

# A Randomized Multicenter Study Comparing the Efficacy and Safety of Intravenous Milrinone and Intravenous Nitroglycerin in Patients With Advanced Heart Failure

EVAN LOH, MD,\* URI ELKAYAM, MD,<sup>†</sup> ROBERT CODY, MD,<sup>‡</sup>  
MICHAEL BRISTOW, MD,<sup>§</sup> BRIAN JASKI, MD,<sup>||</sup>  
WILSON S. COLUCCI, MD<sup>||</sup>

*Philadelphia, Pennsylvania; Los Angeles, California; Ann Arbor, Michigan;  
Denver, Colorado; San Diego, California; Boston, Massachusetts*

---

## ABSTRACT

A randomized, open-label, parallel-group design was used to determine the percentage of patients achieving improvements in predetermined baseline hemodynamic end points (>20% to 30% increase in cardiac index depending on baseline values and >25% decrease in pulmonary capillary wedge pressure), assessed at hour 0 (end of initial dose titration) and 1, 2, 4, 8, and 24 hours after the infusion of milrinone or nitroglycerin. In total, 125 patients (60 milrinone, 65 nitroglycerin) enrolled in this study, and 119 (58 milrinone, 61 nitroglycerin) were evaluable for the efficacy analysis. A significantly greater proportion of milrinone-treated patients reached (45% v 14%,  $P = .005$ ) and maintained (24% v 6%,  $P = .026$ ) hemodynamic goals than did nitroglycerin-treated patients; the time to achieve hemodynamic goals was significantly less in milrinone-treated patients ( $33 \pm 2$  v  $54 \pm 10$  minutes,  $P < .001$ ). Milrinone was also significantly more effective in decreasing systemic vascular resistance ( $P = .004$ ), increasing stroke volume ( $P = .008$ ), and improving global clinical status. Inodilator therapy with milrinone seems more efficacious in attaining sustained hemodynamic improvement than does pure intravenous vasodilator therapy with nitroglycerin in treating patients with decompensated heart failure.

**Key words:** milrinone, nitroglycerin, heart failure, inotropic therapy.

---

---

*From the \*Cardiovascular Division, Department of Medicine, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; <sup>†</sup>University of Southern California, Heart Failure Program, Division of Cardiology, University of Southern California School of Medicine, Los Angeles, California; <sup>‡</sup>Division of Cardiology, The University of Michigan Medical Center, Ann Arbor, Michigan; <sup>§</sup>Division of Cardiology, University of Colorado Health Sciences Center, Denver, Colorado; <sup>||</sup>San Diego Cardiac Center, San Diego, California; and <sup>||</sup>Cardiovascular Division, Department of Medicine, Boston University Medical Center, Boston, Massachusetts.*

Supported in part by an unrestricted educational grant from Sanofi-Synthelabo.

Manuscript received November 6, 2001; revised manuscript received February 12, 2001; revised manuscript accepted February 13, 2001.

Reprint requests: Evan Loh, MD, Wyeth-Ayerst Research, 145 King of Prussia Rd, Radnor, PA 19087.

Copyright © 2001 by Churchill Livingstone®

1071-9164/01/0702-0003\$35.00/0

doi:10.1054/jcaf.2001.24136

Despite an increased knowledge of the pathophysiology and hemodynamic abnormalities observed in patients with heart failure and the increasing availability of effective oral agents, heart failure still poses a significant therapeutic challenge (1). Decompensated, advanced heart failure (New York Heart Association [NYHA] III or IV) is a multifactorial disease requiring a balanced therapeutic program, which includes a standard regimen of digoxin, diuretics, angiotensin-converting enzyme inhibitors, and sometimes intravenous therapy with vasodilators and/or inotropic agents.

The pathophysiology of heart failure includes increased peripheral resistance secondary to activation of the sympathetic nervous system, which results in increased afterload and decreased cardiac output (2). Vasodilator agents, both oral and intravenous, are of value in the treatment of heart failure by decreasing preload and peripheral resistance, resulting in modest increases in cardiac output (2–6). These agents have no direct inotropic effects on myocyte contractility. The use of vasodilators in heart failure, therefore, often requires the addition of an inotropic agent, such as dobutamine, to obtain the desired increases in cardiac output (7). However, patients with severe systolic heart failure have abnormalities in the  $\beta$ -adrenergic receptor-coupled signal-transduction pathways that would impair the inotropic response to intravenous inotropic agonists, such as dobutamine (8).

A vasodilator agent that also possesses positive inotropic activity might offer a more rational approach to the treatment of heart failure than a pure vasodilator. Milrinone, a phosphodiesterase III inhibitor, possesses both positive inotropic and vasodilator activity (9,10). In short-term clinical studies, bolus administrations of milrinone have been shown to increase cardiac index (CI), decrease pulmonary capillary wedge pressure (PCWP), and decrease systemic vascular resistance (SVR) with minimal changes in heart rate (11–14). These therapeutic effects were generally achieved without an increase in myocardial oxygen demand (11–14). By providing both a direct inotropic effect on the heart and a peripheral vasodilation effect, milrinone may offer a distinct advantage over pure vasodilators, such as nitroglycerin, in the treatment of patients with advanced heart failure (9). However, it is important to note that these were only short-term infusion studies, which documented only acute hemodynamic effects of milrinone (10–13,15–17).

To date, no comparative trial has been performed in patients with decompensated heart failure to compare the acute hemodynamic effects of an inodilator (ie, milrinone) with a pure vasodilator (ie, nitroglycerin) for a 24-hour period in the clinical setting. Therefore, the present study was designed to compare the hemodynamic efficacy of intravenous milrinone with intravenous nitroglycerin in patients admitted to the hospital with

decompensated NYHA III or IV heart failure. The hemodynamic response to therapy was assessed by right heart catheterization. The primary end point of this study was the proportion of patients achieving and maintaining (at 24 hours) 2 predetermined hemodynamic goals (>20% to 30% increase in CI [depending on baseline CI] and >25% decrease in PCWP) with either milrinone or nitroglycerin, using a prespecified titration algorithm. If the prespecified hemodynamic end point(s) was not achieved in the initial titration phase, the study also evaluated the potential need for additional intravenous therapy with a second inotropic or vasodilator agent in either of the 2 treatment groups. Secondary clinical efficacy response was assessed by change from baseline in Killip class and clinical symptoms.

## Methods

This was a randomized, open-label, parallel group study comparing the efficacy and safety of intravenous milrinone versus intravenous nitroglycerin. Patients hospitalized in an intensive care setting with advanced decompensated heart failure and requiring intravenous drug therapy were eligible for enrollment in this multicenter study. Inclusion criteria, within 6 months before study entry, consisted of NYHA III or IV symptoms, a left ventricular ejection fraction less than 45% (radionuclide ventriculography or 2-D echocardiography), and cardiomegaly (cardiothoracic ratio > 55% by chest radiograph). Baseline inclusion hemodynamic criteria required a CI 2.5 L/min/m<sup>2</sup> or less and a PCWP 18 mm Hg or greater. All patients were 18 years of age or older. Women of child-bearing potential had to be nonpregnant (negative urine human chorionic gonadotropin measurements). Major exclusion criteria included sustained or uncontrolled arrhythmias; recent myocardial infarction or open heart surgery; and recent intravenous therapy with inotropic agents, vasodilators, or diuretics. All patients signed informed consent, and the study was conducted in accordance with local institutional guidelines. In total, 125 patients from 12 centers were randomized into the study over a period of 14 months, 60 to the milrinone group and 65 to the nitroglycerin group.

Patients who established a reproducible, stable hemodynamic baseline and met all protocol eligibility criteria were randomly assigned to receive either milrinone or nitroglycerin for a minimum of 24 hours and up to a maximum of 5 days. Study drug administration began within 1 hour of the completion of baseline hemodynamic measurements. The primary end point of this study was to determine the percentage of patients who achieved predetermined hemodynamic goals when treated initially with either milrinone or nitroglycerin (ie, 30 minutes after the milrinone loading dose or at the end

of the nitroglycerin titration) (hour 0, see later). The predetermined hemodynamic goal was defined as percent change from baseline in both CI and PCWP. Patients with a baseline CI of greater than 2.3 L/min/m<sup>2</sup> required a 20% increase to achieve the hemodynamic goal; if baseline CI was 2.0 to 2.3 L/min/m<sup>2</sup>, the goal was to achieve an increase of 25%. If baseline CI was less than 2.0 L/min/m<sup>2</sup>, the goal was to achieve an increase of 30%. The hemodynamic goal for PCWP was a decrease of 25%, regardless of baseline values.

Secondary end points in this trial were performed on the randomized treatment groups, regardless of the use of add-on therapy. Secondary end points in the trial included the ability to maintain the combined prespecified favorable effects on CI and PCWP for 24 hours, Killip class, and global clinical status.

### Drug Administration

Patients randomized to receive nitroglycerin therapy began with an intravenous infusion of 5 to 25 µg/min with dose titration increasing at a rate of 10 to 25 µg/min every 3 to 5 minutes until one of the following end points was reached: infusion rate of 200 µg/min, 20 mm Hg reduction in mean arterial pressure (MAP), decrease in MAP (ie, ≤55 mm Hg), or nitroglycerin-related clinically significant adverse event.

Patients randomized to milrinone therapy received a loading dose of 50 µg/kg administered intravenously over 10 minutes followed by a continuous infusion of 0.50 µg/kg/min for the duration of the study. In patients with impaired renal function, the infusion rate was adjusted according to guidelines in the product labeling (17). The occurrence of a clinically significant adverse event required discontinuation of the milrinone infusion.

If the hemodynamic goal was neither achieved nor maintained with single drug therapy, additional therapy was permitted. In the nitroglycerin treatment group, dobutamine was added at an infusion rate of 2.5 µg/kg/min and increased every 5 to 15 minutes until the hemodynamic goal was achieved, a top dose of 15 µg/kg/min was reached, or a clinically significant adverse event attributable to dobutamine occurred.

In the milrinone treatment group, dobutamine was added if a greater improvement in cardiac output was needed. If a greater improvement in PCWP was needed, nitroglycerin was added at the rate previously specified. If improvement in both the cardiac output and PCWP was required, dobutamine and nitroglycerin could both be added.

The following hemodynamic measurements were obtained: 1) cardiac output by thermodilution (L/min) and CI (L/min/m<sup>2</sup>); 2) mean PCWP measured at the end of expiration (mm Hg); 3) systemic arterial pressure (mm Hg); systolic, diastolic, and mean; 4) pulmonary arterial

pressure (mm Hg); systolic, diastolic, and mean; 5) mean right atrial pressure (mm Hg); and 6) heart rate (bpm).

The following parameters were derived from the hemodynamic measurements: 1) SVR (dynes · s/cm<sup>5</sup>); 2) stroke volume (SV [mL]), SV index (L/min<sup>2</sup>), and stroke work index (g · m/m<sup>2</sup>); 3) rate-pressure product (bpm · mm Hg); and 4) pulmonary vascular resistance (dynes · s/cm<sup>5</sup>).

For timing of the measurement of hemodynamic parameters, the 0 hour (hour 0) was designated as 30 minutes after the initiation of the milrinone loading dose and 5 minutes after the end of the nitroglycerin titration. The 0 hour was used to assess successful achievement of the prespecified hemodynamic goal before the addition of a second agent. Hemodynamic responses were measured at 1, 2, 4, 8, and 24 hours after hour 0. If study treatment continued beyond 24 hours, measurements were taken at 12-hour intervals.

Both oral and intravenous diuretics were withheld within 2 hours before the scheduled hemodynamic measurements and until at least the 8-hour measurement. Similarly, oral vasodilators were withheld from 12 hours before the determination of baseline hemodynamic measurements and until at least a point after the 8-hour measurement. β-Blockers were discontinued a minimum of 5 half-lives before the initiation of baseline measurements.

Patients were not included in 24-hour efficacy evaluation when the study drug was permanently discontinued. Those patients not achieving the hemodynamic goals after the addition of another therapy were continued in the study at the discretion of the investigator. Other justifications for discontinuation included an intercurrent illness, adverse event, treatment failure after a prescribed procedure, protocol violation, or administrative reasons.

### Statistical Analysis

The primary efficacy end point for comparison between the 2 study treatments was the proportion of patients reaching the hemodynamic goals with the randomized therapy at hour 0 (as defined in the Methods section). The proportion of patients in each group who were able to maintain this goal at the 24-hour time point was also evaluated. Secondary efficacy end points included the potential need for additional therapy, percent change from baseline in CI and PCWP, the changes in Killip class and global clinical status from baseline to last study observation, and the duration of intensive care.

### Hemodynamic Goal for Evaluable Patients

Treatment comparisons for 1) the proportion of patients who met the hemodynamic goal at hour 0 and 2)

the proportion of patients who met and maintained the hemodynamic goal at the 24-hour measurement were performed by using the Cochran-Mantel-Haenszel test stratified by center. A patient was considered to have met and maintained the hemodynamic goal if the goal was met before and at the 24-hour measurement.

In both the milrinone and nitroglycerin groups, a patient who reached the hemodynamic goal at hour 0 without the addition of a second agent was considered a success. All other patients were considered failures (or missing, if no assessment was done). Hemodynamic comparisons were analyzed for 1) milrinone versus nitroglycerin alone, 2) milrinone alone versus the sum of nitroglycerin alone and nitroglycerin plus dobutamine as add-on therapy, and 3) the sum of milrinone alone and milrinone plus a second agent versus the sum of nitroglycerin alone and nitroglycerin plus dobutamine.

### Secondary End Point Comparisons

All secondary comparisons were performed on the randomized treatment groups by intention-to-treat analysis, regardless of the use of add-on therapy. The percent change from baseline to the last study observation before study medication discontinuation for CI and PCWP was analyzed by analysis of variance on the ranks of the percent change from baseline. The duration of intensive care was analyzed by using a 2-way analysis of variance on the ranked data with center and randomized treatment main effects. Descriptive statistics were used to compare percent changes from baseline with each visit window between the randomized treatment groups with respect to the measured and derived hemodynamic parameters.

The treatment effect on the change in Killip classification from baseline to last study observation was analyzed by using the McNemar test for correlated populations within both of the randomized treatment groups. The McNemar test compares the number of patients who experienced a decrease in Killip classification with the number of patients who experienced an increase in Killip classification.

### Safety Analysis

Safety end points analyzed included 1) proportion of patients who did not tolerate their randomized therapy (permanently discontinued because of an adverse reaction) and incidence of adverse events.

Treatment comparisons with regard to the proportion of patients who did not tolerate their randomized medication were based on the Cochran-Mantel-Haenszel test with center as strata. Statistical significance was achieved if the null hypothesis could be rejected at the  $P < .05$  level.

## Results

Of the 125 patients (60 milrinone, 65 nitroglycerin) entering the study, 119 (58 milrinone, 61 nitroglycerin) were evaluable for analysis of efficacy. Six patients were nonevaluable, 5 (1 milrinone-treated and 4 nitroglycerin-treated) did not meet baseline hemodynamic criteria after study entry, and 1 was discontinued because of a protocol violation. All of the 125 patients randomized into the study were evaluated for safety. There were no baseline clinical or hemodynamic differences in patients between treatment groups (Table 1).

**Table 1.** Patient Characteristics

Characteristic	Milrinone (n = 60)	Nitroglycerin (n = 65)
Age (yr, mean $\pm$ SD)	54 $\pm$ 2	55 $\pm$ 2
Sex (n [%])		
Male	51 (85)	57 (88)
Female	9 (15)	8 (12)
Race (n [%])		
Asian	0 (0)	2 (3)
African American	14 (23)	9 (14)
White	40 (67)	43 (66)
Hispanic	6 (10)	11 (17)
NYHA classification (n [%])		
Class III	37 (62)	40 (62)
Class IV	23 (38)	25 (38)
CT Ratio (%)	62 $\pm$ 3	64 $\pm$ 2
LVEF (%)	19 $\pm$ 1	20 $\pm$ 1
CI (L/min/m <sup>2</sup> )	1.8 $\pm$ 0.4	1.8 $\pm$ 0.4
PCWP (mm Hg)	29.5 $\pm$ 6.9	28.6 $\pm$ 6.5

NOTE. All values presented as mean  $\pm$  standard deviation.

CI, cardiac index; CT, cardiothoracic; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCWP, pulmonary capillary wedge pressure.

Of the 60 patients randomized to the milrinone treatment group, 34 (57%) received milrinone alone, 12 (20%) received milrinone plus dobutamine, 12 (20%) received milrinone plus nitroglycerin, and 2 (3%) received milrinone plus both dobutamine and nitroglycerin. Of the 65 patients randomized to the nitroglycerin treatment group, 13 (20%) received nitroglycerin alone, and 52 (80%) received nitroglycerin plus dobutamine.

### Attainment of Hemodynamic Goals

At hour 0 (designated at 30 minutes after the initiation of the milrinone loading dose and 5 minutes after the end of the nitroglycerin), the proportion of evaluable patients reaching the hemodynamic goals with milrinone alone (26/58, 45%) was significantly greater than those who received nitroglycerin alone (8/59, 14%;  $P < .0005$ ). Posttherapy data were not available for 2 nitroglycerin patients, and therefore, the achievement of hemodynamic goal could not be determined (Table 2).

There was no significant difference between the 2 treatment groups in the proportion of patients who reached both hemodynamic goals when dobutamine was added to the baseline intravenous therapy. As shown in Table 2, the total of successful milrinone plus dobutamine-treated patients was 41/58 (71%) compared with 43/59 (73%) for the nitroglycerin patients who received dobutamine ( $P = \text{NS}$ ). Figure 1 presents the effects of milrinone or nitroglycerin alone on heart rate, CI, and PCWP. Despite comparable changes in PCWP at all time points, milrinone-treated patients showed consistently greater increases in CI. The time to achieve hemodynamic goals at hour 0 was significantly shorter in the milrinone-treated group than in the nitroglycerin-treated group (33 min  $\pm$  2 min  $\nu$  54 min  $\pm$  10 min;  $P < .001$ ). In those patients in whom the hemodynamic goal was not achieved or maintained, additional therapy was provided after hour 0. Figure 2 shows the changes in heart rate, CI, PCWP, and SVR occurring with milrinone and nitroglycerin groups before and after the addition of

dobutamine. The initial rapid rise in CI at hour 0 is followed by an approximation of the curves. After dobutamine administration, the 2 curves approach each other and run parallel for the duration of the study. At hour 0, despite a comparable reduction in PCWP, increases in CI were significantly greater for the milrinone  $\pm$  dobutamine/nitroglycerin patients than for the nitroglycerin  $\pm$  dobutamine group (50%  $\pm$  5%  $\nu$  24%  $\pm$  4%;  $P = .0003$  [Fig. 2]). The percent changes in SVR were significantly greater in the milrinone group than in the nitroglycerin group (31%  $\pm$  3% for milrinone patients  $\nu$  16%  $\pm$  4% for nitroglycerin patients;  $P = .004$ ). Figure 3 presents the effects of milrinone or nitroglycerin alone on MAP and SV. A significantly greater percent increase in stroke work index at hour 0 was also observed for the milrinone group in comparison with the nitroglycerin group (51%  $\pm$  7%  $\nu$  27%  $\pm$  5%,  $P = .008$ ). Approximately twice the percentage of NYHA III patients achieved their hemodynamic goals with milrinone versus nitroglycerin compared with class IV patients (NYHA III: 57%  $\nu$  17%,  $P < .001$ , NYHA IV: 26%  $\nu$  9%,  $P = \text{NS}$ ).

### Maintenance of Hemodynamic Goal at 24 Hours

The proportion of evaluable patients who reached the hemodynamic goal (20% to 30% increase in CI and a 25% reduction in PCWP) and maintained these goals at 24 hours was statistically significantly greater ( $P = .026$ ) with milrinone treatment alone (11/46 patients, 24%) than with nitroglycerin treatment alone (3/51 patients, 6%). When milrinone treatment alone was compared with the sum of nitroglycerin alone and nitroglycerin plus dobutamine, 24% of patients in each treatment group maintained the treatment goal at 24 hours. A significantly greater proportion of patients reached the hemodynamic goal and maintained it at 24 hours in a sum of milrinone alone and milrinone plus add-on therapy-treated patients (20/46 patients, 43%) compared with the sum of nitro-

**Table 2.** Evaluable Patients Reaching Hemodynamic Goal Stratified by NYHA Classification

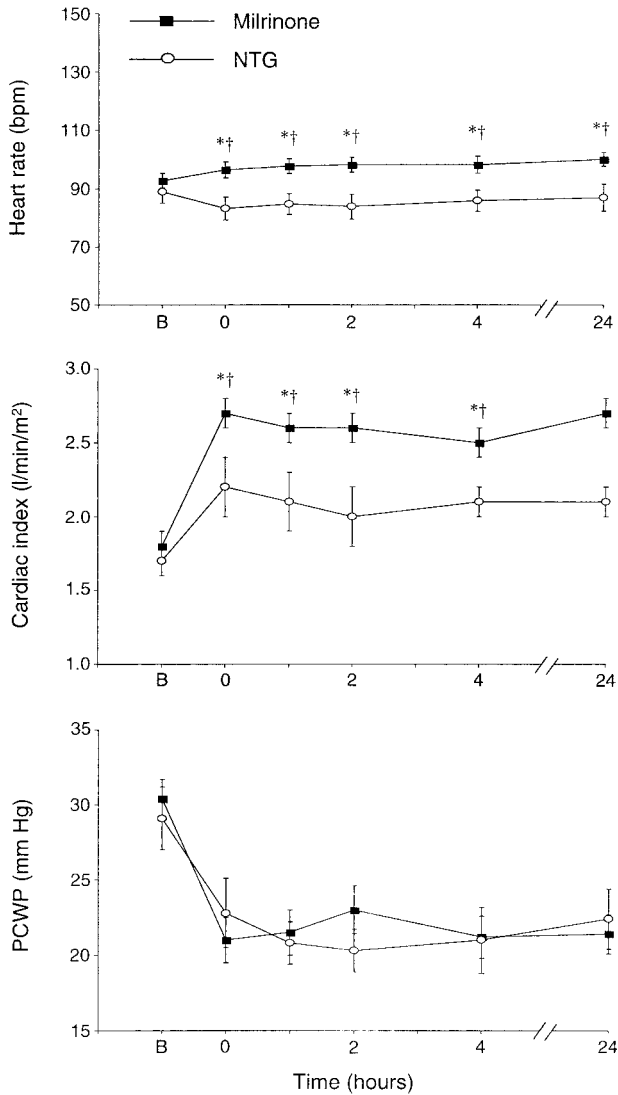
	Milrinone (%)	Sum of Milrinone $\pm$ Add-on Therapy (%)	Nitroglycerin (%)	Sum of Nitroglycerin $\pm$ Dobutamine (%)
Patients reaching hemodynamic goal	26/58 (45)*	41/58 (71) <sup>†</sup>	8/59 (14)	43/59 (73)
NYHA class III	20/35 (57) <sup>‡</sup>	32/35 (91)	6/36 (17)	31/36 (86)
NYHA class IV	6/23 (26) <sup>§</sup>	9/23 (39)	2/23 (9)	12/23 (52)

\* $P = .0005$   $\nu$  nitroglycerin alone.

<sup>†</sup> $P = \text{NS}$   $\nu$  nitroglycerin  $\pm$  dobutamine.

<sup>‡</sup> $P < .001$   $\nu$  nitroglycerin alone.

<sup>§</sup> $P = \text{NS}$   $\nu$  nitroglycerin alone.



**Fig. 1.** Changes in heart rate, CI, and PCWP after administration of milrinone or nitroglycerin (NTG) alone. The first point in each graph is the baseline (B) value obtained before drug administration. \* $P < .05$  v baseline; † $P < .05$  milrinone v nitroglycerin.

glycerin alone and nitroglycerin plus dobutamine-treated patients (12/51 patients, 24%;  $P = .038$ ).

### Change in Killip Class and Global Clinical Status

The treatment effect on the change from baseline to the last study observation was assessed for both Killip class and global clinical status. In the milrinone group, Killip class decreased for 17 patients and remained the same for 41 patients ( $P < .0001$  v baseline); no patients had an

increase in Killip class. In the nitroglycerin group, 11 patients had a decrease; 1 patient had an increase, and 50 patients had no change in Killip class ( $P = .0063$ ) versus milrinone.

### Safety

All 125 patients entering the study were evaluable for analysis of safety data. Adverse events were reported in 33/60 (55%) milrinone-treated patients, compared with 48/65 (74%) patients in the nitroglycerin group. Most adverse events were mild to moderate in severity. The incidence of adverse events ascribed to study medication by the investigator was significantly ( $P = .050$ ) greater in the nitroglycerin group (39/65, 60%) than in the milrinone group (25/60, 42%). Headache, the most commonly observed related adverse event in both groups, occurred less frequently in 7/60 (12%) of milrinone-treated patients compared with 20/65 (29%) in the nitroglycerin-treated patients ( $P = .03$ ).

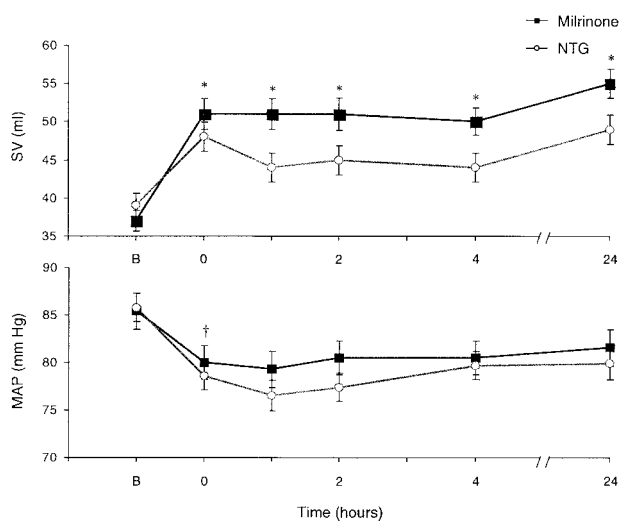
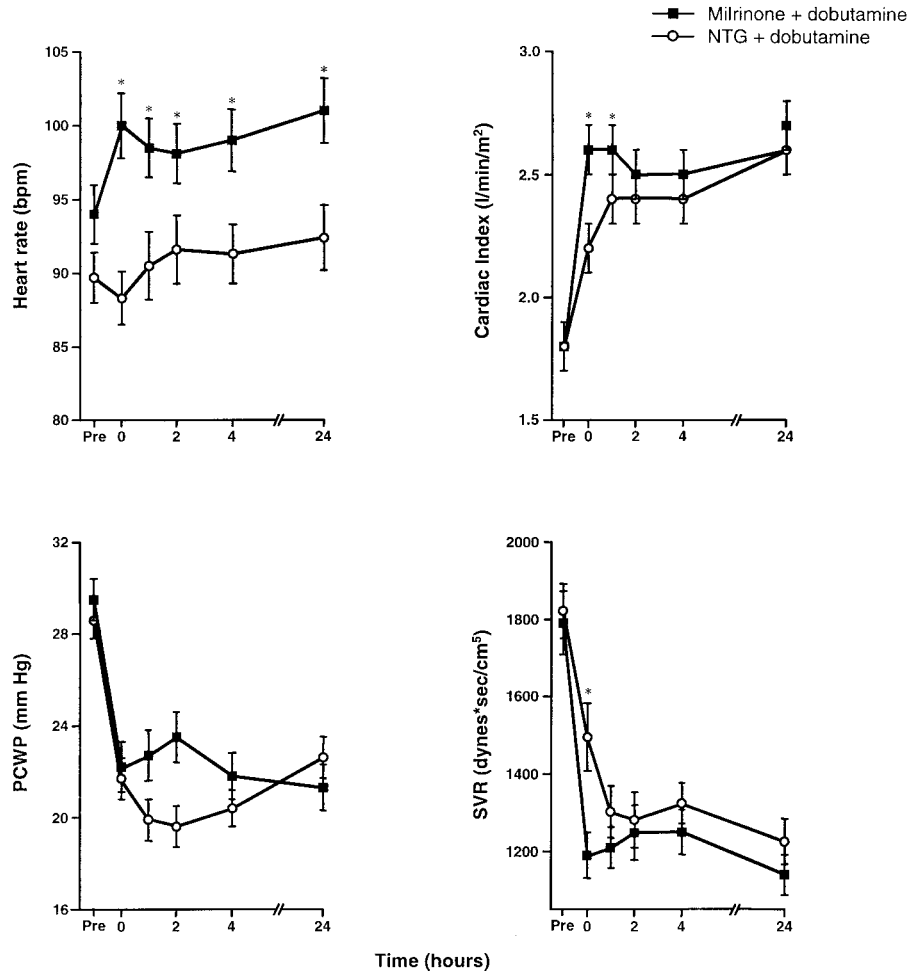
Three patients discontinued milrinone because of adverse events, 1 each for ventricular ectopy, renal insufficiency, and hypokalemia. Four patients discontinued nitroglycerin because of adverse events, 3 for ventricular ectopy and 1 for hypotension.

### Discussion

This study demonstrates the efficacy and safety of intravenous milrinone in the treatment of patients with advanced decompensated heart failure in comparison with intravenous nitroglycerin, a pure vasodilator. This is the first study to show that an intravenous inodilator strategy is both immediately, and over a 24-hour period, more efficacious than a pure vasodilator approach in patients admitted to the hospital with decompensated advanced heart failure. Further, intravenous milrinone was significantly more effective in both the attainment of predetermined hemodynamic goals and in the time to achieve these goals. The need for additional inotropic agents was significantly less in the milrinone-treated group.

A number of clinical studies (11,16) have shown the acute beneficial hemodynamic effect of bolus administration of milrinone in patients with severe decompensated heart failure. In a study comparing intravenous milrinone and intravenous nitroprusside in patients with severe heart failure, Jaski et al (9) reported a significant increase in CI and reduction in left ventricular end-diastolic pressure with milrinone therapy. These hemodynamic changes were associated with an improvement in clinical symptoms. Additionally, others have reported that there was also evidence of an increase in coronary blood flow associated with intravenous milrinone

**Fig. 2.** Changes in heart rate, CI, PCWP, and SVR before (pre) and after addition of dobutamine to milrinone-treated versus nitroglycerin (NTG)-treated patients. The first point in each graph is the baseline (B) value obtained before drug administration. \* $P < .05$  milrinone  $\nu$  nitroglycerin.



**Fig. 3.** Changes in SV and MAP after administration of milrinone or nitroglycerin (NTG) alone. The first point in each graph is the baseline (B) value obtained before drug administration. \* $P < .05$   $\nu$  baseline; † $P < .05$  milrinone  $\nu$  nitroglycerin.

(12,13). There has not been a study that has examined whether these improvements are sustainable for a 24-hour period in the clinical setting.

The patients in this study with severe decompensated heart failure NYHA III or IV achieved the 2 predetermined hemodynamic goals (reduction in PCWP and increase in CI) in a significantly greater percentage of patients treated with milrinone alone than with nitroglycerin alone, suggesting that inodilator therapy may be the preferred initial intravenous therapeutic strategy. Further, given the safety profiles seen in this trial, it seems that milrinone is acceptably safe and tolerable with up to 24 hours of continuous therapy, despite the increase in heart rate. Finally, as the prespecified end point was follow-up at 24 hours only, no comment can be made about the long-term effects of this early, upfront inotropic versus vasodilator approach to patients with decompensated heart failure.

This study shows that milrinone is a more effective alternative to pure vasodilator (eg, nitroglycerin) therapy in patients with NYHA III or IV decompensated heart failure in achieving balanced afterload reduction and

improvement in cardiac output in the clinical setting. The short-term use of intravenous milrinone in patients with decompensated heart failure seems safe and well tolerated. The efficacy and safety profile of intravenous milrinone observed in this study allow for a monotherapy approach that more efficiently improves cardiac and systemic hemodynamics in decompensated heart failure patients admitted to the hospital. These effects will allow for more rapid augmentation of organ perfusion and optimization of a patient's oral regimen. Although yet to be tested, this approach may ultimately reduce hospital length of stay and total cost of care for this complex and challenging group of patients.

## References

- Heart Failure Society of America: HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dysfunction—pharmacological approaches. *J Card Fail* 1999;5:357–382
- Miller RR, Vismara LA, Williams DO, Amsterdam EA, Mason DT: Pharmacological mechanisms for left ventricular unloading in clinical congestive heart failure. Differential effects of nitroprusside, phentolamine, and nitroglycerin on cardiac function and peripheral circulation. *Circ Res* 1976;39:127–133
- Leier CV, Bambach D, Thompson MJ, Cattaneo SM, Goldberg RJ, Unverferth DV: Central and regional hemodynamic effects of intravenous isosorbide dinitrate, nitroglycerin and nitroprusside in patients with congestive heart failure. *Am J Cardiol* 1981;48:1115–1123
- Miller RR, Vismara LA, Zelis R, Amsterdam EA, Mason DT: Clinical use of sodium nitroprusside in chronic ischemic heart disease. Effects on peripheral vascular resistance and venous tone and on ventricular volume, pump and mechanical performance. *Circulation* 1975;51:328–336
- Pierpont G, Hale KA, Franciosa JA, Cohn JN: Effects of vasodilators on pulmonary hemodynamics and gas exchange in left ventricular failure. *Am Heart J* 1980;99:208–216
- Guiha NH, Cohn JN, Mikulic E, Franciosa JA, Limas CJ: Treatment of refractory heart failure with infusion of nitroprusside. *N Engl J Med* 1974;291:587–592
- Colucci WS, Wright RF, Braunwald E: New positive inotropic agents in the treatment of congestive heart failure. Mechanisms of action and recent clinical developments. (First of two parts.) *N Engl J Med* 1986;314:290–299
- Bristow MR, Ginsburg R, Umans V, Fowler M, Minobe W, Rasmussen R, Zera P, Menlove R, Shah P, Jamieson S, Stinson EB:  $\beta_1$ - and  $\beta_2$ -adrenergic-receptor subpopulations in nonfailing and failing human ventricular myocardium: Coupling of both receptor subtypes to muscle contraction and selective  $\beta_1$ -receptor down-regulation in heart failure. *Circ Res* 1986;59:297–309
- Jaski BE, Fifer MA, Wright RF, Braunwald E, Colucci WS: Positive inotropic and vasodilator actions of milrinone in patients with severe congestive heart failure. Dose-response relationships and comparison to nitroprusside. *J Clin Invest* 1985;75:643–649
- Cody RJ, Müller FB, Kubo SH, Rutman H, Leonard D: Identification of the direct vasodilator effect of milrinone with an isolated limb preparation in patients with chronic congestive heart failure. *Circulation* 1986;73:124–129
- Anderson JL, Baim DS, Fein SA, Goldstein RA, LeJemtel TH, Likoff MJ, for the milrinone investigators and their associates: Efficacy and safety of sustained (48 hour) intravenous infusions of milrinone in patients with severe congestive heart failure: a multicenter study. *J Am Coll Cardiol* 1987;9:711–722
- Grose R, Strain J, Greenberg M, LeJemtel TH: Systemic and coronary effects of intravenous milrinone and dobutamine in congestive heart failure. *J Am Coll Cardiol* 1986;7:1107–1113
- Monrad ES, Baim DS, Smith HS, Lanoue A, Braunwald E, Grossman W: Effects of milrinone on coronary hemodynamics and myocardial energetics in patients with congestive heart failure. *Circulation* 1985;71:972–979
- Monrad ES, Baim DS, Smith HS, Lanoue AS: Milrinone, dobutamine, and nitroprusside: Comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation* 1986;73(suppl III):III168–74
- Colucci WS, Wright RF, Braunwald E: New positive inotropic agents in the treatment of congestive heart failure. (Second of two parts.) *N Engl J Med* 1986;314:349–358
- Pflugfelder PW, O'Neill BJ, Ogilvie RI, Beanlands DS, Tanser PH, Tihal H, Mizgala HF, Fitchett DH, Kostuk WJ: A Canadian multicentre study of a 48 h infusion of milrinone in patients with severe heart failure. *Can J Cardiol* 1991;7:5–10
- Konstam MA, Cody RJ: Short-term use of intravenous milrinone for heart failure. *Am J Cardiol* 1995;75:822–826