Pirbuterol, An Oral Beta-adrenergic Receptor Agonist, in the Treatment of Chronic Cardiac Failure

Karl T. Weber, M.D., Virginia Andrews, R.N., Joseph S. Janicki, Ph.D., Mariell Likoff, M.D., and Nathaniel Reichek, M.D.

SUMMARY Pirbuterol (PB), an oral β-adrenergic-receptor agonist, has the pharmacologic effects of vasodilatation and positive inotropy. The present studies were undertaken to determine the value of PB in the long-term therapy of chronic cardiac failure. A double-blind, randomized, 7-week trial comparing PB (20 mg three times daily) with placebo in 12 patients was followed by 12 weeks of open PB therapy. Dose-dependent nervousness and tremulousness limited the unit PB dose to < 20 mg in six patients. In all patients, clinical status, exercise tolerance and maximal oxygen uptake, left ventricular echocardiographic dimension and cardiothoracic ratio were unchanged from control after 7 weeks of placebo or PB or after 12-19 weeks of PB. To assess the adequacy of 20 mg of PB, the dose-response relations of cardiocirculatory effects to 10, 15, 20 and 30 mg of PB were compared in seven of the above patients and nine other patients. Cardiac output was significantly elevated and wedge pressure reduced after all four doses, but these changes were sustained for 6 hours after 20- and 30-mg doses only. Thus, the role of PB in the management of chronic cardiac failure appears limited; judgment of its utility must await the results of additional controlled trials.

The physiologic basis for augmenting the performance of the failing heart is rooted in the principles of cardiac muscle mechanics. Muscle fiber shortening, and thereby cardiac output, are enhanced when myocardial contractile state is raised or the load resisting fiber shortening is reduced. For example, dobutamine is a β1-receptor agonist that augments myocardial contractile state. When given intravenously to patients with severe heart failure refractory to standard medical therapy, dobutamine significantly improves ventricular pump function and has therefore proved useful in the short-term treatment of these patients. Pharmacologic vasodilatation with nitroprusside to attenuate the heightened systemic vascular resistance that accompanies chronic heart failure also raises the output of the failing heart effectively. A theoretically attractive concept for the long-term pharmacologic management of chronic cardiac failure would therefore embrace the principles of augmenting contractility and vasodilatation.

Pirbuterol is an oral β-adrenergic-receptor agonist that has positive inotropic and vasodilator properties in dogs. In patients with chronic heart failure, Awan et al. and Sharma et al. found that pirbuterol significantly increased cardiac output while reducing left ventricular filling pressure, and that these salutary hemodynamic effects compared favorably with those of dobutamine. The long-term efficacy and safety of pirbuterol in the management of chronic cardiac failure, however, remain unclear. In uncontrolled trials, long-term pirbuterol therapy has been reported to provide a sustained improvement in ventricular function and exercise tolerance.

We undertook the present study to establish the dose relation and cardiocirculatory effects of pirbuterol and to determine its value in the long-term treatment of patients with chronic heart failure. The ability of pirbuterol therapy to improve exercise performance and to reduce heart size in these patients was specifically evaluated.

Methods

Double-blind Randomized Trial: Pirbuterol vs Placebo

The study population consisted of seven male and eight female outpatients, mean age 59 years (range 36-78 years), who had stable (> 6 months), chronic class III and IV heart failure by New York Heart Association (NYHA) criteria. All patients received digitalis and diuretics for at least 1 year. Ten patients had valvular heart disease (one with mitral and three with aortic valvular incompetence, three with combined mitral and aortic regurgitation, and three with prosthetic mitral valve replacement), four with primary myocardial disease, and one with ischemic heart disease and documented myocardial infarction. Seven of the patients had chronic atrial fibrillation; the remainder were in sinus rhythm. All patients had radiographic cardiomegaly (cardiothoracic ratio > 50%).

Each patient gave written, informed consent. The effectiveness of pirbuterol in the treatment of these patients was assessed by a weekly interview and physical examination and by periodic assessment of exercise performance, radiographic heart size and echocardiographic left ventricular chamber diameter. Maximal exercise capacity was assessed during upright, progressive treadmill exercise (2-minute stages) using the respiratory gas exchange technique. The aerobic capacity, or maximal oxygen uptake (VO₂ max; ml/min/kg), was determined in all patients; VO₂ max was achieved when oxygen uptake did not change.

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Patients were entered into the study only when their medical therapy had been stable for several months and after two reproducible exercise tolerance tests, an echocardiogram, a chest radiograph and a 24-hour Holter monitor recording were obtained. All patients received a capsule containing lactose (single-blind placebo) three times daily for 1 week, after which an exercise tolerance test was repeated. The patients were then randomized in double-blind fashion to receive either pirbuterol or placebo for 7 weeks. This phase of the study was initiated by a 3-week dose-titration period during which the patients received either one placebo or one 10-mg pirbuterol capsule three times daily during weeks 1 and 2; thereafter, placebo was continued or pirbuterol was increased to one 20-mg capsule three times daily for the remaining 5 weeks. Selection of the final daily dose of pirbuterol was based on patient tolerance to the drug. Three patients did not complete the titration period because of intercurrent illness. The pirbuterol dosage was limited to 45 mg/day in two patients because they developed nervousness, tremulousness and diaphoresis. These symptoms were also present, but tolerable, in two patients who received 60 mg/day. Exercise testing was repeated at 4 and 7 weeks; the chest radiograph, echocardiogram, and 24-hour Holter monitor recording were repeated at week 7. Six patients receiving placebo and six receiving pirbuterol completed this phase of the study. All echocardiograms and chest radiographs were interpreted without prior knowledge of the form of treatment. The plasma concentration of pirbuterol was determined by gas chromatography and mass spectrometry at 7 weeks.

Open Therapy: Pirbuterol

Eleven of the 12 patients who completed the 7-week controlled study and one patient who had been dropped from the double-blind trial because of intercurrent illness received open pirbuterol therapy. For the six patients previously receiving placebo, this represented a crossover to active drug; the maximal tolerated dose was again determined over a 3-week titration period. Two of these six patients developed tremulousness and diaphoresis, which limited their total dose of pirbuterol to 20 mg and 45 mg, respectively.

Four patients (three males and one female, ages 50–73 years) were given pirbuterol without randomization at the request of their referring physician. Three had primary myocardial disease and one ischemic heart disease. These patients had either NYHA class III or IV heart failure. Before these patients were enrolled, two reproducible baseline tolerance tests, chest radiograph, echocardiogram and Holter recording were obtained. Because of nervousness and tremulousness, the pirbuterol dosage was limited to 30 mg/day and 45 mg/day in two of these four patients.

At 12 weeks of open therapy (19 weeks for patients previously taking pirbuterol), all patients underwent treadmill exercise testing, and an echocardiogram and 24-hour Holter recording were obtained. Within 2–16 weeks after pirbuterol therapy was concluded, 11 of the 16 patients underwent a final exercise test.

Dose-Response Relation

The symptoms of nervousness and tremulousness limited the unit dose of pirbuterol to less than the presumed optimum of 20 mg in six patients. Accordingly, we elected to assess the dose-dependent cardiovascular effects of pirbuterol. Sixteen patients with chronic cardiac failure refractory to digitalis and diuretics were admitted to the Clinical Research Center of this hospital for elective right-heart catheterization. Seven of these patients had participated in the controlled trial; pirbuterol had been discontinued for several weeks before their entry into this study. Each patient gave written, informed consent. There were nine males and seven females, ages 27–78 years (mean 54 years). All patients had stable (> 6 months) clinical heart failure (NYHA classes II–IV). One had ischemic heart disease, angiographically demonstrable coronary artery disease and a segmental wall motion abnormality. Five patients had chronic valvular heart disease (two mitral regurgitation, one aortic regurgitation, one combined aortic and mitral incompetence and one prosthetic mitral valve replacement). In the remaining 10 patients, the cause of chronic heart failure could not be determined from standard diagnostic criteria and was therefore considered to represent primary myocardial disease.

Catheterization was performed with a flotation triple-lumen catheter inserted into the pulmonary artery through an arm vein. Right atrial, pulmonary artery and occlusive or wedge pressures were recorded. Systemic arterial pressure was measured by standard sphygmomanometry and heart rate by electrocardiographic monitoring. Cardiac output was determined by thermodilution or the Fick principle, using measured oxygen uptake and arteriovenous oxygen difference. The oxygen content of arterial and mixed venous blood was determined from the percent oxygen saturation and the oxygen carrying capacity. The following hemodynamic variables were derived: cardiac index and stroke volume index as cardiac output and stroke volume (cardiac output divided by heart rate) normalized by body surface area and expressed as l/min/m² and ml/m², respectively; systemic vascular resistance (dyn–sec–cm⁻⁵) as the difference in mean arterial and right atrial pressures divided by cardiac output; and stroke work index (g · m/m²) as the difference in mean ejection and wedge pressures multiplied by stroke volume index.

The usual daily dose of digitalis and diuretics were withheld on the morning of the study. Supine hemodynamic monitoring commenced 30 minutes before oral ingestion of either 10, 15, 20 or 30 mg of pirbuterol. The selected dose of pirbuterol was determined by a computer-generated random-sequence scheme designed to divide the 16 patients into four dose-response groups, with each group of four patients receiving either 10, 15, 20 or 30 mg. The temporal hemodynamic response to pirbuterol was measured hourly for 6 hours.
after administration; the ECG was monitored continuously. The plasma concentration of pirbuterol was determined 3 hours after oral dosing in each group.

Data Analysis

For the dose-response study and for each treatment group in the double-blind trial, a one-factor analysis of variance was used. If the resulting F value indicated a significant difference in any of the variables a modified t test was used to determine times at which the data became significantly different from baseline. Thus, for the dose-response phase, six comparisons were made for each variable. For the double-blind trial, a maximum of four comparisons were made; the minimal levels of acceptable significance, according to the Bonferroni method were p < 0.05/6 and p < 0.05/4, respectively. For the double-blind randomized trial, gas exchange and electrocardiographic data from the placebo and pirbuterol group were compared using the two-factor analysis of variance. With this analysis, "group" was the row factor (fixed) and "data collection period" the column factor (variable). Finally, for the open therapy trial, a paired data analysis was used to compare the crossover patients before and after pirbuterol. All averaged data are presented as mean ± SD.

Results

Pirbuterol vs Placebo

The average baseline exercise tolerance and VO₂ max of the patients randomized to pirbuterol were not statistically different from those of patients randomized to placebo (table 1) and were consistent with advanced impairment in their functional status. Exercise performance in each treatment group was reproducible after 1 week of single-blind placebo therapy. Likewise, their effort tolerance and aerobic capacity after 4 and 7 weeks of double-blind therapy were not significantly different from baseline or single-blind placebo (table 1). Moreover, patients receiving pirbuterol did not improve clinically during therapy. For example, the severity of exertional dyspnea and fatigue did not change in the six patients given pirbuterol for 7 weeks; the clinical status of their cohorts receiving placebo was also unchanged. Two of the patients given pirbuterol experienced nervousness and diaphoresis, which limited their daily dosage to 45 mg. (The presumed optimum is 60 mg.) However, the exercise perform-

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<th>Table 2. Response of Heart Size to Pirbuterol</th>
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<td>LV diastolic diameter (cm/m²)</td>
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<td>Placebo</td>
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<tr>
<td>Pirbuterol</td>
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<tr>
<td>Cardiothoracic ratio (%)</td>
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<tr>
<td>Placebo</td>
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<td>Pirbuterol</td>
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Values are mean ± SD. Abbreviation: LV = left ventricular.

ance of the four patients receiving 60 mg of pirbuterol daily was no different from their baseline control. The mean plasma pirbuterol concentration 3 hours after a unit dose of 20 mg was 23 ng/ml (range 17–30 ng/ml). One patient had a markedly elevated level of 91 ng/ml.

Echocardiographic diastolic chamber size after 7 weeks of pirbuterol was not significantly different from control (table 2); the same was true for the placebo group. The cardiothoracic ratio after 7 weeks of pirbuterol or placebo was similar to the baseline value (table 2).

Open Pirbuterol Therapy

Sixteen patients received open-label pirbuterol therapy. Three of these patients had fewer symptoms of heart failure; this improvement could not be demonstrated during exercise testing. There was no improvement in exercise capacity or VO₂ max (table 1) after 12 weeks of pirbuterol in the six patients who had formerly been given placebo or in patients who received only pirbuterol for 12 or 19 weeks. Six of the 16 patients treated with pirbuterol developed nervousness and tremulousness that restricted their daily dose to 30 mg (three patients) or 45 mg (three patients). Echocardiographic measurement of left ventricular diastolic dimension was unaltered after 12 or 19 weeks of pirbuterol (table 2). Nine of the 12 patients from the control study and two of the four patients assigned directly to open pirbuterol underwent repeat exercise testing 2–16 weeks after completing pirbuterol therapy. Exercise tolerance and VO₂ max were unchanged from control (table 1), which indicates that their exercise performance or functional status did not deteriorate.

<table>
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<th>Table 1. Exercise Response to Pirbuterol</th>
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<td>Exercise capacity (sec)</td>
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<td>Placebo</td>
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<td>Pirbuterol</td>
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<td>Maximum oxygen uptake (ml/min/kg)</td>
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<tr>
<td>Placebo</td>
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<td>Pirbuterol</td>
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Values are mean ± SD.
Arrhythmia Detection

The arrhythmogenic potential of pirbuterol was examined by comparing baseline Holter monitor recordings to those taken during the double-blind and open-therapy trials. Each 24-hour recording was analyzed for the following: the lowest heart rate that occurred during sleep, the mean rates of ventricular and supraventricular premature depolarizations per hour, and the incidence of ventricular tachycardia (defined as more than three consecutive premature complexes).

Eleven patients had Holter recordings before randomization. No significant baseline difference was found in the heart rate response or the incidence of ventricular or supraventricular arrhythmias between the subsequent placebo and pirbuterol groups. Of the six patients randomized to pirbuterol, none showed any significant change in heart rate or arrhythmias. This was also the case for the crossover patients during the open therapy phase. Four patients complained of severe palpitations, and their daily dose was reduced. A significant increase in ventricular or supraventricular ectopic activity could not be documented by Holter recording in any of these patients.

Hemodynamic Dose-Response Relation

The hemodynamic characteristics during supine rest are given in Table 3. There were no statistically significant differences between the groups with respect to their cardiocirculatory state. The dose-dependent response in cardiac index and wedge pressure to pirbuterol is depicted in Figures 1 and 2. Within 1 hour after pirbuterol at all four dose levels, the cardiac index had increased 15% or more above its control value. This improvement in ventricular function was sustained for 6 hours in patients who received 20 mg or 30 mg of pirbuterol; in those receiving 10 mg and 15 mg, the augmentation in cardiac index had dissipated within 2 and 3 hours, respectively. The greatest increase in cardiac output (> 40%) occurred 2 and 3 hours after 20 mg or 30 mg. The average heart rate was not significantly increased after pirbuterol in any of the four dose groups, although in one patient receiving 30 mg, heart rate increased by 20 beats above baseline at hours 2 and 3. The increment in cardiac output with pirbuterol was therefore primarily due to an increase in stroke volume. Commensurate with the augmentation in stroke volume and the reduction in wedge pressure.

Table 3. Baseline Hemodynamic Profile of Pirbuterol Dose-Response Groups

<table>
<thead>
<tr>
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<th>10 mg</th>
<th>15 mg</th>
<th>20 mg</th>
<th>30 mg</th>
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<tr>
<td>Cardiac index (l/min/m^2)</td>
<td>2.44±0.7</td>
<td>1.74±0.3</td>
<td>2.09±0.7</td>
<td>2.01±0.8</td>
</tr>
<tr>
<td>LVFP (mm Hg)</td>
<td>17±12</td>
<td>23±6</td>
<td>17±10</td>
<td>27±9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83±22</td>
<td>86±14</td>
<td>78±10</td>
<td>82±13</td>
</tr>
<tr>
<td>SVR (dyne-sec-cm^-5)</td>
<td>1617±449</td>
<td>2545±576</td>
<td>2083±502</td>
<td>1987±1062</td>
</tr>
<tr>
<td>RA pressure (mm Hg)</td>
<td>9±5</td>
<td>9±4</td>
<td>6±5</td>
<td>9±6</td>
</tr>
<tr>
<td>Stroke work index (g·m/m^2)</td>
<td>40±19</td>
<td>30±12</td>
<td>37±28</td>
<td>30±10</td>
</tr>
</tbody>
</table>

Values are mean ± sd.

Abbreviations: LVFP = left ventricular filling pressure; SVR = systemic vascular resistance; RA = right atrial.

Figure 1. Dose-response relation to pirbuterol for cardiac index (mean ± sd) (n = 16).

Figure 2. Dose-response relation to pirbuterol for left ventricular filling or pulmonary capillary wedge pressure (mean ± sd).
after 20 mg and 30 mg of pirbuterol, calculated stroke work increased significantly.

Mean arterial pressure decreased by no more than 6% in any of the dose groups. This reduction occurred 2–4 hours after 15, 20 and 30 mg of pirbuterol and represented an insignificant change from baseline. Mean right atrial pressure was unchanged from control after pirbuterol in all of the dose groups.

In accordance with the significant elevation in cardiac output in the 15-, 20- and 30-mg groups, mean arterial and right atrial pressures remained unchanged, but calculated systemic vascular resistance fell significantly. Within 60 minutes after 15, 20 or 30 mg, resistance had fallen 15% or more. The peak reduction in resistance occurred between hours 2 and 3 and persisted to hour 6 in the 20-mg and 30-mg groups.

The plasma concentrations of pirbuterol 3 hours after 10, 15, 20 and 30 mg were 12 ng/ml (range 9–17 ng/ml), 25 ng/ml (range 13–43 ng/ml), 26 ng/ml (range 23–33 ng/ml) and 36 ng/ml (range 19–66 ng/ml), respectively.

Discussion

Pirbuterol (2-hydroxymethyl-3-hydroxy-6-[1-hydroxy-2-test-butylamine ethyl] pyridine), like salbutamol, is structurally related to the isoproterenol group of synthetic catecholamines. Because of pirbuterol’s chemical structure, its metabolic degradation by the methyl transferase system is retarded and, consequently, its therapeutic activity more prolonged than isoproterenol’s. The major use of pirbuterol has been as a bronchodilator emphasizing its β2-receptor agonistic properties. Pirbuterol’s positive inotropic properties (β1-receptor agonist) have been demonstrated. The appealing combination of vasodilation and positive inotropy for the treatment of heart failure has prompted a series of investigations to determine the efficacy and safety of pirbuterol in the treatment of this entity.

Awan et al. and Sharma et al. were the first to report the beneficial hemodynamic effects of pirbuterol in patients with severe heart failure. Their observations on the left ventricular functional response to a single oral dose of 20 mg are similar to those we found in the present study. Timmis and associates reported that pirbuterol and salbutamol each produced an average peak increase of 53% in the first time derivative of left ventricular pressure in patients with severe heart failure, despite the accompanying decrease in ventricular filling pressure. These salutary hemodynamic effects were not accompanied by an increase in myocardial oxygen consumption in patients with coronary artery disease or valvular heart disease.

The long-term results with pirbuterol in uncontrolled studies have varied. Awan and co-workers reported that after 6 weeks of pirbuterol therapy (20 mg three times daily), 10 of 11 patients with heart failure due to coronary artery disease had a significant increase of 25–29% in their baseline radionuclide ejection fraction and an average increase of 100 seconds in their maximal treadmill exercise tolerance. Colucci et al. found that the improvement in ejection fraction noted on the first day (from 20% baseline to 27%) of pirbuterol therapy (60 mg/day) was not sustained after 1 and 4 weeks in 12 patients with heart failure (seven with primary myocardial disease and five with ischemic heart disease). Dawson and colleagues reported a mixed experience. In 16 patients who responded clinically to pirbuterol, the hemodynamic effectiveness of 20 mg of pirbuterol was sustained after 3 months of therapy, but 15 other patients had to be withdrawn from pirbuterol because it was ineffective (10 patients) or because of adverse effects. Pamela et al. reported that nine of 16 patients (all five with cardiomyopathy and four of 11 with coronary artery disease) taking 60 mg of pirbuterol daily for 6 weeks had symptomatic improvement, which was associated with a persistent improvement in ventricular pump function at recatheterization. Our controlled studies in 16 patients with heart failure of diverse causes could not demonstrate an improvement in exercise performance or a consistent improvement in clinical status. From a statistical standpoint, an increase in maximal effort tolerance of two stages (240 seconds) of treadmill exercise or VO2 max of 2.6 ml/min/kg would be necessary to represent a significant improvement. Moreover, left ventricular chamber size and radiographic heart size were not altered with pirbuterol. Adverse effects limited pirbuterol dosage to less than the optimal daily dose of 60 mg in six of our patients.

Although the explanation for these diverse responses to pirbuterol is unclear, several possibilities exist. Colucci et al. suggested that drug tolerance due to “down regulation” in myocardial and vascular smooth muscle β-receptor responsiveness may occur with chronic pirbuterol therapy. This hypothesis was based on their findings that the density of β receptors on lymphocytes from their patients treated with pirbuterol was depressed. Jenne et al. reported a similar experience in asthmatics whose airway responsiveness declined with chronic β-adrenergic agonist therapy. Hence, the dose-response curve may be altered such that larger doses of pirbuterol are required. Similarly, dosing requirements for dobutamine are increased when patients receive an infusion of this agent for more than 72 hours. Adverse effects, however, appear to limit one’s ability to increase pirbuterol dosage. Several groups have demonstrated a persistent hemodynamic responsiveness and sustained benefit to pirbuterol in some of their patients. Thus, the issue of tolerance remains unclear.

Another explanation may relate to an intrinsic deterioration of the diseased myocardium or a worsening of the heart failure state. However, in our patients, clinical status, chest radiograph, therapeutic regimen and exercise tolerance after 3–5 months of pirbuterol were unchanged from control. In fact, the reproducibility in exercise performance suggests that the study design, with its serial exercise testing, did not promote a training effect. A training effect may occur in patients who can engage in more physical activity as their symptomatic heart failure is improved in response to effective forms of therapy.
Physical activity and the attendant increase in oxygen use by working skeletal muscle requires increased oxygen delivery. Cardiac output and skeletal muscle blood flow must therefore increase with exercise. Hoback and associates have suggested that the \( \beta_2 \)-agonist properties of pirbuterol may favor a preferential increase in skeletal and splanchnic blood flow. A reapportionment in systemic flow secondary to \( \beta_2 \)-agonist properties of pirbuterol may actually prove detrimental during exercise if it favors nonworking muscle and the splanchnic circulation. Maskin and her colleagues found that despite an acute increment in exercise cardiac output induced by dobutamine infusion, VO\(_2\) max was not increased. This finding implied that systemic flow had been diverted from working muscle because of the concomitant pharmacologic vasodilation of dobutamine.

Despite the apparently negative experience of our study, other investigators have noted an improvement in some of their patients. Additional, controlled studies must be performed. One point, however, is clear: A favorable acute hemodynamic response to an agent does not portend its outcome in the long-term management of chronic cardiac failure. Long-term controlled trials must be conducted in association with these acute studies before such a judgment may be rendered.

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