Reports on Therapy

Amrinone in the Treatment of Chronic Cardiac Failure

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The efficacy and safety of oral amrinone were examined in 17 patients with moderately severe to severe heart failure that was refractory to standard medical therapy and vasodilators. The short-term and 28 week response to open amrinone therapy was assessed first, followed by a placebo-controlled, double-blind withdrawal study of two 13 week stages in nine patients. Rest and exercise ventricular function were determined before and after 32 hours of amrinone; aerobic capacity was serially assessed. After 2 hours, 1.64 mg/kg amrinone produced a 40% (p < 0.001) increase in cardiac output and a 32% (p < 0.02) decrease in pulmonary wedge pressure without altering heart rate or blood pressure. The exercise cardiac index-wedge pressure curve obtained 32 hours after the first oral dose was significantly shifted (p < 0.05) above control values. A sustained improvement in maximal oxygen uptake was noted during long-term open amrinone therapy.

Subsequently, seven of the patients randomized to placebo therapy had a significant deterioration of symptoms or exercise tolerance, or both. After 4 weeks of readministration of amrinone, clinical stability was once again established and exercise tolerance was improved by Weeks 8 to 16. Adverse effects of thrombocytopenia (one patient) and hepatic dysfunction (one patient) attributable to amrinone were observed. It is concluded that amrinone is effective in the long-term treatment of chronic cardiac failure.

The long-term management of patients with chronic cardiac failure remains a difficult problem. In patients who remain symptomatic despite administration of digitalis and diuretic agents, salutary hemodynamic benefits have been obtained with various pharmacotherapeutic agents having positive inotropic (1) or vasodilator (2) properties, or both. These benefits have not necessarily been accompanied by an improvement in exercise performance (3,4) or an enhancement of the patient’s quality of life. Therefore, the search continues for an orally active compound that provides a sustained improvement in cardiac performance, as well as effort tolerance.

Amrinone is a synthetic cardiotonic agent with positive inotropic and vasodilator properties (5). Its mechanism of action is not entirely known, although it has been suggested that amrinone may have properties of phosphodiesterase inhibition (6). Administered either intravenously (7,8) or orally (9) to patients with chronic severe heart failure refractory to standard therapy, amrinone has been shown to acutely increase rest cardiac output and decrease rest left ventricular filling pressure without significant changes in systemic arterial pressure or heart rate. The hemodynamic response to upright exercise performance, measured within 24 hours of the initiation of intravenous amrinone administration, was also improved (10,11). In a small number of patients followed up for 4 weeks on oral amrinone therapy, aerobic capacity was increased (11) while no demonstrable tolerance to the drug has been observed (12).

Amrinone, therefore, appears to be a promising agent for the treatment of chronic cardiac failure. To date, however, long-term controlled trials with amrinone have not been reported. Accordingly, we examined the efficacy of oral amrinone in the long-term treatment of heart failure, as well as the invasive and noninvasive measurements of exercise performance in a controlled, double-blind withdrawal study.

Methods

Patients. The study group consisted of 17 patients (7 women and 10 men with a mean age of 56 years [range 45 to 67]) with stable, chronic, moderately severe to severe...
heart failure. Four had ischemic heart disease as judged by a previously documented myocardial infarction or electrocardiographic or enzyme criteria, or both. Seven patients had congestive cardiomyopathy of uncertain origin despite cardiac catheterization or echocardiographic studies, or both. Mitral or aortic valve incompetence, or both, with poor ventricular function accounted for the heart failure in the remaining six patients. Two of these six patients had undergone mitral valve replacement, but had residual myocardial dysfunction; the other four were judged to be poor surgical risks for valve replacement. Six patients had chronic atrial fibrillation; 11 had normal sinus rhythm.

As part of their baseline evaluation, all patients were interviewed and underwent physical and chest X-ray examination, nuclear ejection fraction measurement by gated blood pool imaging with technetium-99m, 24 hour ambulatory electrocardiographic Holter monitoring and a pulmonary function test. Weekly diaries were kept to establish a baseline subjective measurement of the patients’ functional capacity and to assess relative quality of life. Each patient gave a history of exertional breathlessness or fatigue, orthopnea and paroxysmal nocturnal dyspnea, despite the long-term administration of digitalis and one or more diuretic agents and was, therefore, considered to be refractory to standard medical therapy. No patient had significant obstructive airway or restrictive pulmonary disease. Fourteen patients had also received a trial of one or more vasodilators before entering the study. These included one patient who had received an oral nitrate preparation alone and four patients who had received it in combination with another vasodilator. Ten had received hydralazine alone or in combination with another vasodilator, and six patients underwent individual trials of prazosin, captopril or trimazosin. All vasodilators were given in maximal doses tolerated by the patient. Because of the persistent symptoms of failure and no improvement in functional capacity, the response to vasodilator therapy was considered inadequate in all. Vasodilator therapy was discontinued a minimum of 2 weeks before entry into the study. No patient had an exacerbation of cardiac failure on withdrawal of vasodilator therapy.

As further requirements for entry into the study, the dosage of diuretic drugs and digitalis for each patient had to be stable for at least 4 weeks, as did the degree of symptomatic and clinical failure. Exercise tolerance had to be reproducible (± 10%) on two occasions measured days to weeks apart. Finally, all patients had to meet one or more of the following criteria: a left ventricular filling or pulmonary wedge pressure greater than 15 mm Hg, a cardiac index less than 2.5 liters/min per m², an ejection fraction less than 30% and cardiomegaly on chest X-ray film estimated by a cardiothoracic ratio greater than 50%.

The functional capacity of each patient and the severity of cardiac failure were objectively graded on the basis of maximal oxygen uptake (VO₂ max) achieved during progressive upright treadmill exercise and the criteria previously reported from this laboratory (13). Six patients had moderately severe failure (class C) achieving a VO₂ max between 10 and 15 cc/min per kg, while 11 patients had severe failure (class D) achieving a VO₂ max of less than 10 cc/min per kg. VO₂ max was defined as VO₂ being unchanged (< 1 cc/min per kg) despite an increase in treadmill work.

Hemodynamic monitoring and exercise testing. All patients gave informed written consent; the investigational protocol and consent form were approved by the institutional review board of this hospital. After admittance to our clinical research center, a flotation catheter was inserted at the bedside through an antecubital vein to obtain baseline right heart, pulmonary artery and pulmonary capillary wedge pressures and cardiac output by thermodilution technique. Patients were then taken by wheelchair to our exercise facility where they underwent upright, progressive treadmill exercise to exhaustion to establish VO₂ max. The treadmill program, consisting of 2 minute stages during which speed or grade, or both, is varied, has been reported elsewhere (14). Right atrial, pulmonary artery and pulmonary capillary wedge pressures were measured during each stage of exercise; mixed venous blood was obtained during the last 30 seconds of each stage and its oxygen content subsequently determined.

Before and throughout exercise, respiratory gas exchange was monitored as previously described (13) to determine the response in oxygen uptake, carbon dioxide production and minute ventilation. Cardiac output by Fick principle was calculated for each exercise stage from VO₂ and the arteriovenous oxygen difference. The response in exercise performance, including hemodynamic measurements, was determined in each patient before and after 32 hours of oral amrinone therapy (discussed later).

Drug protocol: in-hospital phase. After 60 minutes or more of recovery from exercise, patients were given oral amrinone (Sterling-Winthrop). Previous experience with intravenous amrinone in this laboratory (11) has suggested that a mean unit dose of 1.8 ± 0.1 mg/kg dry body weight would produce a salutary hemodynamic effect, that is, an increase in cardiac output greater than 30% and a decrease in pulmonary wedge pressure greater than 30%. Bioavailability data (15) suggest that intravenous and oral dosing should be similar. Because oral amrinone during this study was only available in 75 and 100 mg capsules, the unit oral dose was slightly lower (1.6 ± 0.1 mg/kg). Rest hemodynamic variables and cardiac output were measured 30 minutes before and at 0.5, 1, 2, 3, 4 and 5 hours after amrinone administration to establish the hemodynamic response curve. Plasma samples were obtained throughout the dosing interval for determination of amrinone and its N-acetyl metabolite plasma concentrations by high-performance liquid chromatography (16).
Oral amrinone administration was continued on an every 8 hour basis. One to 2 hours after the fourth (32nd hour) dose of amrinone had been given, patients were returned to the exercise laboratory with the right heart catheter in place and a repeat exercise test was performed to $V_O^2$ max. Respiratory gas exchange, cardiac output and the hemodynamic response to exercise were measured as before. These determinations represented the exercise response to steady-state levels of amrinone, because mean amrinone half-life in these patients were $4.8 \pm 1.0$ hours (17).

Patients were discharged 24 hours later on a regimen of oral amrinone, $1.6 \pm 0.1$ mg/kg every 8 hours, for long-term treatment before the placebo-controlled withdrawal phase of the study.

**Drug protocol: outpatient phase.** Patients were followed up weekly for 4 weeks and then at biweekly intervals for the remainder of the study. Office visits included a diary review of symptoms and daily weight, a capsule count to assess compliance, physical examination and blood and urine determinations. Concomitant medications, such as digoxin and diuretic drugs, were maintained at baseline dosage unless diuretic dosage could be reduced on the basis of symptomatic improvement or the appearance of intravascular volume depletion. Exercise testing utilizing noninvasive respiratory gas exchange and chest X-ray examination were periodically performed. Open label amrinone therapy was continued for an average of 25 weeks (range 18 to 30) before the double-blind, placebo withdrawal phase.

*Eight patients did not complete the open label portion of the trial.* These included: three class D patients (severe failure) who died suddenly during Weeks 1, 4 and 12, respectively; two class D patients who developed an intercurrent illness unrelated to their cardiac condition at Weeks 16 and 29, respectively; one class D patient who developed an increased paravalvular leak around her mitral valve prosthesis 4 weeks into therapy and underwent successful corrective surgery; one class C patient (moderately severe failure) who proved unreliable on follow-up visits after 14 weeks; and one class C patient who developed abnormal liver function tests that resolved after amrinone withdrawal and recurred on rechallenge with the drug 12 weeks later. Randomization to the controlled withdrawal phase was, therefore, carried out in nine patients (four class C, five class D). Diuretic drug and digitalis dosages remained unchanged for at least 6 weeks before the double-blind, placebo withdrawal phase.

*These nine remaining patients underwent a two-phase study (13 weeks per phase).* The first phase was a double-blind randomization with the patient assigned to amrinone or placebo therapy. During the second phase, only those patients receiving amrinone underwent a second randomization.

All nine patients were subsequently placed on open amrinone therapy, either at the completion of the randomization period or when the clinical condition of the patient had deteriorated significantly to warrant breaking the blinded code and determining whether placebo was being received.

**Statistical analysis.** Patients were grouped into either functional class C or D according to their $V_O^2$ max. The averaged results for each group are presented as mean ± standard error of the mean. Group comparisons were made using the one-factor analysis of variance and the modified t test (18). In addition, group comparisons were always made with equal numbers of patients in each group. Thus, whenever a patient died or withdrew from the study, the baseline data in that case were not used in subsequent comparisons. In accordance with the Bonferroni method, a probability (p) value of less than 0.05/k was considered statistically significant ("k" is the number of comparisons performed for a given set of data) (18). For example, when the acute response in cardiac output was being statistically compared with baseline, a total of six comparisons were performed. Accordingly, p would have to be less than 0.008 for the increases in cardiac output to be considered statistically significant.

**Results**

**Amrinone: in-hospital phase.** Cardiac index and pulmonary wedge pressure. With the patient in the supine position, the mean cardiac index was $1.9 \pm 0.2$ liters/min per

![Figure 1](image-url)
and the mean pulmonary wedge pressure was 22 ± 3 mm Hg. The mean cardiac output and pulmonary capillary wedge pressure responses of the 17 patients given an average unit dose of oral amrinone of 1.64 ± 0.05 mg/kg are illustrated in Figure 1. Within 30 minutes after oral amrinone administration, the cardiac output had increased 26 ± 5% (p < 0.001) with a concomitant decrease in pulmonary wedge pressure of 8 ± 10%. A peak increase in cardiac output of 40 ± 6% (p < 0.001) was observed 2 hours after drug administration with a simultaneous peak decrease in wedge pressure of 33 ± 12% (p < 0.02). The salutary hemodynamic effects were sustained for 5 hours. Note­worthy are two patients who had a marked (44 and 80%, respectively) decrease in filling pressure to less than 14 mm Hg, 2 hours after a single dose of oral amrinone. Despite this large decrease in filling pressure, their cardiac output was significantly increased (49 and 51%, respectively) over control values.

The increase in cardiac output was temporally related to the attainment of peak plasma amrinone concentrations. Peak concentrations ranged from 0.5 to 4.2 µg/ml and occurred 0.5 to 2 hours after drug administration.

Blood pressure and heart rate. The control mean arterial pressure of the study group was 90 ± 2 mm Hg, with a corresponding heart rate of 77 ± 2 beats/min. At the time of the peak hemodynamic effect of amrinone, mean arterial pressure (87 ± 3 mm Hg) and heart rate (80 ± 2 beats/min) were unchanged. This was the case throughout the 5 hour monitoring period. Supraventricular or ventricular tachycardia was not observed during the dosing interval.

Exercise hemodynamics. Before amrinone, cardiac index and wedge pressure increased with exercise in both classes (Fig. 2). For the class C patients (moderately severe failure), the mean peak exercise wedge pressure was 28 ± 6 mm Hg and the corresponding maximal cardiac index was 4.1 ± 0.3 liters/min per m². In contrast, the class D patients (severe failure) reached a higher wedge pressure of 36 ± 7 mm Hg and a lower cardiac index of 3.0 ± 0.3 liters/min per m² during exercise.

After four doses of amrinone, both class C and D patients were able to walk additional stages on the treadmill. Furthermore, the cardiac index-wedge pressure curves for both classes were shifted to the left, indicating a significant (p < 0.05) hemodynamic improvement (Fig. 2). After amrinone, the maximal cardiac index for class C patients improved to 5.3 ± 0.5 liters/min per m² at a corresponding wedge pressure of 27 ± 8 mm Hg. Thus, at similar filling pressures as before amrinone, patients could generate a higher cardiac output and sustain it for longer periods. Likewise, the class D patients improved their maximal cardiac index to 4.0 ± 0.4 liters/min per m², while lowering maximal wedge pressure to 28 ± 5 mm Hg. The mean plasma concentration of amrinone at steady state was 0.87 ± 0.21 µg/ml.

Amrinone: outpatient phase. Exercise performance. (Fig. 3). At baseline, the mean maximal oxygen uptake (VO₂ max) was 12.5 ± 0.7 cc/min per kg for class C patients (moderately severe failure) and 8.7 ± 0.3 cc/min per kg for class D patients (severe failure). After steady state plasma levels of amrinone had been achieved, the aerobic capacity of class C patients was improved 18% (p < 0.05) to a VO₂ max of 14.8 ± 0.9 cc/min per kg. Similarly, the class D patients improved their aerobic capacity 22% (p < 0.05) to 10.6 ± 0.6 cc/min per kg.

Figure 2. For each stage of exercise, cardiac index is shown as a function of pulmonary wedge pressure before and 32 hours after amrinone treatment for patients with moderately severe (class C) and severe (class D) heart failure. The additional number of points with amrinone reflects the ability of the patients to exercise to higher levels of work.
This significant improvement in exercise performance as compared with baseline was sustained throughout the 28 week period. For the three class C patients who undertook an exercise test after 28 weeks of amrinone therapy, the VO₂ max continued to be significantly (p < 0.05) improved (14.9 ± 0.6 cc/min per kg) over the baseline value of 12.0 ± 1.0 cc/min per kg, as it did for the six class D patients (10.5 ± 0.6 versus 9.0 ± 0.3 cc/min per kg; p < 0.05).

**Functional capacity.** In addition to the objective measurement of aerobic capacity, each patient was assessed clinically and by their subjective functional capacity. Weekly diaries were reviewed to determine any change in the patients’ quality of life. Table 1 lists the results of this analysis for 11 patients who were on continuous amrinone therapy for more than 12 weeks. Importantly, six patients (55%) had a reduction of their diuretic requirements while in the study, without subsequent weight gain. More than 90% of the patients reported their ability to walk a flight of stairs without pause and a marked improvement in daily walking capacity. Nine patients (82%) stated that with amrinone they were able to complete all household chores with ease. Four patients (36%) (two class C and two class D) were able to perform more vigorous chores such as mowing the lawn or washing the car. Three patients previously unemployed because of disability returned to work. The remaining seven patients were able to participate in volunteer or service activities.

**Heart size.** Four patients had a clear reduction in radiographic heart size as measured by the cardiothoracic ratio. The average decrease for this subset was 13% (range 7 to 19), the most striking example of which is illustrated in Figure 4. The remaining patients had no significant change in cardiothoracic ratio.

**Randomization phase.** Nine patients were randomized to the double-blind, placebo phase of the study; four had moderate (class C) and five severe (class D) heart failure. Figure 5 depicts the response in maximal aerobic capacity obtained during exercise for all nine patients during baseline, open label therapy, double-blind randomization and subsequent rechallenge with amrinone.

**Aerobic capacity.** All of the nine patients who were randomized demonstrated a sustained improvement in aerobic capacity. At the time of the first 13 week randomization, four patients (three class C and one class D) were assigned to placebo while the remaining one class C and four class D patients received amrinone. During this period, one patient developed a severe respiratory infection with subsequent clinical deterioration and a possible drug interaction with erythromycin. This necessitated breaking the code and discovering that she had been taking amrinone at the time of her illness. She was subsequently placed on open therapy.

### Table 1. Quality of Life During Long-Term (>12 weeks)

<table>
<thead>
<tr>
<th>Medications</th>
<th>Patients (no.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced diuretic dosage</td>
<td>6</td>
</tr>
<tr>
<td>Physical activities compared with baseline</td>
<td>10</td>
</tr>
<tr>
<td>Flight of stairs without pause</td>
<td>10</td>
</tr>
<tr>
<td>Doubled subjective walking time</td>
<td>9</td>
</tr>
<tr>
<td>Completed all household chores with ease</td>
<td>4</td>
</tr>
<tr>
<td>Vigorous chores (mowing lawn, washing car)</td>
<td>4</td>
</tr>
<tr>
<td>Felt so well, desired or took vacation</td>
<td>4</td>
</tr>
<tr>
<td>Employment</td>
<td></td>
</tr>
<tr>
<td>Previously disabled, returned to work.</td>
<td>3</td>
</tr>
<tr>
<td>Able to participate in volunteer or service-related activities comparable with part-time employment.</td>
<td>7</td>
</tr>
</tbody>
</table>

**Figure 3.** Maximal oxygen uptake (VO₂ max) is shown for the patients with moderately severe (class C) and severe (class D) heart failure (excluding the patient who died during Week 1 of therapy) at baseline, 32 hours after and at discrete intervals during the 28 weeks of continuous amrinone treatment.
and has continued to do well for more than 52 weeks of continuous therapy, sustaining a significant improvement in exercise performance over baseline. The remaining eight patients including the four patients receiving placebo, exhibited no clinically apparent change in their failure or significant alteration in exercise performance throughout the first 13 weeks. Two of the four patients treated with placebo, however (both class C), demonstrated a progressive deterioration in aerobic capacity that became more pronounced by Week 14. In one of these patients, bilateral pleural effusions and cardiomegaly became present (Fig. 4).

**Placebo administration.** At the point of second randomization, the four patients receiving amrinone were randomly assigned to placebo while the other four continued to receive placebo. It should be noted that the double-blind nature of this two-phase period was still preserved. During this 13 week period, a variable decline occurred in the exercise tolerance and symptomatic improvement that was achieved during open therapy. Two patients in class C and three patients in class D developed significant worsening of their symptoms and had markedly reduced subjective and objective exercise tolerance. This marked deterioration occurred in less than 2 weeks of placebo therapy for three of the patients (one in class C and two in class D). The other two patients (one in class C, one in class D) required a full 18 weeks of placebo therapy before clinical worsening occurred to such a degree that the code was broken. The progression of cardiac failure symptoms was so severe in three of these patients (one in class C and two in class D) that they required hospitalization.

Three patients, two in class C and one in class D, failed to show a significant deterioration in symptoms while receiving placebo. One class C patient demonstrated a sustained improvement in exercise capacity over baseline, while the remaining two patients returned to baseline aerobic capacity. Thus, seven of the eight patients who completed the entire randomization period of 26 weeks had a serious deterioration of symptoms or exercise tolerance, or both, as a result of receiving placebo.

**Return to open therapy.** By 4 weeks of the return to open label amrinone therapy, the three class C and four class D patients whose condition had deteriorated during placebo administration were once again clinically stable. The concomitant medical regimen of all seven patients was identical to that used during the first open label phase after initial restabilization. No increase in maintenance diuretic dosage was required to improve their clinical symptoms or aerobic capacity after amrinone was reinstituted.

Of the three class C patients who demonstrated a decrease in their VO₂ max during placebo administration, two returned to their previously augmented aerobic capacity at-
Heart disease is the leading health problem in the United States. In 1965, it was estimated that 3 of every 1,000 persons in the United States with heart disease had cardiac failure that limited their lifestyle and shortened their survival (19). In 1980, the incidence of heart failure had increased dramatically; in fact, 400,000 hospitalized persons were discharged with this diagnosis (National Center for Health Statistics, unpublished data). Heart failure is the most common mortal disorder in hospitalized patients with heart disease (20). With current medical therapy including vasodilators, the 2 year survival rate of patients with severe heart failure is 30% or less (21). In light of the clear need for more effective therapy for both the short- and long-term management of patients with cardiac failure, an increasing number of pharmacologic approaches have emerged for the management of these patients (2,22,23).

Limitations of study. Before reviewing our experience, a number of shortcomings inherent to this study should be discussed. First, this study, although controlled and covering a period of 12 months or longer, involves only a small number of patients. Our ability to evaluate patients with advanced heart failure, whose prognosis is poor, over a long period of time is difficult. Cause and effect relations of side effects are obscured by the multiple medications that these patients receive, often including one or more diuretic drugs, digitalis, potassium chloride and anticoagulant agents, or both. In addition, these patients often have other acute and chronic illnesses that occasionally interrupt their stability and require additional therapeutic intervention. The incidence of dropouts from this study as a result of these problems is similar to our previous experiences (14,24).

Another potential shortcoming of this study relates to its design and the use of drug withdrawal to assess drug efficacy. Although recommended as a useful approach (25), the withdrawal design has several limitations. These include...
“carryover” effects, whereby a favorable response induced by the drug may be sustained during the withdrawal phase, and complicate the evaluation. For example, a marked reduction in heart size would be partially sustained during randomization despite the administration of placebo. As a result, a longer withdrawal period may be necessary to negate this persistent beneficial effect. Furthermore, there is the dilemma of determining when the heart failure state will reestablish itself and to what degree. There is no reason to expect that the new equilibrium state and its attendant neurohumoral characteristics achieved during withdrawal will necessarily resemble the steady state of failure present during the baseline stabilization period. This would certainly be the case if diuretic drugs were reduced during open label therapy and the patient was randomized to treatment with less saluretic agents.

Finally, any study conducted to assess the efficacy of therapy requires that an objective sensitive measure of the severity of failure be available and monitored serially. For this purpose we have chosen maximal oxygen uptake, which has been shown to predict cardiac reserve and functional capacity (13). However, it does not necessarily characterize exercise performance or symptoms at submaximal levels of work. Moreover, it is not known whether measured aerobic capacity can be used to detect subtle changes in cardiovascular function that may occur during drug withdrawal. Despite these shortcomings, this trial suggests that amrinone was effective in the treatment of chronic cardiac failure.

**Effects of amrinone.** In this study, amrinone was given to 17 patients with moderately severe to severe heart failure refractory to standard medical therapy and vasodilators. When measurements were made acutely, 1.6 mg/kg of oral amrinone exerted its salutary hemodynamic effects by increasing cardiac output at rest by 40% while simultaneously decreasing left ventricular filling pressure to a similar extent without changing heart rate or mean arterial pressure. The ability of this compound to improve ventricular function during exercise was also demonstrated. The increment in myocardial contractile state with an agent having positive inotropic properties permits greater muscle fiber shortening without the same dependence on fiber length (26). Hence, a reduction in filling pressure and volume greater than that obtained with pure vasodilator agents may be possible (27,28). A reduction in filling pressure may help to attenuate the exertional dyspnea these patients typically experience during exercise.

**Comparisons with other drugs.** Ideally, pharmacologic interventions designed for the long-term treatment of heart failure should improve not only myocardial performance but also blood flow to each end organ according to its metabolic requirements. An obvious increase in aerobic capacity of working muscle was apparent after amrinone administration and was accompanied by an improved VO₂ max. Such responses have not been observed during short-term vasodilator therapy, where exercise cardiac output increases, but arteriovenous oxygen difference narrows and, therefore, oxygen consumption is not enhanced (3,29,30). Recent studies from this laboratory (31) indicate that even though leg blood flow was increased after hydralazine administration, the aerobic capacity of the working leg muscles was not enhanced, suggesting that a shunting of blood flow to less metabolically active tissues had been produced by this nonspecific vasodilator. Moreover, we were not able to demonstrate an improvement in aerobic capacity with long-term hydralazine therapy (32), or in a controlled study of a beta-adrenergic agonist in similar patients (24). In contrast, the present experience demonstrated after 32 hours of oral amrinone therapy a significant improvement in aerobic capacity that was sustained for 28 weeks. Subjectively, our patients experienced less dyspnea and enjoyed a greater freedom of activity. Fairly vigorous activities became possible on a routine basis for some patients with severe heart failure. Objectively, in 55% of the patients improvement was great enough to permit a decrease in diuretic dosage without subsequent weight gain.

**Amrinone withdrawal and readministration.** The necessity of performing placebo-controlled trials as part of any investigational drug evaluation is obvious. Nine patients entered the double-blind amrinone withdrawal phase of our study. Of the eight patients who completed the 26 weeks of randomization, seven had a serious deterioration of symptoms or exercise tolerance, or both, after receiving placebo. The temporal relation between placebo administration and the exacerbation of the heart failure state, however, was widely disparate. Deterioration occurred within 2 weeks for three patients, all of whom were in remarkably stable condition for more than 20 weeks of open label amrinone therapy. Two other patients exhibited a slower progression of disability with placebo that may represent a “carry over” effect. All patients again had an improvement in aerobic capacity after readministration of amrinone.

**Side effects.** The side effect profile of amrinone requires comment. Adverse effects such as fever, thrombocytopenia and gastrointestinal disturbance have all been reported after amrinone therapy (8–11,33). In our study, amrinone had to be discontinued in one patient because of hepatic dysfunction clearly attributable to the drug. Regrettably, the patient died shortly thereafter of heart failure. Mild thrombocytopenia (100,000 to 150,000 mm³) occurred in most patients; moderate thrombocytopenia (50,000 to 100,000 mm³) appeared to be dose-related in one patient and was not associated with overt bleeding. Further studies are required to elucidate alterations in amrinone clearance and drug interaction and to establish its therapeutic to toxic ratio. In this respect, a more rapid assay of amrinone plasma levels may facilitate the correlation of side effects and amrinone concentration, allowing more intelligent utilization of the drug. Although not observed in this study, gastrointestinal upset
with epigastric cramping occurred in three patients in a previously reported experience (11). The broader distribution of concomitant medications throughout the day and administration of amrinone with meals was often helpful in alleviating these symptoms.

Effect on morbidity and mortality. Final consideration must be given to the influence of any new therapy on morbidity and mortality. To assess these end points, larger trials of much longer duration are needed. Nine patients completed the 54 week study. Three patients died within the first 12 weeks of the study; two others developed intercurrent illnesses. The morbidity and mortality of heart failure are extremely high (21,34), and our group of patients proved no exception. We are extremely encouraged, however, that 9 of the 17 study patients remain well at the time of this report. All have been receiving amrinone for more than 12 months of continuous therapy.

We sincerely appreciate the technical expertise and dedication of Tom Nusbickel and David Ward and the secretarial assistance of Jeannette Forte.

References


