

REPORTS ON THERAPY

Survival of Patients With Severe Congestive Heart Failure Treated With Oral Milrinone

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The safety and efficacy of long-term oral milrinone therapy were evaluated over a 2½ year period in 100 patients who had severe congestive heart failure despite conventional therapy. Long-term oral milrinone therapy (27 ± 8 mg/day initial dose) was well tolerated; drug-related side effects occurred in only 11% of patients and led to drug withdrawal in only 4% of patients. Of 94 patients evaluated after 1 month of therapy, 51% had improved by at least one New York Heart Association functional class. Despite hemodynamic and clinical improvements, life table analysis showed a 39% mortality rate at 6 months and a 63% mortality rate at 1 year of therapy. Characteristics at study entry that predicted death within 6 months included more advanced functional class, impaired renal function, lower right ventricular ejection fraction, presence of nonsustained ventricular tachycardia on 24 hour ambulatory electrocardiography, more

impaired baseline hemodynamic function and absence of clinical improvement after 1 month of milrinone therapy.

Multivariate analysis selected lower baseline cardiac index and aortic systolic pressure as the most significant variables in predicting death; patients who died of progressive heart failure had less frequent use of antiarrhythmic drugs and greater increases in furosemide and milrinone doses during long-term follow-up than did those who died suddenly. Thus, although milrinone is well tolerated and produces early symptomatic benefits in approximately half of patients with congestive heart failure refractory to conventional therapy, there is no evidence that it improves the high baseline mortality in this disorder.

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Congestive heart failure, a common manifestation of the late stages of coronary, valvular or myocardial disease, affects approximately 2 million individuals in the United States (1,2). Numerous studies of patients with heart failure have demonstrated an accelerated mortality which corresponds to a number of clinical indexes of severity, including New York Heart Association functional class, hemodynamic status at rest and the presence of ventricular arrhythmia (3-12). Although a variety of therapeutic agents (cardiac glycosides, diuretics and vasodilators) are capable of producing short-

term hemodynamic and clinical improvement, and maintaining this improvement to varying degrees and for various durations during long-term administration, there is no firm evidence that any of these groups of agents, administered individually or in combination, prolong the survival of patients with severe congestive heart failure (13-15).

Because many patients treated with conventional agents fail to achieve or maintain adequate clinical improvement, there has been ongoing interest in the development of orally active positive inotropic/vasodilator drugs such as the bipyridine compound milrinone. We and other investigators (16-20) have previously described the acute hemodynamic and chronic clinical improvements produced by milrinone, but have not adequately assessed the influence of milrinone on patient survival. Such a study is particularly important, as some investigators (21-23) have suggested that inotropic therapy might actually have a deleterious long-term effect in patients with heart failure by predisposing them to myocardial ischemia, ventricular arrhythmia or accelerated myo-

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ocyte degeneration. In an effort to begin to address this important issue, the present report reviews our experience with long-term oral therapy in the first 100 patients with congestive heart failure to receive milrinone at the Beth Israel and Brigham and Women's Hospitals between July 1982 and January 1985.

Methods

Study patients. This study is based on 100 patients with severe congestive heart failure despite treatment with digitalis glycosides, diuretics and one or more oral vasodilators. Eighty-five patients had received vasodilator therapy at maximally tolerated doses for at least 1 month immediately before entry into the study. The agents administered included captopril in 51 patients (105 ± 75 mg/day), prazosin in 13 patients (5 ± 3 mg/day), hydralazine in 16 patients (139 ± 75 mg/day), long-acting nitrates as a single agent in 9 patients or combined with other vasodilators in 41 patients, and nifedipine in 1 patient. In the remaining 15 patients, vasodilator therapy had been attempted with one or more of these agents, but had been unsuccessful because of side effects or limiting hypotension.

Each patient was evaluated by clinical examination, 24 hour ambulatory electrocardiography, gated equilibrium radionuclide left and right ventriculography and serum chemistry determinations before enrollment. In addition, radioenzymatic measurement of plasma norepinephrine levels at rest (20) was performed at baseline in 29 of the 35 patients studied at the Brigham and Women's Hospital. The results of coronary angiography were available in 94 patients, and endomyocardial biopsy was performed in 22 of the 42 patients without underlying coronary artery disease. No patient with recent (within 3 months) myocardial infarction, significant ongoing angina pectoris, symptomatic ventricular arrhythmia despite drug therapy, surgically treatable valvular disease, biopsy-proved active myocarditis or clinically significant renal or pulmonary disease was included.

Hemodynamic measurements. At entry, each patient underwent right heart catheterization after overnight withdrawal from vasodilator and diuretic agents to evaluate baseline hemodynamics and the response to acute intravenous milrinone administration. After paired baseline measurements, the initial dose of milrinone was administered intravenously and hemodynamic measurements were repeated. Cardiac output was measured by the thermodilution or Fick technique, and other hemodynamic variables were calculated according to standard formulas (4).

Oral milrinone therapy. After the intravenous milrinone infusion, oral milrinone was administered three to six times per day in a total daily dose of 20 to 50 mg in addition to ongoing digitalis, diuretic, vasodilator and antiarrhythmic therapy as clinically indicated. Twenty-four hour electrocardiography was repeated 48 hours after the initiation of

oral milrinone therapy. Patients were evaluated monthly on an outpatient basis during long-term oral milrinone therapy, under a protocol approved by the Hospitals' Human Subjects Committees. At each visit, patients were evaluated by interview and physical examination, and medication doses were changed as required. The dose of furosemide was altered to maintain an edema-free state, whereas the doses of the vasodilator and milrinone were adjusted to obtain maximal improvement in clinical symptoms. In the event of death outside the study hospital, information was obtained from the patient's family and physician. When possible, the cause of death was ascribed either to progressive heart failure or to sudden death (death occurring in the absence of premonitory symptoms during the previous hour, in a patient who was otherwise clinically stable).

Statistical analysis. Clinical and hemodynamic variables at baseline and during milrinone therapy were evaluated for the 100 patients as a whole and for several subgroups based on survival outcome. Data were expressed as mean \pm SD, and initial univariate comparisons were made using either an unpaired *t* test or 2×2 frequency table (chi-square) analysis, with statistical significance taken at probability (*p*) less than 0.05. Multivariate analysis was subsequently performed using discriminant analysis (24,25). Cumulative survival curves were obtained for the group as a whole and for various clinical subgroups, using both the life table (26) and Kaplan-Meier (27) survivorship methods, in which patients withdrawn from milrinone therapy were treated as "dropouts" according to the first method and as "censored data" according to the second method. Life table survivor curves were tested for significant differences by standard methods, whereas the Kaplan-Meier curves were compared using both the Mantel-Cox log rank test (28) and the Gehan-Breslow statistic (29).

Results

Baseline findings. Patient characteristics are summarized in Table 1. The mean duration of heart failure was 34 months, and 95 patients had experienced significant worsening of heart failure during the 6 months before entry. The cause of heart failure was ischemic heart disease in 58 patients, the majority of whom had obstructive coronary disease involving three vessels. Twenty-six (45%) of the patients with ischemic heart disease had previously undergone coronary artery bypass surgery. Congestive heart failure was due to dilated cardiomyopathy in 42 patients; dilated cardiomyopathy followed adriamycin treatment in 2 patients, occurred in the setting of moderate alcohol intake in 2 patients, followed valve replacement in 5 patients and was idiopathic in the remaining 33 patients.

Despite conventional therapy as described earlier, 39 patients were in functional class IV before milrinone therapy, and the remaining 61 were in functional class III. Hemo-

Table 1. Patient Characteristics by Survival Outcome

	Total Group (n = 100)	Survivors > 6 Months (n = 25)	Nonsurvivors (n = 48)	Sudden Death (n = 15)	CHF Death (n = 21)
Clinical variable					
Age (yr)	59 ± 12	57 ± 15	61 ± 11	63 ± 8	61 ± 10
Male (%)	79	84	75	37	76
NYHA class IV (%)	39	28	46	53	38
CAD (%)	58	56	54	73	52
with CABG (%)	45	50	50	45	45
LVEF (%)	17 ± 8	18 ± 8	17 ± 7	19 ± 8	18 ± 8
RVEF (%)	28 ± 17	35 ± 19	—p < 0.02— 24 ± 13	29 ± 10	24 ± 15
BUN (mg/dl)	31 ± 18	26 ± 13	—p < 0.01— 36 ± 20	36 ± 20	40 ± 24
Creatinine (mg/dl)	1.6 ± 0.6	1.4 ± 0.5	—p < 0.01— 1.8 ± 0.7	1.8 ± 0.7	1.8 ± 0.9
VT > 3					
Baseline (%)	59	33	—p < 0.02— 62	67	52
Milrinone (%)	68	52	73	80	67
Concomitant drugs (mg/day)*					
Milrinone					
Discharge	27 ± 8	28 ± 9	26 ± 6	24 ± 6	26 ± 7
Last follow-up	34 ± 11	36 ± 11	36 ± 12	29 ± 10	41 ± 13
Furosemide					
Discharge	108 ± 54	88 ± 54	122 ± 54	119 ± 38	111 ± 61
1 Month	105 ± 74	83 ± 68	123 ± 80	94 ± 52	152 ± 95
Last follow-up	151 ± 97	126 ± 85	170 ± 109	113 ± 72	—p < 0.01— 214 ± 109
Antiarrhythmic drug					
Captopril					
Discharge	32% (57 ± 39)	40% (49 ± 43)	33% (52 ± 21)	40% (56 ± 26)	24% (50 ± 23)
Last follow-up	36% (57 ± 56)	40% (68 ± 84)	38% (41 ± 23)	33% (38 ± 23)	33% (42 ± 24)
Hemodynamics†					
RAP (mm Hg)					
Baseline	13 ± 7	11 ± 7	—p < 0.01— 16 ± 7	15 ± 6	15 ± 7
Milrinone	8 ± 5 (-38%)	7 ± 5 (-35%)	9 ± 5 (-40%)	8 ± 6 (-48%)	9 ± 4 (-39%)
PCWP (mm Hg)					
Baseline	28 ± 7	27 ± 6	29 ± 7	27 ± 7	30 ± 7
Milrinone	18 ± 9 (-34%)	17 ± 10 (-38%)	19 ± 9 (-37%)	17 ± 8 (-38%)	19 ± 8 (-38%)
AoSP (mm Hg)					
Baseline	108 ± 19	118 ± 32	—p < 0.05— 106 ± 16	106 ± 15	100 ± 15
Milrinone	104 ± 18 (-3%)	108 ± 22 (-8%)	104 ± 17 (-1%)	107 ± 18 (+1%)	98 ± 15 (-1%)
CI (liters/min per m²)					
Baseline	2.0 ± 0.6	2.1 ± 0.6	—p < 0.01— 1.8 ± 0.4	1.7 ± 0.3	1.8 ± 0.4
Milrinone	2.9 ± 0.8 (+51%)	2.9 ± 0.7 (+43%)	2.7 ± 0.7 (+58%)	2.7 ± 0.8 (+57%)	2.8 ± 0.7 (+56%)
SVR (dynes·s·cm⁻⁵)					
Baseline	1,603 ± 583	1,664 ± 480	1,703 ± 670	1,611 ± 402	1,565 ± 576
Milrinone	1,085 ± 429 (-32%)	1,156 ± 518 (-29%)	1,115 ± 411 (-30%)	1,145 ± 486 (-30%)	998 ± 351 (-39%)
LVSWI (g·m/m²)					
Baseline	22 ± 10	27 ± 12	—p < 0.01— 18 ± 6	19 ± 6	17 ± 5
Milrinone	32 ± 13 (+57%)	36 ± 17 (+42%)	29 ± 11 (+69%)	30 ± 7 (+62%)	29 ± 12 (+76%)
RVSWI (g·m/m²)					
Baseline	13 ± 5	14 ± 6	—p < 0.05— 12 ± 5	12 ± 5	13 ± 5

*Drug doses are shown as mean ± SD (in mg/day), at the time of hospital discharge (Discharge) and at the time of last follow-up. Percent figures for antiarrhythmic drug and captopril refer to percent of patients receiving the given drug or drug class at the time indicated, with the captopril dose (mean ± SD in mg/day) given in parentheses. †Values are shown at baseline and after intravenous milrinone, with the percent change after milrinone indicated in parentheses. AoSP = aortic systolic pressure; BUN = blood urea nitrogen; CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; CI = cardiac index; LVEF = left ventricular ejection fraction; LVSWI = left ventricular stroke work index; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure; RAP = right arterial pressure; RVEF = right ventricular ejection fraction; RVSWI = right ventricular stroke work index; SVR = systemic vascular resistance; VT > 3 = percent of patients with at least one episode of ventricular tachycardia exceeding three beats in length on 24 hour ambulatory electrocardiography.

dynamic studies showed severe depression of ventricular performance (Table 1). The baseline plasma norepinephrine at rest in the 29 patients in whom it was measured was markedly elevated, averaging 709 ± 616 pg/ml (normal value = 213 ± 60); this group did not differ significantly from the remaining 71 patients according to any of the variables in Table 1. High grade ventricular arrhythmia was common (Fig. 1); 24 hour electrocardiograms obtained before administration of milrinone showed at least one episode of nonsustained asymptomatic ventricular tachycardia (three or more consecutive ventricular premature complexes) in 57 patients. Episodes of ventricular tachycardia were three to six cycles in length in 35 patients and greater than six consecutive beats in an additional 22 patients, despite ongoing antiarrhythmic drug treatment (with quinidine or procainamide) in 56% of patients at the time of study entry.

Acute effects of milrinone. Significant hemodynamic improvement was evident after the acute intravenous administration of milrinone 5 ± 3 mg (80 ± 40 μ g/kg) (Table 1). Repeat 24 hour electrocardiographic monitoring after 48 hours of oral milrinone therapy showed no significant change in ventricular ectopic rhythm, with episodes of nonsustained asymptomatic ventricular tachycardia of three to six beats in length in 44 patients, and episodes exceeding six beats in length in an additional 20 patients (Fig. 1). Comparing pre- and post-milrinone 24 hour electrocardiographic recordings in 97 patients, the level of ventricular arrhythmia increased in 23, decreased in 23 and remained unchanged in 51 patients.

Clinical response to long-term therapy. Oral milrinone therapy at an average initial dose of 27 ± 8 mg/day was associated with a decrease in the symptoms of heart failure in 48 of the 94 patients whose data are shown in Figure 2 (the 6 additional patients in the total group of 100 had been followed up for less than 1 month after entry by January 1, 1985). If the nine patients who died during the first month of therapy and the three patients who were withdrawn during the first month of the study are excluded (see later), heart failure symptoms improved by at least one functional class in 48 (59%) of 82 patients, were unchanged

Figure 1. Highest grade of ventricular ectopic activity (VEA) on 24 hour ambulatory electrocardiogram at baseline and after 48 hours of oral milrinone therapy. FREQ. = frequent; OCCAS. = occasional; VPB's = ventricular premature beats; VT = ventricular tachycardia.

	BASELINE	MILRINONE
NO VEA	6	2
OCCAS VPB's	10	5
FREQ VPB's	24	26
VT 3-6 BEATS	35	44
VT >6 BEATS	22	20

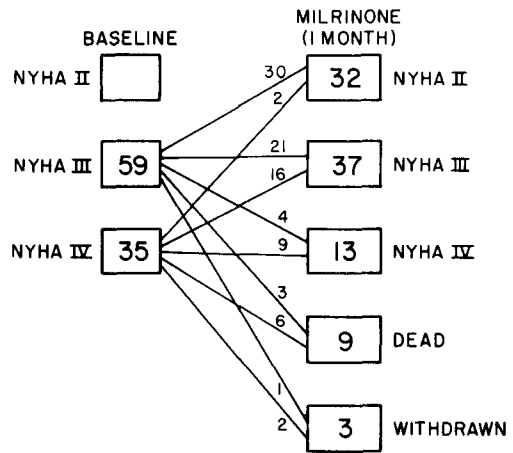
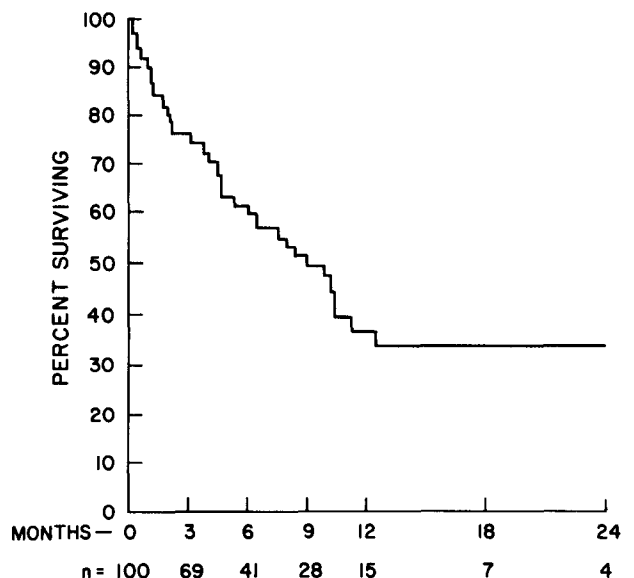


Figure 2. New York Heart Association (NYHA) symptomatic class at baseline and after 1 month of milrinone therapy, in the 94 patients followed up for at least 1 month.

in 30 (35%) and worsened by one functional class in only 4 (5%).

This improvement could not be explained by an increase in furosemide dose, which was unchanged from 107 ± 68 mg/day before milrinone to 105 ± 74 mg/day at 1 month. Nor could it be explained by the concomitant use of conventional vasodilators, which were reduced significantly in both number of patients treated and dose per patient. While 51 patients had received captopril at a dose that averaged 105 ± 75 mg/day before milrinone therapy, only 24 patients continued to receive captopril at the 1 month visit and their dose was reduced to 57 ± 39 mg/day ($p < 0.01$). Similarly, only 3 of 13 patients continued to receive prazosin, and only 2 of 16 patients continued to receive hydralazine. During the 9 ± 5 months of follow-up, the dose of milrinone

Figure 3. Survival curve for the 100 patients receiving chronic oral milrinone therapy. The figures at the bottom refer to the number of patients at risk at the indicated times.



was increased to an average of 34 ± 11 mg/day, and the dose of furosemide to 151 ± 97 mg/day, but there was no significant increase in concomitant vasodilator use or dosage (Table 1).

Side effects and patient withdrawal. During the course of the study, 14 patients were withdrawn from milrinone therapy. Withdrawal was prompted by lack of response in three patients, poor compliance with the study protocol in two patients and surgical intervention obviating further milrinone therapy in five patients (one aortic valve replacement at 10 months, one mitral valve replacement at 4 months and three cardiac transplantations at 0.25, 3 and 14 months, respectively). An additional four patients were withdrawn because of side effects possibly related to milrinone therapy, including one patient each with headache, muscular weakness, insomnia and increased ventricular arrhythmia. Milder side effects occurred in seven patients, but did not prevent continuation of milrinone therapy; four of these patients reported headache during the initial days of milrinone therapy, which subsequently resolved. Muscular weakness worsened after several months of therapy in one other patient with preexisting muscular dystrophy, but failed to improve after 1 week of milrinone withdrawal, so that milrinone was reinstated to control ongoing symptoms of heart failure. An increase in anginal symptoms was reported by three patients during the increased activity permitted by the control of heart failure symptoms, but was managed by additional medical therapy in two patients and by coronary artery bypass grafting in the third. One patient sustained an acute myocardial infarction during milrinone therapy; this patient had undergone coronary artery bypass graft surgery 5 years before study entry, sustained a lateral wall myocardial infarction due to graft thrombosis after 9 months of milrinone

Figure 4. Survival curves for patients with coronary artery disease (CAD) and dilated cardiomyopathy (CM).

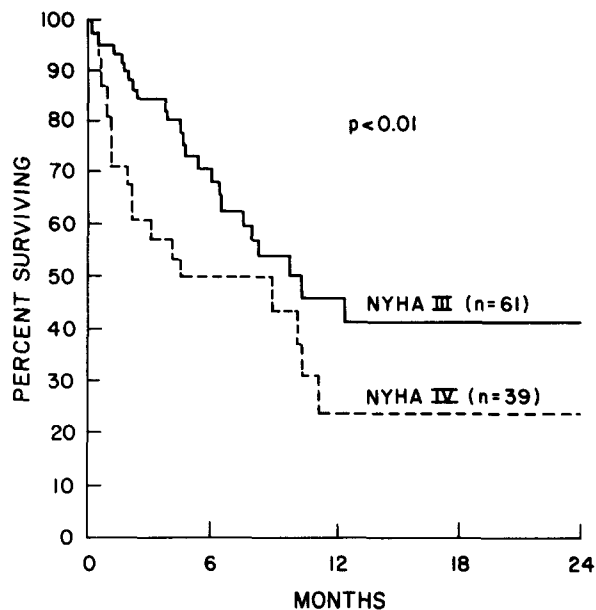
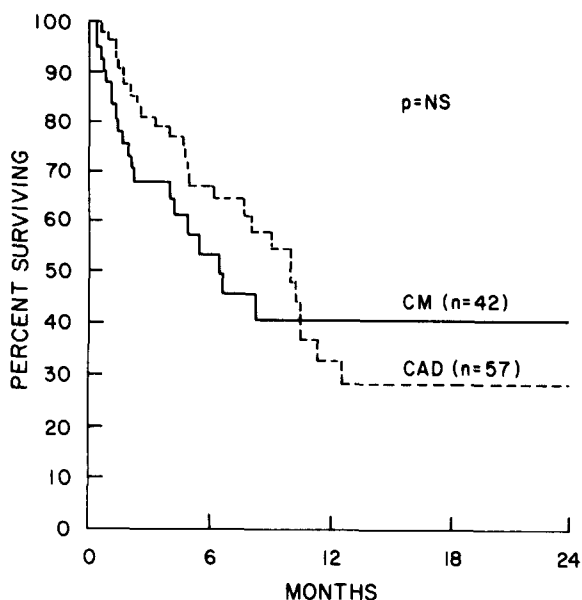


Figure 5. Survival curves for patients with NYHA class III and IV symptoms at study entry.

therapy and died of progressive heart failure 2 months later.

Mortality. Despite the aforementioned hemodynamic and clinical improvements and a relatively low incidence of side effects requiring discontinuation or reduction of the dose of milrinone, a substantial early mortality rate was noted (Fig. 3). Life table analysis disclosed a 39% mortality rate after 6 months, and a 63% mortality rate after 12 months of milrinone therapy. The 6 and 12 month mortality rates were not significantly different (40 and 75%) for the subgroup of patients whose baseline plasma norepinephrine levels at rest had been measured.

Predictors of early mortality. Comparison of the 25 patients who survived for more than 6 months with the 48 patients who died during milrinone therapy reveals several univariate correlates of early mortality (Table 1). Patients surviving for more than 6 months had significantly higher baseline right ventricular ejection fraction, systolic aortic pressure, cardiac index and left ventricular stroke work index than did nonsurvivors. Survivors also had significantly lower baseline values for blood urea nitrogen and creatinine, a lower incidence of ventricular tachycardia on the baseline 24 hour ambulatory electrocardiogram and a lower baseline right atrial pressure than did nonsurvivors. Other factors, including the magnitude of the acute hemodynamic response to intravenous milrinone, did not correlate with survival. Multivariate analysis selected baseline cardiac index and systolic arterial pressure as the key variables defining survival outcome.

Additional factors corresponding to early mortality during milrinone therapy were evident using life table analysis. Although there was no difference in survival between patients with coronary artery disease (with or without prior bypass surgery) and patients with dilated cardiomyopathy

(Fig. 4), a significantly lower mortality was observed in patients who at baseline were in functional class III than was observed in those in class IV (39 versus 50% at 6 months, and 54 versus 76% at 12 months, respectively) (Fig. 5). Patients whose heart failure symptoms had shown improvement by one or more functional classes after 1 month of milrinone therapy also had a significantly lower subsequent mortality than did patients without such improvement (23 versus 45% at 6 months) (Fig. 6). Finally, patients without episodes of ventricular tachycardia on the baseline 24 hour ambulatory electrocardiogram had a significantly lower mortality than did patients with such episodes (37 versus 52% at 6 months, and 52 versus 89% at 12 months, respectively) (Fig. 7). Although survivors also tended to be less likely to exhibit episodes of ventricular tachycardia while receiving oral milrinone, neither the level of arrhythmia during milrinone therapy nor the relation between baseline and post-milrinone ectopic activity was a statistically significant predictor of early mortality.

Mode of death. The mode of death could be classified in 36 of the 48 patients who died during chronic milrinone therapy; 15 patients sustained sudden death after 5 ± 4 months, whereas 21 patients died of progressive heart failure after 4 ± 3 months. Not unexpectedly, patients dying of progressive heart failure received greater increases of doses of both milrinone and furosemide during the course of the study, compared with the subgroup of patients who died suddenly and the subgroup of patients surviving longer than 6 months. While patients dying suddenly were more likely to be receiving antiarrhythmic drugs, neither the prevalence of ventricular tachycardia on the baseline or post-milrinone

Figure 6. Survival curves for patients who did and did not improve their symptomatic status by one or more NYHA classes after 1 month of oral milrinone therapy.

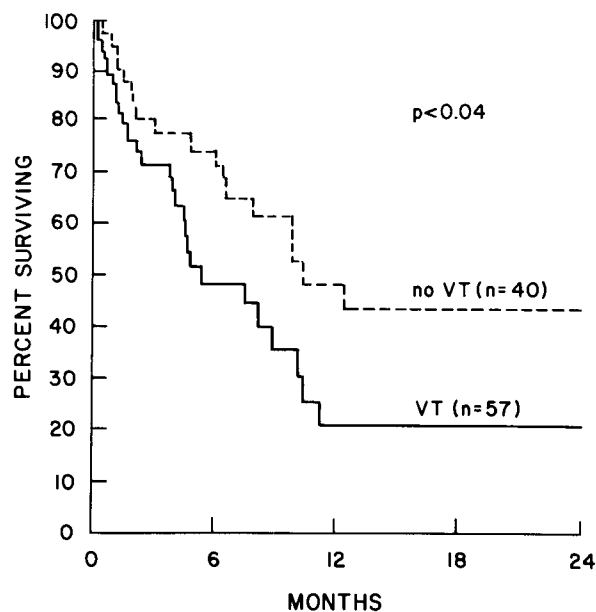
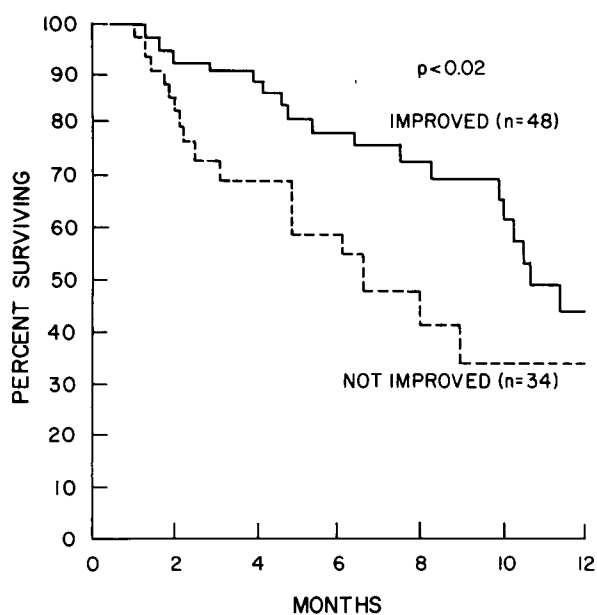


Figure 7. Survival curves for patients with and without episodes of nonsustained ventricular tachycardia (VT) on the baseline 24 hour ambulatory electrocardiogram.

24 hour ambulatory electrocardiogram nor the hemodynamics at baseline or after intravenous milrinone were significant predictors of sudden death as opposed to death from progressive heart failure.

Discussion

Hemodynamic and clinical effects of milrinone. Milrinone is a methyl, carbonitrile derivative of the earlier bipyridine agent amrinone, which has been approved for intravenous use in the short-term treatment of severe congestive heart failure. Both animal and clinical studies have shown milrinone to have 10 to 30 times the potency of the parent compound (30). Its mechanism of action relates in part to selective inhibition of phosphodiesterase in cardiac and vascular smooth muscle. Other direct effects on calcium handling have been suggested, but milrinone, like amrinone, does not appear to inhibit sodium-potassium adenosine triphosphatase as do cardiac glycosides, nor does it stimulate beta-adrenergic or histaminergic receptors (30). Although milrinone does act on vascular smooth muscle to produce significant direct peripheral vasodilation (31), several studies have demonstrated a clear positive inotropic effect at therapeutic plasma concentrations. These studies include demonstration of an increase in peak positive left ventricular first derivative of pressure (dP/dt)—which is not observed with pure vasodilators such as nitroprusside—during both intravenous (16,32) and low dose intracoronary (33) milrinone administration to patients with heart failure, as well as an increase in the slope of the end-systolic pressure-dimension relation in normal subjects (34). In addition to

these vasodilator and positive inotropic effects, milrinone also appears to improve diastolic left ventricular function in patients with heart failure (35). The aggregate effect of these several actions on the patient with severe heart failure is a marked acute hemodynamic improvement after acute intravenous milrinone administration.

Recent studies have suggested that oral administration of milrinone, 30 to 40 mg/day in divided doses, produces comparable acute hemodynamic effects and few drug-related side effects (16,19,36). These hemodynamic benefits appear to persist during 1 month of chronic oral therapy, are associated with improvements in exercise tolerance (20) and led to a reduction in clinical symptoms in approximately one-half of patients who had failed to respond adequately to conventional therapy (19). Moreover, this experience with long-term oral milrinone therapy contrasts with the earlier bipyridine amrinone, which caused adverse reactions in 83% of patients (requiring drug withdrawal in 34% of patients), and in a multicenter trial (37) failed to cause significant symptomatic improvement at maximally tolerated doses.

Mortality: comparison with prior studies. Despite the preceding observations, long-term milrinone therapy was associated with a substantial early mortality in our patients; 39% were dead within 6 months and 63% were dead within 1 year of the beginning of therapy. This appears somewhat better than the experience of Simonton et al. (19), who reported a 6 month mortality of 66% in 37 patients with a more advanced average functional class and a slightly lower average stroke work index, treated with a higher milrinone dose averaging 48 mg/day. Several patient characteristics at entry correlated with early mortality in our study, including functional class, renal function, ventricular ectopic activity, hemodynamic function (right atrial pressure, systolic arterial pressure, cardiac index, left and right ventricular stroke work index, right ventricular ejection fraction) and the clinical response to 1 month of oral milrinone therapy. Although many of these variables have been previously identified as predictors of early mortality in studies of patients with heart failure treated with conventional agents (digitalis, diuretic agents or vasodilators, or both) (1-12), accurate comparison of survival outcome in the current study with that expected for patients with comparably severe heart failure is difficult.

One example of the complexity of comparing different patient populations with heart failure is the use of entry functional class, which has constituted an important predictor of survival outcome in virtually all trials. However, patients entering the current study with functional class IV heart failure *despite* vasodilator therapy might have more advanced disease than patients entering prior studies with a similar degree of heart failure in the *absence* of a potent vasodilator. Selection of an appropriate comparison group would require matching of other hemodynamic and clinical

variables as well. Vasodilator-treated patients with a comparable mean baseline plasma norepinephrine level of 700 pg/ml have been reported by Cohn et al. (38) to have a 1 year mortality rate of approximately 50%, which is similar to the mortality in the three prior vasodilator trials in which the mean baseline left ventricular stroke work index was below 25 g·m/m² (5,8,38). The presence of ventricular ectopic activity may also influence survival (5,11,12). In a study of 35 vasodilator-treated heart failure patients with hemodynamic dysfunction and ventricular ectopic activity comparable with that observed in our patient population, Maskin et al. (39) reported a 1 year mortality rate in excess of 60%. Thus, the 63% 1 year mortality rate in our study is clearly at or above that reported in previous vasodilator trials. This may be explicable in part by our selection of patients who had severe heart failure despite therapy with conventional vasodilators and who may therefore have had more advanced disease; however, given the difficulties in selecting an appropriate comparison group, it would be impossible to exclude a concomitant adverse effect of milrinone on patient survival except by performance of a prospective randomized trial.

Potential mechanisms of mortality. An alternative approach to evaluating the effect of milrinone on patient survival would be to examine the individual mechanisms by which adverse effects might be mediated: worsening of ischemia, a proarrhythmic effect or hastening the development of myocardial cell death or dysfunction.

Myocardial ischemia. Because of the frequent presence of epicardial coronary stenoses, high left ventricular wall stress at rest and decreased effective coronary perfusion pressure, patients with advanced congestive heart failure may be particularly sensitive to agents that worsen the imbalance between myocardial oxygen supply and demand (40). However, previous clinical studies (41) suggest that both amrinone and milrinone increase hemodynamic performance *without* significantly increasing myocardial oxygen consumption, because of offsetting actions on the individual determinants of myocardial oxygen consumption (MVO₂). Although this may be an advantage of the bipyridines as compared with sympathomimetic positive inotropic agents such as dobutamine (which increase MVO₂ by approximately 30% at doses that provide a comparable improvement in hemodynamic status [42]), it should be contrasted with pure vasodilators that may decrease MVO₂ by 10 to 20%. There were no significant differences in the survival characteristics of milrinone-treated patients with and without underlying coronary artery disease, and worsening of ischemic symptoms was uncommon in our study. In addition, the occurrence of only one documented myocardial infarction during follow-up (that due to saphenous vein graft thrombosis) suggests that precipitation of overt ischemia by milrinone therapy would be an unlikely explanation for the high mortality that was observed. This com-

parative lack of adverse ischemic events in the current study contrasts with the observations of Packer et al. (23) in 29 patients treated with oral amrinone, but nearly half of our patients with coronary artery disease had undergone prior bypass surgery, and patients with limiting angina had been excluded from entry into the study.

Ventricular ectopic activity. A second mechanism by which inotropic agents have been postulated to worsen survival is by enhancing ventricular ectopic activity. The present and previous studies (5,11,12,39) demonstrate a high prevalence of nonsustained ventricular tachycardia in patients with advanced congestive heart failure, with or without concomitant antiarrhythmic therapy. Our data support a relation between baseline episodes of nonsustained ventricular tachycardia and subsequent cardiac mortality, but fail to demonstrate any significant correlation between the presence of this arrhythmia and the mode of death (sudden death versus death due to progressive heart failure). A more important concern, however, would be that milrinone may have increased ventricular ectopic activity or mortality, or both. In fact, therapeutic concentrations of milrinone may improve conduction and reduce postrepolarization refractoriness in "ischemic gap" preparations (43), which could exert either a proarrhythmic or an antiarrhythmic effect in patients with areas of decremental conduction. On the other hand, our 24 hour ambulatory electrocardiographic monitoring data show no overall change in ventricular ectopic activity after milrinone administration, and no difference in subsequent mortality for the patients who showed a slight increase or decrease in ectopic activity on milrinone therapy. This lack of an overt proarrhythmic effect was recently substantiated by Goldstein et al. (44), who showed that intravenous milrinone did not change the incidence of ventricular arrhythmia on electrocardiographic monitoring, and significantly reduced the inducibility of ventricular tachycardia during programmed right ventricular stimulation. On the basis of these observations, there is not evidence that the high 1 year mortality observed during milrinone therapy can be explained by a proarrhythmic effect.

Myocardial degeneration. The final mechanism that has been suggested as a possible deleterious effect of inotropic therapy in heart failure is an acceleration of myocardial cell death due to "flogging" the failing heart (21-23). If this mechanism were operative, one would expect more rapid worsening of ventricular function in patients receiving long-term oral inotropic therapy than could be explained simply by continued progression of the underlying heart disease. In this regard, Sinoway et al. (17) reported a reduction in drug-free stroke volume index in a group of seven patients who had received 2 to 9 weeks of oral milrinone therapy. It should be noted that 21 of our patients died of progressive heart failure after a mean of 4 months of treatment and that we observed a tendency for milrinone and furosemide doses to be increased as heart failure worsened with the passage

of time. On the other hand, Simonton et al. (19) reported no change in the drug-free cardiac index, pulmonary capillary wedge pressure or stroke work index in 25 patients treated with milrinone for an average of 37 days, supporting our recent experience (45) in 13 patients who were restudied after 8 ± 4 months of continuous oral milrinone therapy and showed no worsening in average drug-free myocardial function or milrinone responsiveness after long-term treatment. Although worsening of myocardial function thus does not seem to be an inevitable consequence of milrinone therapy, a placebo-controlled study will be required to accurately evaluate the possibility that milrinone therapy may affect—favorably or adversely—the rate of deterioration of myocardial function in excess of that expected simply as the result of the progression of the underlying cardiac disease in patients who receive conventional therapy alone.

Limitations of study. The main limitations of the current study are its open label design, use of a subjective end point (functional class) to determine clinical responsiveness (although the principal end point was mortality) and lack of a concurrent control population treated with conventional therapy. In part, these limitations are inherent in the initial clinical investigation of a new inotropic agent in a patient population with disabling symptoms despite conventional therapy. Until proposed randomized trials with milrinone are completed, however, careful analysis of detailed non-randomized "data bank" studies provides the only means of assessing long-term drug safety and efficacy (1).

A second limitation concerns the statistical treatment of patients withdrawn from the study. According to standard life table methods, these patients are treated as "lost to follow up" or "censored points" at the time of withdrawal. If preterminal patient withdrawal is used excessively, however, it may reduce apparent mortality and contribute to misleading results. In part because of the low incidence of side effects during long-term oral milrinone therapy, only 14 patients were withdrawn, of whom only 5 might be considered suspect (2 patients with poor compliance with the protocol and 3 patients with lack of clinical response). Reanalysis of the data with continued inclusion of these five patients beyond the point of withdrawal does not significantly alter the findings.

Implications. Our experience in 100 patients with severe congestive heart failure suggests that long-term oral milrinone therapy is well tolerated, and that significant clinical improvement occurs initially in approximately one-half of patients whose symptoms had failed to respond adequately to conventional therapy. Early mortality, however, remains at or above that reported in previous vasodilator trials. Although this may be due in part to more advanced hemodynamic derangement in our patients, it is impossible to exclude a contribution of milrinone therapy to poor overall survival. On the other hand, analysis of three potential mechanisms (increased ischemia, enhanced ventricular ec-

topic activity, accelerated myocardial degeneration) do not suggest any single mechanism by which milrinone might worsen survival. Pending more definitive, appropriately blinded, placebo-controlled trials, it is important to realize that despite the initial salutary hemodynamic and clinical effects, therapy with milrinone does not appear to improve the prognosis of patients with advanced heart failure, and should not delay more definitive interventions such as cardiac transplantation (46) in patients for whom this alternative is available.

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