemide; Inf = inferior; ISO = oral isosorbide dinitrate; MI = myocardial infarction; NYHA class = New York Heart Association functional class; HD = hydralazine.

### Pirbuterol Administration

After hemodynamic stability was confirmed for 60 minutes in each patient, control cardiac and peripheral circulatory dynamics were recorded and oral pirbuterol, 0.4 mg/kg body weight, was given. The temporal hemodynamic effects of this dose of the agent were measured sequentially at 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 5 hours and 6 hours after pirbuterol. Forearm plethysmography was repeated 2 hours after pirbuterol administration. The ECG was continuously monitored.

### Statistical Analysis

The data were analyzed using paired t test and analysis of variance.

### Results

Nine of our 10 patients with severe congestive heart failure responded markedly to this 0.4-mg/kg dose of oral pirbuterol.

### Heart Rate and Blood Pressure

After pirbuterol, the control heart rate of 80 ± 4.3 beats/min (mean ± SEM) increased slightly to 86 ± 3.7 beats/min at 1 hour (p < 0.05) and remained mildly elevated (p < 0.05) at this level throughout the study. Ventricular ectopy was not induced by the agent. Mean systemic arterial blood pressure was modestly decreased by pirbuterol (fig. 1A), from a control of 82 ± 5.3 mm Hg to 73 ± 3.2 mm Hg at 1 hour (p < 0.01) and remained diminished for 5 hours.

### Left Ventricular Filling Pressure

The control elevated left ventricular filling pressure of 24 ± 2.2 mm Hg (fig. 1B) declined to 19 ± 2.4 mm Hg (p < 0.005) at 30 minutes after administration of pirbuterol and remained reduced for the entire 6-hour
period of hemodynamic measurements, reaching its nadir of 18 ± 2.6 mm Hg (p < 0.005) at 3 hours.

Cardiac Index and Stroke Index

The control abnormally low cardiac index of 1.7 ± 0.16 l/min/m² was markedly augmented by 30 minutes after pirbuterol to 2.3 ± 0.23 l/min/m² (p < 0.01) and reached a peak of 2.6 ± 0.25 (p < 0.001) at 1 hour (fig. 2A). The cardiac index remained elevated throughout the measurement period of 6 hours and was 2.2 ± 0.19 l/min/m² (p < 0.001) 6 hours after pirbuterol. Similarly, the control reduced stroke volume index of 22 ± 2.6 ml/beat/m² (fig. 2B) increased to 29 ± 3.2 ml/beat/m² (p < 0.01) at 30 minutes and 31 ± 3.3 ml/beat/m² (p < 0.005) at 1 hour. The stroke volume index remained elevated throughout the observation period and was 27 ± 2.7 ml/beat/m² (p < 0.05) at 6 hours.

Stroke Work Index, Systemic Vascular Resistance and Double Product

The control stroke work index of 17.8 ± 2.7 g · m/m² (fig. 3A) increased to 23.1 ± 4.0 g · m/m² (p < 0.01) 30 minutes after pirbuterol. This index of left ventricular pump function remained augmented throughout the study period. Total systemic vascular resistance decreased after pirbuterol (fig. 3B) from a control of 2095 ± 237 dyn-sec-cm⁻⁸ to 1486 ± 219 dyn-sec-cm⁻⁸ (p < 0.01) at 30 minutes and to 1274 ± 208 dyn-sec-cm⁻⁸ (p < 0.001) at 1 hour. This variable reached its nadir (1208 ± 134 dyn-sec-cm⁻⁸, p < 0.001) 2 hours after pirbuterol and gradually returned toward the control value, although total systemic vascular resistance was substantially reduced at 6 hours. The product of HR · SAP did not change significantly (p > 0.05) with pirbuterol (fig. 3C) during the 6 hours of measurement.

Forearm Vascular Resistance and Venous Tone

The control lowered forearm blood flow increased from 1.8 ± 0.4 ml/100 g/min to 2.4 ± 0.5 ml/100 g/min (p < 0.05) at 2 hours after pirbuterol (fig. 4A), while the elevated forearm vascular resistance (fig. 4B) of 52.2 ± 6.2 mm Hg/ml/100 g/min decreased to 36.7 ± 6.9 mm Hg/ml/100 g/min (p < 0.05). Concomitantly, the raised forearm venous tone of 39.9 ± 9.1 mm Hg/ml decreased (fig. 4C) to 17.1 ± 5.6 mm Hg/ml (p < 0.05) after pirbuterol.

Discussion

The present study of the temporal hemodynamic effects of oral pirbuterol clearly shows that this pharmacologic agent results in sustained and dramatic improvement of impaired left ventricular function in patients with chronic coronary disease. Thus, in our patients with severe congestive heart failure, marked augmentation of depressed pump output occurred concordantly with considerable reduction in increased cardiac preload, while mean blood pressure decreased only slightly. Because pirbuterol resulted in a modest decline in systemic blood pressure, the rate-pressure product was unaltered despite minimal increase in heart rate. These results are consistent with subsequent experience with this agent in heart failure.9, 10

**Figure 1.** Sequential effects of oral pirbuterol on mean intra-arterial pressure (panel A) and on left ventricular (LV) filling pressure (panel B) in the 10 patients with chronic refractory congestive heart failure. Average values ± SEM are shown throughout the 6 hours of evaluation after ingestion of a single dose. *p < 0.05, **p < 0.01, ***p < 0.005.
Physiologically, the beneficial cardiocirculatory responses to ingested pirbuterol may be related to the known positive inotropic action of the agent\(^{11}\) causing a markedly enhanced cardiac output for several hours after a single oral dose. In addition to the improved cardiac contractile state, the considerable simultaneous decline in elevated left ventricular preload is partially the result of systemic vasodilation produced by pirbuterol. Similarly, while the predominant means of cardiac output augmentation is probably due to increased contractility effected by \(\beta_1\) agonism, the concomitant reduction in systemic vascular resistance may greatly facilitate ventricular emptying. Although the precise magnitude of the contributions of the cardio tonic and vasorelaxant properties of pirbuterol to its resultant salutary hemodynamic actions is difficult to ascertain, the powerful inotropic stimulation may be paramount, because cardiac output was markedly augmented while peripheral vasodilation was modest.

Pirbuterol (2-hydroxy methyl-3-hydroxy-6-[1-hydroxy-2-tert-butylamino-ethyl] pyridine) is a new sympathomimetic amine considered in animal studies to have major \(\beta_1\) adrenergic actions.\(^{11}\) Although the drug produced major augmentation of myocardial contractile force,\(^{11}\) its \(\beta_1\) adrenergic properties were not emphasized. Thus, this study represents the first clinical demonstration of the substantial \(\beta_1\) adrenergic stimulating actions of pirbuterol, which are potentially useful in therapy of myocardial dysfunction caused by chronic coronary heart disease. The mechanism of the relative lack of \(\beta_2\) selectivity in clinical heart failure is uncertain, but may relate to the higher blood levels of the drug observed in this setting.

Concerning potentially untoward effects related to \(\beta\)-receptor activation or other mechanisms, neither cardiac dysrhythmias nor conduction abnormalities developed during 6 hours of continuous electrocardiographic monitoring after administration of pirbuterol. The only side effect noted was mild restlessness for 2–3 hours in three of the 10 patients. Therefore, the 0.4 mg/kg dose of pirbuterol was well tolerated without toxicity during this acute hemodynamic evaluation. Although data from long-term studies in heart failure patients are not available, experience with this agent in the prolonged treatment of bronchial asthma attests to pirbuterol's general freedom from toxicity.

Although pirbuterol produced positive inotropic and vasodilator actions in our patients, the latter property of the drug is relatively modest. Thus, whereas oral pirbuterol can effect marked enhancement of pump output in patients with left ventricular
dysfunction, our data indicate that the addition of a systemic venodilator may be useful in optimizing preload reduction in severe congestive heart failure. Combined therapy with vasorelaxant agents provides a potential mechanism for greater augmentation of depressed cardiac output. That the beneficial effects of pirbuterol are additive to those of digitalis is shown in the present study by the enhancement of left ventricular function caused by pirbuterol in our previously digitalized heart failure patients.

We conclude that a single oral dose of pirbuterol achieves considerable improvement of cardiac performance in patients with severe left ventricular dysfunction. This salutary response is characterized by a marked increase of lowered cardiac output and a moderate decrease in elevated ventricular filling pres-
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The cardiocirculatory benefit was sustained for several hours, suggesting that long-term ambulatory therapy of congestive heart failure with pirbuterol is potentially feasible.

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References

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