Hemodynamic and clinical limitations of long-term inotropic therapy with amrinone in patients with severe chronic heart failure

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ABSTRACT To determine the hemodynamic and clinical effects of long-term positive inotropic stimulation on the myocardium, we treated 31 patients with severe chronic heart failure with oral amrinone (600 mg daily) and performed invasive hemodynamic studies during short- and long-term treatment with the drug. Stroke volume and stroke work indexes increased markedly during the first 48 hr of therapy (p < .01) but returned to pretreatment values after 2 to 10 weeks; upon drug withdrawal, both variables deteriorated rapidly to values significantly lower than those observed before treatment with amrinone (p < .01), despite similar values for left ventricular filling pressure, mean arterial pressure, and systemic vascular resistance. This pattern of response indicated that progression of the underlying heart disease had occurred during treatment with amrinone and contributed importantly to its failure to produce long-term benefits. Progression of left ventricular dysfunction was associated with a progressive increase in heart rate and plasma renin activity and a decline in serum sodium concentration. Clinically, amrinone therapy was complicated by sustained symptomatic ventricular tachycardia in four patients, worsening myocardial ischemia in four patients, and worsening congestive heart failure in eight patients, all of whom had been stable before entry into the study; only three of the 31 patients improved clinically. Ten patients died during the first 2 weeks of treatment, and 16 (52%) were dead within 3 months, a mortality rate twice as great as that seen during comparable trials with vasodilating drugs. Although noncardiac adverse effects were frequent, they were not the primary reason for drug failure. In conclusion, long-term therapy with amrinone may accelerate progression of left ventricular dysfunction, exacerbate myocardial ischemia, and provoke life-threatening ventricular tachyarrhythmias, thereby shortening survival in patients with severe chronic heart failure. Prolonged administration of inotropic drugs may achieve short-term gains at the expense of long-term detrimental effects on the myocardium.

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ating drugs was frequently caused by the development of pharmacologic tolerance\textsuperscript{20–22}; discontinuation of amrinone, however, commonly resulted in immediate hemodynamic and clinical deterioration.\textsuperscript{23, 24} Hence, it remains unclear why a drug that produces short-term hemodynamic benefits and to which tolerance does not appear to develop fails to produce long-term clinical improvement. To address this question directly, we evaluated the short- and long-term hemodynamic and clinical responses to amrinone in a large series of patients with severe chronic heart failure, using a study design we have successfully employed to demonstrate the efficacy (and lack of efficacy) of vasodilating drugs.\textsuperscript{20–22}

**Methods**

**Patients.** The patient population for the present study consisted of 31 consecutive patients with severe chronic heart failure who received treatment with oral amrinone. There were 26 men and five women, ranging in age from 41 to 88 years (mean 69). The cause of heart failure was ischemic heart disease in 22 patients, primary congestive cardiomyopathy in eight patients, and persistent severe left ventricular dysfunction after aortic and mitral valve replacement in one patient. All patients had symptoms at rest or on minimal exertion; no patient had experienced an acute exacerbation of heart failure within 2 weeks. Nine patients had previously failed therapy with oral captopril, but the remaining 22 patients had not received prior treatment with therapeutic doses of vasodilating drugs.

**Hemodynamic measurements.** Before receiving amrinone, each patient was observed in the hospital for at least 5 days, during which time doses of digoxin and diuretics remained constant, and all vasodilating drugs were withdrawn. After written informed consent was obtained according to the protocol approved by the local institutional review board, right heart catheterization was performed with a triple-lumen flow-directed catheter for measurement of right atrial, pulmonary arterial, and pulmonary capillary wedge pressures. An arterial cannula was inserted into the radial artery for measurement of systemic pressures. Measurements were made with zero reference level at the midaxillary line with the patient supine. Left ventricular filling pressure was measured as the mean pulmonary capillary wedge pressure or as the pulmonary arterial diastolic pressure after its identity with wedge pressure was established. Thermodilution cardiac outputs were determined in triplicate by a bedside cardiac output computer with the use of iced injectate. Heart rates were derived from a continuously recorded electrocardiogram.

**Drug administration.** After insertion of the intravascular catheters, each patient was permitted to rest for 12 to 24 hr. The next morning, after all medications (including digoxin and diuretics) had been withheld and the patient was maintained in a postabsorptive state, the following hemodynamic variables were determined repeatedly for at least 2 hr (with a variation of less than 10%) to ensure the stability of the hemodynamic state before the administration of amrinone: mean arterial pressure, heart rate, left ventricular filling pressure, mean right atrial pressure, and cardiac output. Each patient then received an initial dose of 100 mg of amrinone orally, followed (2.5 hr later) by an additional oral dose of 200 mg of the drug, and then 200 mg orally every 8 hr for 48 hr; we had previously shown that these large doses were required to produce sustained hemodynamic responses in patients with severe heart failure and that lower doses produced only modest and short-lived effects.\textsuperscript{25} All hemodynamic variables were measured before and every 30 min for at least 3 hr after each dose of the drug. During this 48 hr period, digoxin and diuretics were administered in unchanged doses, but these were separated from the administration of amrinone so as not to interfere with the evaluation of independent drug effects.

The hemodynamic responses to amrinone were reevaluated 2 to 10 weeks later (mean 4.2 weeks). During this time patients were placed on 2 g sodium diets, and the doses of digoxin and diuretics that each patient had been taking before entry into the study remained unaltered. The daily dose of amrinone (600 mg orally) also remained constant; every effort was made to encourage patients to tolerate adverse reactions so that at least 2 weeks of treatment with 600 mg daily could be completed. No vasodilating drugs were added during the trial. After 2 to 10 weeks patients were rehospitalized for a second observation period of 5 days, at the end of which right heart catheterization and arterial cannulation were again performed under conditions identical to those of the first study. To ensure evaluation of uninterrupted therapy, these invasive procedures preceded the timing of the next dose of amrinone by at least 8 hr; this permitted time for rest and for establishment of a stable hemodynamic state before the next scheduled dose of the drug. Amrinone was then administered in the same dose (200 mg) as during the preceding 2 to 10 weeks, and hemodynamic determinations were performed every 30 min for 3 hr. Amrinone therapy was then abruptly withdrawn, and while digoxin and diuretics were continued, repeat hemodynamic measurements were made periodically for the next 48 hr.

**Humoral and clinical determinations.** In 12 of the 15 patients who underwent a second hemodynamic study, blood samples were collected for determination of plasma renin activity (by radioimmunoassay) before the first dose of amrinone and 2 hr after the first 200 mg dose (on day 1), after the seventh dose (on day 3), after the dose evaluated after 2 to 10 weeks of treatment, and 48 hr after withdrawal of the drug. All samples were taken at the same time of day, with patients maintaining the 2 g sodium diet, 24 hr after the last dose of diuretic, and after at least 4 hr in the supine position. Serum sodium concentration was measured on the morning of the first and second hemodynamic evaluations.

The clinical status of each patient was evaluated during a control period of 3 days before institution of therapy with amrinone and after 2 to 10 weeks of treatment with the drug. Changes in the severity of dyspnea and fatigue at rest, in exercise tolerance, and in body weight were noted. Because all patients had symptoms at rest and/or on minimal exertion, formal exercise testing was not performed.

**Data analysis.** Mean systemic pressures were determined by electronic filtration. Derived hemodynamic variables were calculated as follows: cardiac index (CI) = CO/body surface area (liters/min/m\(^2\)), stroke volume index (SVI) = CI/HR (ml/beat/m\(^2\)), stroke work index (SWI) = SVI×(MAP – LVFP)×0.0136 (g-m/m\(^2\)), systemic vascular resistance (SVR) = 80×(MAP – MRAP)/CO, where CO is cardiac output, HR is heart rate, MAP is mean arterial pressure, LVFP is left ventricular filling pressure, and MRAP is mean right atrial pressure.

The responses to short- and long-term amrinone therapy were compared at five points: before amrinone, after the initial 200 mg dose of the drug, after 48 hr of therapy, during long-term drug administration (2 to 10 weeks), and 48 hr after drug withdrawal. At each point during therapy all hemodynamic variables were measured at peak effect of amrinone on cardiac output and left ventricular filling pressure (2.0 ± 0.5 hr). Changes in each hemodynamic variable and in plasma renin activity were compared at each of the five reference points by a repeated-measures
two-way analysis of variance procedure in which Duncan's multiple range test was used to differentiate among significant responses. Qualitative and quantitative differences between subgroups of patients were evaluated by the t test for independent variables and by the chi-square statistic using Yates' correction for continuity, respectively. Group data are expressed as mean ± SEM.

Results

Short- and long-term hemodynamic responses. Of the 31 patients who entered the trial, two failed to show an increase in cardiac output of 25% or greater or a decrease in left ventricular filling pressure of 5 mm Hg or less with 600 mg of amrinone daily for 48 hr and therefore did not receive long-term treatment with the drug. Of the remaining 29 patients, 14 patients did not complete at least 2 weeks of treatment because of adverse effects or death; only 15 patients underwent repeat hemodynamic studies during long-term therapy.

The hemodynamic responses in the 15 patients who underwent short- and long-term invasive evaluations are shown in figures 1 to 3. Cardiac index increased markedly (by 0.80 liter/min/m²; p < .01) with first doses of amrinone, remained elevated after 48 hr, became partially attenuated in magnitude after 2 to 10 weeks (p < .05), but declined significantly (by 0.79 liter/min/m²; p < .01) upon withdrawal of the drug. The persistent increase in cardiac index that we observed during long-term treatment with amrinone, however, was the result of a progressive rise in heart rate that occurred during the trial. Although there was little change in heart rate during the first 48 hr of treatment with amrinone, heart rate increased significantly (by 15.6 beats/min; p < .01) during long-term therapy and remained significantly elevated (by 6.6 beats/min; p < .01) 48 hr after drug withdrawal. Consequently, when stroke volume index and stroke work index were calculated to correct for these changes in heart rate, both variables improved substantially during the first 48 hr of amrinone therapy but returned to pretreatment values after 2 to 10 weeks despite continued administration of the drug and deteriorated to below pretreatment values upon drug withdrawal (p < .01).

With initial doses of amrinone, left ventricular filling pressure fell dramatically, and this improvement was sustained for 48 hr without attenuation (figure 2). After 2 to 10 weeks, however, left ventricular filling pressures increased significantly toward pretreatment values (p < .05) despite continued therapy and deteriorated further when the drug was withdrawn. A similar pattern of response was seen in terms of changes in mean right atrial pressure.

In contrast to changes in stroke work index and left ventricular filling pressure, the magnitude of the decreases in mean arterial pressure and systemic vascular resistance seen during the short-term administration of amrinone did not become attenuated during long-term therapy. The immediate declines in these two variables were sustained for 48 hr and after 2 to 10 weeks and promptly returned to pretreatment values (p < .01) upon drug withdrawal.

Individually, when the hemodynamic state before amrinone was compared with that observed 48 hr after withdrawal of long-term treatment with the drug, eight FIGURE 1. Values for cardiac index, stroke volume index, and stroke work index before amrinone (C), after the first 200 mg dose of the drug (D₁), after 48 hr of treatment with 600 mg daily (D₃), after 2 to 10 weeks (long-term, LT), and 48 hr after drug withdrawal (W) in the 15 patients who completed the trial. Asterisks indicate significant difference from control values. Data are expressed as mean ± SEM.
Amrinone produced little change in plasma renin activity during initiation of treatment, but plasma renin activity increased significantly during long-term therapy (figure 2); this reactive hyperreninemia, however, was not reversed by withdrawal of the drug. The rise in plasma renin activity corresponded to a decrease in serum sodium concentration during long-term treatment with amrinone in the 15 patients who underwent repeat hemodynamic studies (137.0 ± 1.5 to 133.5 ± 1.0 mEq/liter; p < .05).

Of the 12 patients who had determinations of plasma renin activity, seven patients showed at least a two-fold increase in plasma renin activity during the trial, of whom six had hemodynamic evidence for progression of their underlying heart disease; of the remaining five patients without reactive hyperreninemia, only one showed such progression. In the eight patients who

**FIGURE 2.** Values for mean arterial pressure, left ventricular (LV) filling pressure, and systemic vascular resistance at the five reference points depicted in figure 1.

of 15 patients had values for cardiac index, stroke volume index, and/or stroke work index after completion of the trial that were at least 20% lower than the corresponding pretreatment values, despite similar values for left ventricular filling pressure and systemic vascular resistance; these patients were considered to have experienced progression of their underlying heart disease during the course of the study. In three other patients, hemodynamic variables during long-term therapy with amrinone returned to their pretreatment state, but there was no deterioration after withdrawal of the drug; these patients were considered to have developed hemodynamic tolerance. Only four of 15 patients showed immediate and sustained increases in stroke work index during long-term amrinone therapy with a return to pretreatment values upon drug withdrawal.

**FIGURE 3.** Values for heart rate and plasma renin activity at the five reference points depicted in figure 1.
showed progression, serum sodium concentration fell significantly (137.6 ± 1.7 to 133.2 ± 1.0 meq/liter; p < .05) but did not change in the seven patients in whom progression was not observed. Patients who showed progression did not differ from those who did not with respect to age, sex, cause of heart failure, previous drug history, or pretreatment hemodynamic variables. Five of the eight patients with progression and five of the seven patients without progression had underlying ischemic heart disease; only one of the eight patients who showed progression had failed prior treatment with captopril, whereas four of the seven patients who did not demonstrate progression had received captopril in the past.

**Short- and long-term adverse reactions.** Of the 29 patients who received long-term amrinone therapy, all but two experienced adverse reactions during the course of the 2 to 10 week trial. Four adverse reactions were considered life-threatening. Four patients experienced sustained ventricular tachycardia resulting in circulatory collapse, none of whom were known to have had this arrhythmia before treatment; in three patients, this arrhythmia occurred within 24 hr of initiation of amrinone therapy. All four patients were successfully resuscitated, but three experienced irreversible neurologic sequelae during the arrhythmia, which eventually led to their deaths; the remaining patient recovered completely, and after amrinone was withdrawn did not have further symptomatic arrhythmias during the following 6 months. Four patients experienced worsening myocardial ischemia within several days of institution of amrinone therapy, none of whom had a recent history of active angina pectoris; an acute myocardial infarction was confirmed in three patients, two of whom died from the event. Eight patients experienced worsening congestive heart failure during treatment with amrinone, all of whom had been clinically stable before entry into the study; three patients died of progressive circulatory failure within 2 weeks. Two patients experienced acute oliguric renal failure within 4 days of institution of therapy with amrinone; both patients, however, were receiving concomitant therapy with potentially nephrotoxic drugs, indomethacin in one (for the treatment of gout) and tobramycin in the other (for the treatment of drug fever); neither patient recovered renal function and both died. Hence, 10 patients died during the first 2 weeks of treatment with amrinone (ventricular tachycardia in three, acute myocardial infarction in two, worsening heart failure in three, and renal failure in two). These patients did not differ from those who survived with respect to age, sex, or cause of heart failure; only three of the 10 patients had previously failed vasodilating therapy with captopril.

Five other adverse reactions were noted during the trial. Thirteen patients experienced gastrointestinal distress (anorexia, nausea, and diarrhea) during treatment with amrinone; these symptoms were in part responsible for the significant decline in weight that was observed during the study (65.2 ± 2.2 to 61.6 ± 2.1 kg; p < .001). Except for one patient who discontinued the drug, all patients tolerated these symptoms long enough to undergo a second hemodynamic evaluation, but having failed to improve clinically, they generally refused to tolerate continued treatment even with lower doses of the drug; these gastrointestinal adverse reactions resolved upon drug withdrawal. Although all patients had a platelet count greater than 150,000/cm³ before treatment with amrinone, seven showed a decline in platelet count to below 100,000/cm³ during the trial, and in two patients platelet counts fell to less than 50,000/cm³; thrombocytopenia was reversible in all but one patient after discontinuation of the drug, and no patient experienced any hemorrhagic events. Other adverse reactions included drug fever in three patients, elevation in liver function tests in two patients, and severe myalgias in one patient; these adverse reactions rapidly resolved upon withdrawal of the drug.

**Short- and long-term clinical responses.** Of the 31 patients who entered the trial, 22 received amrinone for more than 5 days, of whom 14 experienced amelioration of symptoms of heart failure within the first week of treatment. However, this clinical improvement was not sustained in most patients during long-term therapy with amrinone; only three patients felt improved after 2 to 10 weeks. Upon withdrawal of the drug, these three patients and five others who had not improved experienced notable clinical deterioration; this was reversed by reinitiation of amrinone in the three responders and by the administration of dobutamine or captopril in the other five patients.

Long-term therapy with amrinone was maintained in the three patients who improved hemodynamically and clinically with the drug, one of whom received additional therapy with captopril after the second hemodynamic study. Of the two patients who completed the trial and who received long-term treatment with amrinone alone, one died suddenly and the other experienced symptoms of worsening heart failure during the following 2 weeks.

Of the 13 patients who had not previously received treatment with captopril and who survived but did not benefit from amrinone therapy, 12 patients were sub-
Discussion

Our findings indicate that long-term therapy with amrinone does not produce long-lasting hemodynamic and clinical benefits in patients with severe chronic heart failure and is associated with frequent, severe, and life-threatening adverse reactions. Although immediate hemodynamic effects could be demonstrated in most of our patients and many experienced short-term clinical responses, hemodynamic and clinical improvement was not maintained during long-term treatment. More importantly, long-term positive inotropic stimulation accelerated progression of the underlying heart failure state, provoked sustained ventricular tachyarrhythmias, and exacerbated symptoms of myocardial ischemia. These observations raise serious questions about the value of long-term positive inotropic therapy in the management of patients with severe chronic heart failure.

Hemodynamic or clinical evidence for worsening heart failure developed in 11 of the 22 patients in our study who received amrinone for longer than 5 days; this was confirmed by invasive hemodynamic measurements in eight patients. In these individuals short-term amrinone therapy produced marked hemodynamic benefits, but during long-term therapy stroke volume and stroke work indexes returned to their pretreatment values despite sustained decreases in left ventricular filling pressures and systemic vascular resistance. This return to pretreatment values was not caused by the development of pharmacologic tolerance to the drug, since hemodynamic and clinical deterioration followed drug withdrawal. Stroke volume and stroke work indexes were significantly lower after completion of the trial than before institution of amrinone therapy, despite similar loading conditions (left ventricular filling pressure, mean arterial pressure, and systemic vascular resistance). The failure of amrinone to produce sustained improvement in cardiac performance in our patients with heart failure may explain why patients failed to improve clinically with amrinone in our study and in the experience of other investigators who have evaluated the drug in controlled trials.17,19 Furthermore, the decline in cardiac performance that we observed upon withdrawal of amrinone confirms previous reports of hemodynamic and clinical deterioration after discontinuation of the drug.23,24 These combined findings indicate that evidence for worsening of left ventricular function after withdrawal of a cardioactive agent cannot be used to indicate that the drug was beneficial in the treatment of congestive heart failure.

It is our belief that the progression of left ventricular dysfunction that we noted during the trial was related to treatment with amrinone. Maskin et al.25 attributed the deterioration in cardiac performance that they observed after 20 to 72 weeks of treatment with amrinone to the natural history of patients with severe chronic heart failure; they believed that such progression was as likely to occur in patients treated with amrinone as those treated with vasodilating drugs.26 We disagree, however, that such progression may occur over a period of only 2 to 10 weeks in clinically stable patients. Hemodynamic studies in patients with severe congestive heart failure treated with placebo have revealed little evidence of worsening left ventricular performance for periods of up to 3 months.2,3 This is supported by evidence from our own laboratory. When we compared the hemodynamic state before therapy to that after withdrawal of long-term treatment (2 to 12 weeks) with a number of vasodilating drugs (hydralazine,20 prazosin,21 and captopril22; figure 4), values for stroke work index did not deteriorate during the course of the three trials. In contrast, stroke work index after a similar duration of therapy with amrinone was significantly lower than before treatment with the drug; similar results have been noted during 1 to 3 months’ treatment with other phosphodiesterase inhibitors.27 We cannot attribute the evidence for progression of disease with amrinone to differences in entry criteria or in the conduct of these trials, since the study design and the

![Graph](image)
clinical and hemodynamic characteristics of the patients in the present report were similar to those who entered our studies with vasodilating drugs. Furthermore, a similar number of patients (about 30%) had previously failed treatment with other cardioactive drugs. In this regard, patients who showed progression of disease with amrinone did not differ from those who did not with respect to their pretreatment hemodynamic state, cause of heart failure, or prior drug history. For these reasons, we believe that the deterioration in cardiac performance that we observed during the course of the study was related to therapy with amrinone.

The reasons why amrinone may cause progression of left ventricular dysfunction in patients with severe chronic heart failure remain unclear. Progression of heart disease in our patients was associated with a sustained rise in heart rate and plasma renin activity and in a decline in serum sodium concentration. Hence, it is possible that amrinone causes the activation of endogenous neurohumoral forces that may oppose the beneficial effects of the drug by producing peripheral vasoconstriction. Such stimulation may lead to attenuation of a drug’s hemodynamic effects during long-term therapy and the occurrence of rebound deterioration in cardiac function after abrupt discontinuation of the agent, as these hormonal forces outlast the direct effects of the drug and cause unopposed vasoconstriction. Such an attenuation of effect followed by transient rebound phenomena has been reported after the administration and discontinuation of short-acting vasodilating drugs such as nitroprusside and nitrates. It is unlikely, however, that such mechanisms could explain our observations. Amrinone did not activate the sympathetic nervous or renin-angiotensin systems during short-term administration, and the increases in heart rate and plasma renin activity during long-term administration were only minimally reversed by drug withdrawal. Furthermore, reactive systemic vasoconstriction did not take place during the course of amrinone therapy; the decrease in systemic vascular resistance seen after first doses of amrinone did not become attenuated during the course of the trial, and there was no rebound vasoconstriction upon drug withdrawal. It is therefore likely that the activation of the renin-angiotensin and sympathetic nervous systems was the result of worsening cardiac performance and not the cause of such hemodynamic deterioration.

This evidence therefore suggests that the accelerated progression of left ventricular dysfunction that we observed during the course of treatment with amrinone was the result of a direct effect of the drug on the myocardium. In the failing heart there is an impaired ability to deliver to the myofibrillar elements the calcium ions necessary to activate the heart’s contractile proteins; the resultant decline in the number of tension-generating sites leads to a reduction in the maximum force that can be achieved during systole. This impairment of contractility has long been considered to be the primary defect in patients with congestive heart failure, but Katz has hypothesized that this decrease in contractile state is an important compensatory mechanism that decreases energy utilization by the failing heart and thereby improves the long-term survival of the cardiac muscle cell. Consequently, augmentation of the inotropic state by a variety of drugs, including amrinone, could produce a temporary improvement in cardiac contractile performance at the expense of increasing myocardial energy consumption and accelerating death of the myocardial cell. Such a sequence of events may be particularly likely to occur with drugs that enhance inotropy by increasing intracellular levels of cyclic AMP; this nucleotide exerts a direct toxic effect on myocardial cells, which is heightened by agents that stimulate its synthesis (such as catecholamines) or retard its degradation (such as phosphodiesterase inhibitors). Accordingly, interventions that increase myocardial cyclic AMP may adversely affect clinical outcome, whereas those that decrease cyclic AMP may prolong survival in patients with congestive heart failure.

This balance between energy production and energy consumption is particularly precarious in the patient with underlying coronary artery disease. In the nonfailing heart, regional myocardial ischemia may be intensified by interventions that increase myocardial oxygen demand and/or reduce myocardial oxygen delivery; hence, positive inotropic agents increase ischemic damage, whereas negative inotropic drugs reduce the extent of necrosis. This balance of factors may be altered, however, in subjects with congestive heart failure. Since myocardial oxygen consumption is determined not only by the inotropic state but also by systolic wall tension, the administration of a positive inotropic agent may reduce energy utilization if the decrease in ventricular volumes that accompanies treatment causes a decline in systolic wall stress sufficient to offset the metabolic cost of enhanced myocardial contraction. In accordance with these concepts, experimental studies have confirmed that amrinone increases myocardial oxygen consumption in the nonfailing heart but may decrease energy expenditures in failing left ventricle. Unfortunately, al-
though the overall metabolic costs in the heart may be reduced, it is not clear what effects amrinone might have on the local ischemic process itself, since the influence of drug therapy on blood flow, wall motion, intramyocardial $\text{PCO}_2$ and epicardial electrocardiograms in the ischemic region has not been assessed.\textsuperscript{46}

Our finding that four of the 22 patients with underlying coronary artery disease experienced clinically overt ischemic events after institution of therapy with amrinone suggests that positive inotropic therapy may exacerbate ischemia in the failing left ventricle as well; similar reports of worsening angina have followed the administration of other inotropic drugs to patients with heart failure.\textsuperscript{48, 49}

An increase in intracellular levels of cyclic AMP together with an enhancement of regional myocardial ischemia may have contributed to the high frequency of life-threatening tachyarrhythmias we observed with amrinone in our study. Although asymptomatic malignant ventricular ectopy is common in patients with severe chronic heart failure,\textsuperscript{7} the occurrence of sustained \textit{symptomatic} ventricular tachyarrhythmias within 24 hr of institution of therapy in previously clinically stable patients strongly suggests a causal role for amrinone. Other agents that increase myocardial contractility by increasing intracellular levels of cyclic AMP (i.e., $\beta$-adrenergic agonists, caffeine, and theophylline) have also been reported to be arrhythmogenic\textsuperscript{49-54}; amrinone may also increase circulating levels of free fatty acids that may increase ventricular irritability.\textsuperscript{55, 56} It is not surprising, therefore, that an increased frequency of ventricular ectopy and tachyarrhythmias has been observed during intravenous and oral therapy with amrinone and other phosphodiesterase inhibitors.\textsuperscript{15-17, 26} We administered doses of amrinone that were larger than those used in previous trials of oral therapy, and thus we observed a correspondingly greater frequency of serious ventricular tachyarrhythmias.

We might expect that had amrinone enhanced the progression of heart disease, provoked myocardial ischemic events, and exacerbated ventricular arrhythmias, survival in patients with heart failure would be adversely affected by long-term treatment with the drug. Of the 31 patients who entered our trial, 16 patients (52%) were dead within 3 months; this event rate contrasts with the 15% to 30% 3 month mortality rates we and other investigators have noted in patients with severe chronic heart failure treated with vasodilating drugs such as hydralazine, nitrates, or captopril.\textsuperscript{5-7, 57} The excessive mortality that we observed is similar to experience of Kinney et al.\textsuperscript{58} but is in contrast to that noted in a recently completed placebo-controlled randomized clinical trial,\textsuperscript{19} in which mortality in amrinone- and placebo-treated groups was similar. In this multicenter trial, however, the average dose of amrinone was less than 400 mg daily, a dose we and others have not found to produce consistent hemodynamic and clinical benefits\textsuperscript{17-19, 25}; larger doses could not be administered for prolonged periods because they produced gastrointestinal distress, thrombocytopenia, drug fever, and liver function abnormalities,\textsuperscript{17-19, 59} which also limited long-term therapy in our trial. We suspect that had larger doses been better tolerated, other trials may also have noted the excessive mortality we observed in our patients.

Our findings that long-term therapy with amrinone produces long-term positive inotrophic effects characteristic of long-term positive inotropic stimulation lends support to the concept that this drug and other phosphodiesterase inhibitors exert many of their short-term beneficial effects in patients with heart failure by increasing myocardial contractility. Recent investigations have suggested that these drugs may not enhance inotropy at all but may improve cardiac performance entirely by their exerting direct dilating effects on the peripheral circulation.\textsuperscript{55, 60} The elevation in intracellular levels of cyclic AMP that follows phosphodiesterase inhibition leads not only to an increase in cardiac contractility but also to a decrease in vasomotor tone in vascular smooth muscle\textsuperscript{61-64}; the direct dilating effects of these drugs on peripheral arteries and veins have been confirmed in experimental and clinical studies.\textsuperscript{65-66} Our data confirm that the fall in systemic vascular resistance during long-term amrinone therapy is a direct effect and is not the reflex withdrawal of vasoconstrictive influences (which may follow any drug-induced hemodynamic improvement\textsuperscript{67}), since amrinone reduced systemic vascular resistance after 2 to 10 weeks, at a time when the drug produced minimal hemodynamic and clinical benefits. This vasodilating action appears to predominate at low doses of phosphodiesterase inhibitors, whereas high doses produce an additional inotropic response.\textsuperscript{68} In our study with high doses of amrinone, this positive inotropic effect likely accounted for the adverse effects we observed; the concomitant occurrence of direct drug-induced vasodilation did not appear to protect the myocardium from the deleterious effects of therapy.

Our findings must be interpreted in the context of certain precautions and limitations. We did not have a control group that received no treatment or was treated with placebo; hence, we cannot conclude with certainty that the adverse circulatory effects we observed were
the result of treatment. Our patients, however, were similar to those we have studied in previous trials of vasodilating drugs; furthermore, patients who survived treatment with amrinone subsequently responded to captopril in a manner similar to patients who had never received inotropic therapy.22 Nevertheless, future long-term trials with placebo-treated patients will be needed to address these concerns definitively. Furthermore, the doses we used in this trial were large (600 mg daily), and fewer adverse effects on the heart may have been noted had lower doses been administered; lower doses of amrinone (i.e., 300 mg daily), however, produce only transient hemodynamic effects and little long-term improvement in symptoms, left ventricular function, or exercise capacity17–19,25.

In conclusion, our results with long-term therapy with amrinone suggest that prolonged positive inotropic stimulation may accelerate progression of left ventricular dysfunction, exacerbate myocardial ischemia, and provoke life-threatening ventricular tachyarrhythmias, thereby shortening survival in patients with severe chronic heart failure. These deleterious effects were the principal reason why patients treated with amrinone in our study failed to improve hemodynamically or clinically during long-term treatment with the drug despite dramatic short-term hemodynamic benefits. Although a substantial number of our patients also experienced severe noncardiac adverse effects that frequently required discontinuation of amrinone, symptoms of heart failure were not improved even in patients who could tolerate long-term treatment with the drug. These findings suggest that the development of positive inotropic agents that are similar to amrinone in their ability to increase contractility but that have fewer noncardiac adverse effects69,70 may not be an effective approach to the treatment of patients with severe chronic heart failure; prolonged administration of such drugs may achieve short-term gains at the expense of long-term detrimental effects on the myocardium.

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