

# Positive Inotropic and Vasodilator Actions of Milrinone in Patients with Severe Congestive Heart Failure

## Dose-Response Relationships and Comparison to Nitroprusside

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### Abstract

Milrinone is a potent positive inotropic and vascular smooth muscle-relaxing agent *in vitro*, and therefore, it is not known to what extent each of these actions contributes to the drug's hemodynamic effects in patients with heart failure. In 11 patients with New York Heart Association class III or IV congestive heart failure, incremental intravenous doses of milrinone were administered to determine the dose-response relationships for heart rate, systemic vascular resistance, and inotropic state, the latter measured by peak positive left ventricular derivative of pressure with respect to time ( $dP/dt$ ). To clarify further the role of a positive inotropic action, the relative effects of milrinone and nitroprusside on left ventricular stroke work and  $dP/dt$  were compared in each patient at doses matched to cause equivalent reductions in mean arterial pressure or systemic vascular resistance, indices of left ventricular afterload. Milrinone caused heart rate, stroke volume, and  $dP/dt$  to increase, and systemic vascular resistance to decrease in a concentration-related manner. At the two lowest milrinone doses resulting in serum concentrations of  $63 \pm 4$  and  $156 \pm 5$  ng/ml, respectively, milrinone caused significant increases in stroke volume and  $dP/dt$ , but no changes in systemic vascular resistance or heart rate. At the maximum milrinone dose administered (mean serum concentration,  $427 \pm 11$  ng/ml), heart rate increased from  $92 \pm 4$  to  $99 \pm 4$  bpm ( $P < 0.01$ ), mean aortic pressure fell from  $82 \pm 3$  to  $71 \pm 3$  mmHg ( $P < 0.01$ ), right atrial pressure fell from  $15 \pm 2$  to  $7 \pm 1$  mmHg ( $P < 0.005$ ), left ventricular end-diastolic pressure fell from  $26 \pm 3$  to  $18 \pm 3$  ( $P < 0.005$ ), stroke volume index increased from  $20 \pm 2$  to  $30 \pm 2$  ml/m<sup>2</sup> ( $P < 0.005$ ), stroke work index increased from  $14 \pm 2$  to  $21 \pm 2$  g · m/m<sup>2</sup> ( $P < 0.01$ ), and  $dP/dt$  increased from  $858 \pm 54$  to  $1,130 \pm 108$  mmHg/s ( $P < 0.005$ ). When compared with nitroprusside for a matched reduction in mean aortic pressure or systemic vascular resistance, milrinone caused a significantly greater increase in stroke work index at the same or lower left ventricular end-diastolic pressure. Milrinone caused a concentration-related increase in  $dP/dt$  (32% increase at maximum milrinone dose), whereas nitroprusside had no effect. These data in patients with severe heart failure indicate that in addition to a vasodilating effect, milrinone exerts a concentration-related positive inotropic action that contributes

significantly to the drug's overall hemodynamic effects. The positive inotropic action occurs at drug levels that do not exert significant chronotropic or vasodilator effects.

### Introduction

Milrinone, a potent new bipyridine analogue of amrinone, exerts a positive inotropic action *in vitro* (1, 2), and causes marked beneficial changes in hemodynamic function in patients with severe congestive heart failure, with decreases in right and left heart-filling pressures and increases in stroke volume and work (3, 4). However, milrinone also possesses potent direct vascular smooth muscle-relaxing properties *in vitro* (5, 6), and causes a reduction in mean arterial pressure in patients with heart failure (3, 4), indicating that some, if not all, of the agent's overall hemodynamic effects are due to a reduction in left ventricular afterload.

The purpose of this study was to determine whether milrinone exerts a positive inotropic action in patients with severe congestive heart failure, and if so, whether this action contributes significantly to the overall hemodynamic effects of the drug. To analyze the relative contributions of milrinone's inotropic, vascular, and chronotropic actions, two basic strategies were combined. First, the effects of milrinone were studied at four successive doses in order to determine the relative dose-response relationships for changes in heart rate, systemic vascular resistance, and inotropic state, which was assessed by measurement of peak positive left ventricular derivative of pressure with respect to time ( $dP/dt$ ).<sup>1</sup> Second, since the reduction in mean arterial and left ventricular filling pressures caused by milrinone is similar to that caused by the balanced vasodilator nitroprusside (7, 8), the relative effects of milrinone and nitroprusside on left ventricular stroke work and peak positive  $dP/dt$ , two measures of inotropic state (9, 10), were compared in each patient at doses matched for equal reductions in both mean arterial pressure, a directly measurable determinant of left ventricular afterload (11), and systemic vascular resistance.

### Methods

**Patient population.** The study population consisted of 11 patients with New York Heart Association functional class III or IV congestive heart failure despite optimal conventional therapy with digitalis, diuretics, and systemic vasodilators in all cases (Table I). The etiology of congestive heart failure was coronary artery disease in eight patients and cardiomyopathy in three. Patients with symptomatic angina pectoris, myocardial infarction within 3 months, or significant mitral or aortic

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1. Abbreviation used in this paper:  $dP/dt$ , derivative of pressure with respect to time.

Table I. Characteristics of the Study Population

Patient	Age	Sex	NYHA Class	Etiology	Rhythm	LVEF
1	69	M	III	CAD	SR	0.16
2	52	M	III	CAD	SR	0.21
3	65	M	III	CAD	SR	0.15
4	49	F	III	CAD	SR	0.15
5	74	M	IV	CMP	AF	0.26
6	65	M	IV	CAD	SR	0.15
7	65	M	IV	CAD	SR	0.11
8	65	M	III	CAD	SR	0.30
9	48	M	III	CMP	SR	0.03
10	72	M	IV	CMP	Paced	0.24
11	24	M	II	CMP	SR	0.08

M, male; F, female; CAD, coronary artery disease; CMP, idiopathic cardiomyopathy; SR, sinus rhythm; AF, atrial fibrillation; LVEF, left ventricular ejection fraction measured by gated blood-pool radionuclide ventriculography; NYHA, New York Heart Association.

stenosis were excluded from the study. Nine patients were in sinus rhythm, one was in chronic atrial fibrillation, and one had a fixed-rate ventricular pacemaker. The left ventricular ejection fraction measured by radionuclide-gated blood-pool imaging was  $<0.30$  in all patients (mean  $\pm$  SEM,  $0.18 \pm 0.08$ ). The study protocol was approved by the Committee for the Protection of Human Subjects from Research Risks of the Brigham and Women's Hospital, and informed written consent was obtained in all cases.

**Study protocol.** All vasodilators were withheld for at least 48 h before the time of study, and digitalis and diuretics were withheld on the morning of study. Patients were taken to the Cardiac Catheterization Laboratory where catheters were placed percutaneously under local anesthesia with lidocaine (1%) as follows: (a) a 7F balloon-tipped, flow-directed pulmonary artery catheter with a proximal right atrial port was advanced to the distal pulmonary artery from the right internal jugular or femoral vein; (b) a 7F pigtail catheter was advanced to the left ventricle from the right femoral artery; (c) a 2F or 4F micromanometer-tipped catheter (Mikro-tip, Millar Instruments, Inc., Houston, TX), was advanced to the tip of the left ventricular pigtail catheter and calibrated externally against a mercury reference with simultaneous matching to the left ventricular luminal pressure; (d) an 8F femoral arterial sheath with a side-arm port (Cordis, Laboratories, Inc., Miami, FL) was used to monitor femoral artery pressure. The following measurements were made: heart rate; femoral arterial, left ventricular, right atrial, pulmonary arterial and pulmonary capillary wedge pressures; the first time-derivative of left ventricular pressure (peak positive  $dP/dt$ ) by electronic differentiation (Electronics for Medicine, Inc., Pleasantville, NY); oxygen consumption measured by Douglas bag collection; and serum milrinone concentration by the method of Edelson et al. (12). Cardiac output was calculated by the Fick method as oxygen consumption divided by the difference between femoral arterial and pulmonary arterial oxygen contents. Oxygen consumption was measured at base line and again at the highest nitroprusside and milrinone doses; since oxygen consumption was not affected by either drug, the mean of these three values was used for calculation of cardiac output. At each hemodynamic measurement point, arterial and venous blood oxygen contents were determined in duplicate by reflectance oximetry. The following standard hemodynamic formulae were used: systemic vascular resistance (SVR) in  $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5} = 80 (\text{MAP}-\text{RAP})/\text{CO}$ ; pulmonary vascular resistance (PVR) in  $\text{dyne} \cdot \text{s} \cdot \text{cm}^{-5} = 80 (\text{MPAP}-\text{PCW})/\text{CO}$ ; stroke volume index (SVI) in milliliters per minute =  $\text{CI}/\text{h}$ ; stroke work index (SWI) in  $\text{g} \cdot \text{m}/\text{m}^2 = \text{SVI} (\text{MAP}-\text{LVEDP}) (0.0136)$ ; where MAP = mean arterial pressure, RAP = mean right atrial pressure,

CO = cardiac output (liters/minute), CI = cardiac index (liters per minute per square meter), MPAP = mean pulmonary artery pressure, PCW = mean pulmonary capillary wedge pressure, and LVEDP = left ventricular end-diastolic pressure (all pressures expressed in millimeters of Hg).

Base-line hemodynamics were established as the mean of two sets of measurements separated by at least 10 min and differing by  $<10\%$ . The infusion rate of sodium nitroprusside (Elkins-Sinn, Inc., Cherry Hill, NJ) was then increased at 10-min intervals according to the following schedule: 10, 25, 50, 75, 100, 150, 200, and 300  $\mu\text{g}/\text{min}$ . Hemodynamic measurements were made at the end of each infusion rate. Following nitroprusside titration to a mean arterial pressure reduction of 15–20 mmHg, nitroprusside was discontinued, and base-line hemodynamics were remeasured by waiting at least 20 min and until all measurements had returned to within 10% of the initial base-line value. Milrinone was then administered as an intravenous bolus over 15–60 s in the following doses: 12.5, 25, 50, and 75  $\mu\text{g}/\text{kg}$  per min. Hemodynamic measurements were made 7–10 min after bolus infusion, and incremental boluses were administered at 10-min intervals. Seven patients received all four doses, and four patients received only three doses because mean arterial pressure had fallen by 15–20 mm Hg after the third dose. Serum milrinone concentration was measured at the recontrol point, and 7–10 min after each milrinone bolus, simultaneously with the hemodynamic measurements.

**Statistical methods.** All data are presented as mean  $\pm$  1 SEM. Significant changes among multiple observations for each variable were detected by two-way analysis of variance, and individual differences between observations were determined by Wilcoxon's nonparametric test for paired data using Bonferroni's method for multiple simultaneous comparisons, such that statistical significance was assumed if the null hypothesis could be rejected at the  $0.05/n$  probability level (where  $n$  = number of comparisons) (13).

## Results

**Base-line hemodynamics and effects of nitroprusside.** Base-line hemodynamic measurements indicated severe hemodynamic impairment consistent with the clinical diagnosis of congestive heart failure in all patients (Fig. 1). Because the threshold for the nitroprusside effect varied considerably, the number of incremental infusion rates needed to achieve a maximum desired effect ranged from two (25  $\mu\text{g}/\text{min}$ ) to eight steps (300  $\mu\text{g}/\text{min}$ ), with a mean maximum infusion rate for the group of  $125 \pm 30 \mu\text{g}/\text{min}$ . The data presented in Fig. 1 are for the control, maximum, and immediately preceding infusion rate of nitroprusside; and for the recontrol, maximum, and the two preceding doses of milrinone in each subject.

At the maximum nitroprusside infusion rate, mean arterial pressure fell from  $82 \pm 4$  to  $66 \pm 2$  mmHg ( $P < 0.005$ ), heart rate was unchanged, right atrial pressure fell from  $16 \pm 2$  to  $8 \pm 2$  mmHg ( $P < 0.01$ ) and left ventricular end-diastolic pressure fell from  $28 \pm 3$  to  $18 \pm 3$  mmHg ( $P < 0.005$ ). Cardiac index increased from  $1.8 \pm 0.2$  to  $2.6 \pm 0.2$  liter/min per  $\text{m}^2$  ( $P < 0.005$ ) and stroke volume index increased from  $20 \pm 3$  to  $30 \pm 2$  ml/min per  $\text{m}^2$  ( $P < 0.01$ ). Stroke work index (control,  $14 \pm 2 \text{ g} \cdot \text{m}/\text{m}^2$ ; nitroprusside,  $18 \pm 1 \text{ g} \cdot \text{m}/\text{m}^2$ ;  $P = \text{NS}$ ) and peak positive  $dP/dt$  (control,  $847 \pm 54 \text{ mmHg/s}$ ; nitroprusside  $846 \pm 55 \text{ mmHg/s}$ ;  $P = \text{NS}$ ) were unchanged.

After cessation of the nitroprusside infusion, all hemodynamic variables were allowed to return to a stable base-line such that second control values for heart rate, mean arterial pressure, right atrial pressure, mean pulmonary capillary wedge pressure, left ventricular end-diastolic pressure, arterial-mixed venous oxygen difference, systemic vascular resistance, and

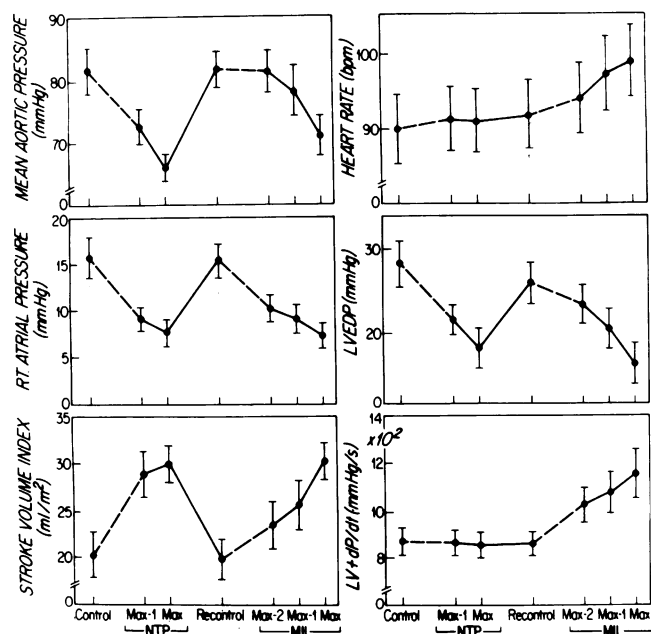


Figure 1. Hemodynamic effects of nitroprusside (NTP) and milrinone (MIL) in 11 patients with New York Heart Association class III or IV congestive heart failure. Data (mean $\pm$ SEM) are presented as the maximum effect achieved for each drug, and for the one (NTP) or two (MIL) previous doses, referred to as max-1 and max-2, respectively. Repeat control measurements in all cases did not differ significantly from the initial control values. LVEDP, left ventricular end-diastolic pressure; LV + dP/dt, peak positive left ventricular dP/dt.

stroke volume were all unchanged compared with their respective control values ( $P = \text{NS}$  for control versus recontrol in all cases) (Fig. 1).

**Effects of milrinone.** Four incremental doses of milrinone were administered to seven subjects, whereas in four subjects the titration was concluded with the third dose due to achievement of a reduction in mean arterial pressure of 15–20 mmHg (Fig. 1). Milrinone caused a dose-related reduction in mean arterial pressure, which at the maximum dose decreased from  $82\pm3$  to  $71\pm3$  mmHg ( $P < 0.01$ ). Heart rate was increased at the two highest milrinone doses, increasing from  $92\pm4$  to  $99\pm4$  bpm at the maximum milrinone dose ( $P < 0.01$ ). At the maximum dose, right atrial pressure fell from  $15\pm2$  to  $7\pm1$  mmHg ( $P < 0.005$ ), and left ventricular end-diastolic pressure decreased from  $26\pm3$  to  $18\pm3$  mmHg ( $P < 0.005$ ). Likewise, cardiac index rose from  $1.7\pm0.2$  liter/min per  $\text{m}^2$  to  $3.0\pm0.2$  liter/min per  $\text{m}^2$  ( $P < 0.005$ ), stroke volume index rose from  $20\pm2$  ml/min per  $\text{m}^2$  to  $30\pm2$  ml/min per  $\text{m}^2$  ( $P < 0.005$ ), and stroke work index rose from  $14\pm2$  g $\cdot$ m/ $\text{m}^2$  to  $21\pm2$  g $\cdot$ m/ $\text{m}^2$  ( $P < 0.01$ ). Cardiac index, stroke volume index, and stroke work index all increased in a dose-related manner. Peak positive dP/dt increased by 32% at the maximum milrinone dose (control,  $858\pm54$  mmHg/s; maximum milrinone,  $1,130\pm108$  mmHg/s;  $P < 0.005$ ). The mean serum milrinone concentration measured at the time of hemodynamic determinations increased progressively from  $66\pm3$  ng/ml at the lowest milrinone dose to  $427\pm11$  ng/ml at the maximum milrinone dose.

**Comparative hemodynamic effects of nitroprusside and milrinone at matched mean arterial pressures.** Because multiple

incremental doses of each drug were administered, it was possible to select for analysis in each patient a dose of nitroprusside that caused a change in mean arterial pressure that closely matched the change caused by the maximum dose of milrinone. This matching was done by an objective protocol as follows: In each patient, the effects of the maximum milrinone dose administered were compared with the effects of the nitroprusside dose that caused the closest numerical change in the variable being matched (i.e., mean aortic pressure or systemic vascular resistance). Of the 11 patients, one was excluded from this analysis because mean arterial pressure was not decreased by milrinone, and therefore, could not be matched to any nitroprusside dose. In the remaining 10 patients matched in this manner, mean arterial pressure was reduced to  $70\pm3$  mmHg at the maximum milrinone dose and to an identical value,  $70\pm4$  mmHg with nitroprusside. After matching, the magnitude of mean arterial pressure reduction was very similar for the two drugs (milrinone,  $-11.8\pm1.1$  mmHg; nitroprusside,  $-11.2\pm1.8$  mmHg). At these matched mean arterial pressures, heart rate was unchanged by nitroprusside, but was increased significantly by milrinone (Fig. 2). Right atrial pressure decreased to a similar degree with both drugs, whereas left ventricular end-diastolic pressure decreased to a significantly lower level with milrinone (Fig. 2). Cardiac index increased to a significantly higher level with milrinone (nitroprusside,  $2.5\pm0.2$  liter/min per  $\text{m}^2$ ; milrinone,  $3.0\pm0.3$  liter/min per  $\text{m}^2$ ;  $P < 0.02$ ). Although stroke volume increased to a similar degree with both drugs, left ventricular end-diastolic pressure was lower with milrinone, and therefore, stroke work index was increased to a significantly higher level with milrinone (Fig. 3). Peak positive dP/dt was unchanged by nitroprusside, but increased significantly by 32% with milrinone (Fig. 2).

Similar results were obtained if the doses of milrinone and nitroprusside were selected in each patient to cause matched decreases in systemic vascular resistance, rather than mean arterial pressure. When compared at matched reductions in systemic vascular resistance (nitroprusside,  $1,091\pm113$  dyn $\cdot$ s $\cdot$ cm $^{-5}$ ; milrinone,  $1,041\pm134$  dyn $\cdot$ s $\cdot$ cm $^{-5}$ ); stroke work index was thus increased to a significantly higher value with milrinone (nitroprusside,  $19.0\pm1.2$  g $\cdot$ m/ $\text{m}^2$ ; milrinone,  $22.1\pm1.5$  g $\cdot$ m/ $\text{m}^2$ ;  $P < 0.03$ ). Likewise, cardiac index was higher with milrinone (milrinone,  $3.0\pm0.2$  liter/min per  $\text{m}^2$ ; nitroprusside,  $2.7\pm0.2$  liter/min per  $\text{m}^2$ ;  $P < 0.02$ ); while mean aortic pressure and stroke volume index were not significantly different for the two drugs.

**Hemodynamic effects of milrinone versus nitroprusside at matched cardiac indices.** In all subjects, it was possible to select doses of nitroprusside and milrinone that resulted in equivalent cardiac indices. When cardiac index was matched in this manner (nitroprusside,  $2.7\pm0.2$  liter/min per  $\text{m}^2$ ; milrinone,  $2.7\pm0.2$  liter/min per  $\text{m}^2$ ), left ventricular end-diastolic pressure was equal for the two groups (nitroprusside,  $20\pm2$  mmHg; milrinone,  $19\pm2$  mmHg;  $P = \text{NS}$ ). However, both mean arterial pressure (nitroprusside,  $70\pm2$  mmHg; milrinone,  $75\pm3$  mmHg;  $P < 0.05$ ) and systemic vascular resistance (nitroprusside,  $1,086\pm112$  dyn $\cdot$ s $\cdot$ cm $^{-5}$ ; milrinone,  $1,180\pm126$  dyn $\cdot$ s $\cdot$ cm $^{-5}$ ;  $P < 0.04$ ) were significantly higher with milrinone than with nitroprusside.

**Milrinone dose-response relationships.** The dose-response relationship between serum milrinone concentration and the

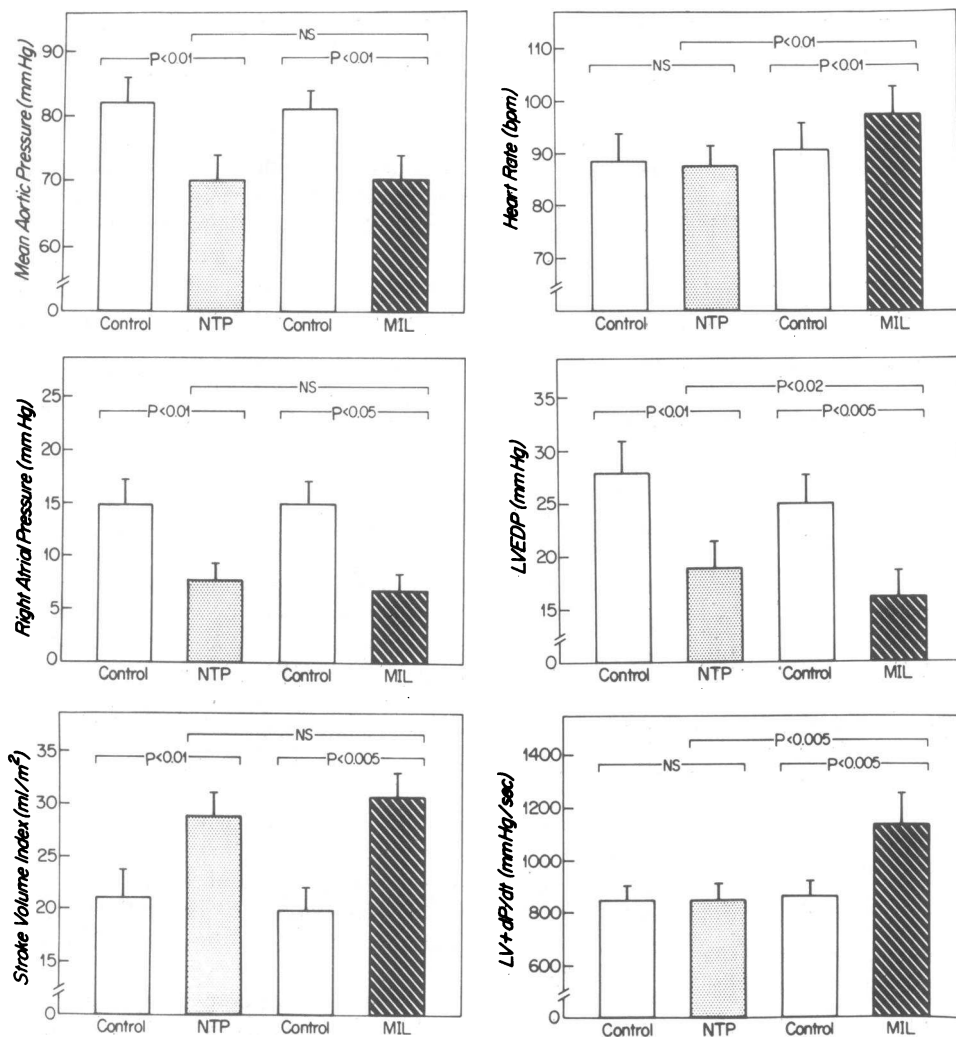


Figure 2. Comparative hemodynamic effects of nitroprusside (NTP) and milrinone (MIL) at the maximum milrinone dose administered and the nitroprusside dose that caused an equivalent reduction in mean aortic pressure.

change in peak positive  $dP/dt$  was assessed in the seven patients who received all four doses of milrinone (Fig. 4). The dose-related increase in  $dP/dt$  was significant at the lowest dose ( $12.5 \mu\text{g/kg}$ ), and reached a maximum of 35% at the highest milrinone dose.

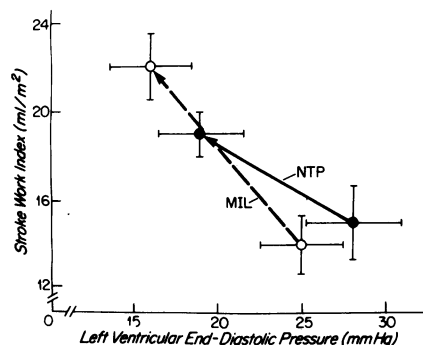


Figure 3. Comparative effects of milrinone (MIL) and nitroprusside (NTP) on left ventricular function at a matched mean aortic pressure. Despite a significantly lower left ventricular end-diastolic pressure ( $P < 0.02$ ), milrinone caused a significantly greater increase in left ventricular stroke work index ( $P < 0.03$  vs. NTP). A similar result was obtained if the two drugs were compared at matched systemic vascular resistances.

Since all 11 patients received at least three milrinone doses, the dose-response data for stroke volume index, heart rate, systemic vascular resistance, and  $dP/dt$  could be analyzed for the first three doses in all patients (Fig. 5). At the lowest milrinone dose of  $12.5 \mu\text{g/kg}$  (mean serum concentration,  $63 \pm 4 \text{ ng/ml}$ ), heart rate and systemic vascular resistance were unchanged, whereas  $dP/dt$  and stroke volume index were both significantly increased.

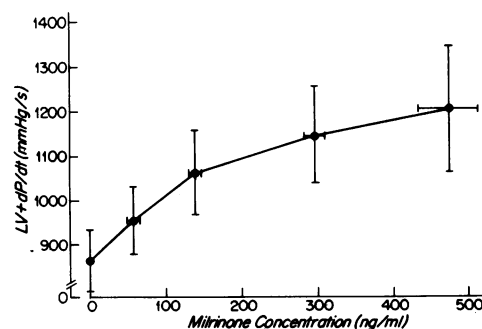


Figure 4. Milrinone serum concentration-response relationship for left ventricular peak positive  $dP/dt$  in the seven patients who received all four milrinone doses.

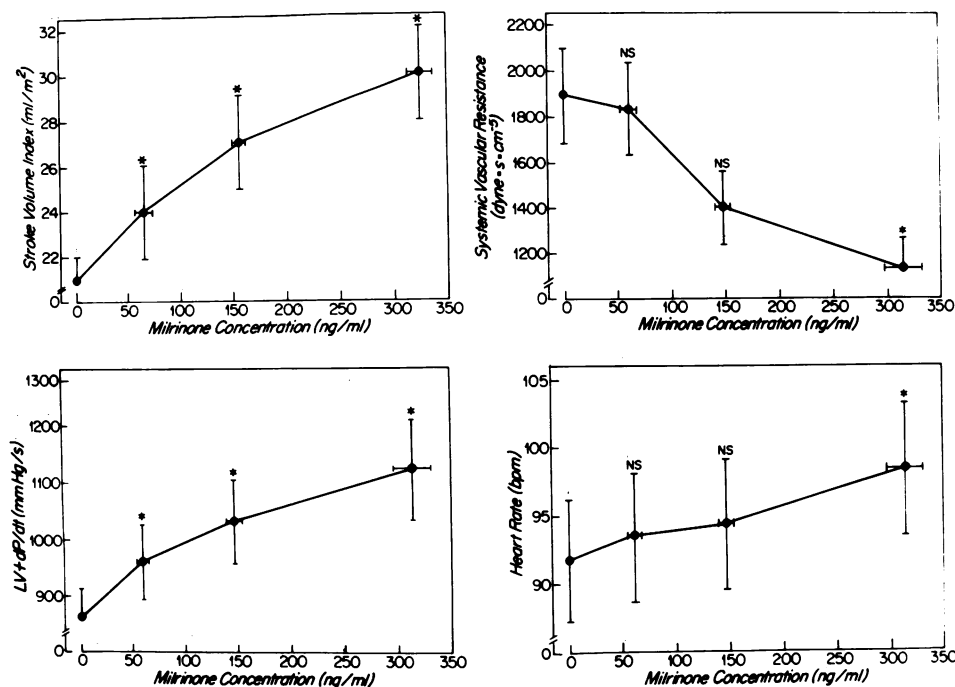


Figure 5. Milrinone serum concentration-response relationships for stroke volume index, left ventricular  $dP/dt$ , systemic vascular resistance, and heart rate for the first three milrinone doses in all 11 patients. Stroke volume index and  $dP/dt$  were increased at the two lowest milrinone doses tested, whereas systemic vascular resistance and heart rate were not significantly changed (\* indicates a significant change from control).

**Adverse effects.** No adverse reactions were observed during nitroprusside infusion. During milrinone infusion, two subjects developed a change in cardiac rhythm that may have been related to drug administration. In patient 8, ventricular tachycardia at a rate of 150 bpm occurred 17 min after administration of 50  $\mu\text{g/kg}$  of milrinone. The patient was stable with this rhythm, and reverted to normal sinus rhythm after cardioversion and administration of procainamide. Patient 3 developed atrial fibrillation following the 75- $\mu\text{g/kg}$  milrinone dose, spontaneously reverted to normal sinus rhythm several hours later, and subsequently was placed on oral milrinone without recurrence of atrial fibrillation. In both cases, the tachyarrhythmia occurred after completion of the hemodynamic protocol.

## Discussion

Milrinone causes a marked increase in myocardial contractile force in vitro (1, 2), and consequently, it has been assumed that an increase in inotropic state is responsible, at least in part, for the marked beneficial hemodynamic effects of this agent in patients with severe congestive heart failure (3, 4). However, milrinone (5, 6), like amrinone (14, 15), is also a potent direct vascular smooth muscle relaxing agent in vitro. In patients with congestive heart failure, milrinone causes reductions in mean arterial pressure, ventricular filling pressures, and systemic vascular resistance (5, 6) in excess of that expected for a pure positive inotropic agent. By contrast, the administration of dobutamine to patients with heart failure generally causes no change or an increase in mean arterial pressure, and little or no decrease in pulmonary capillary wedge or right atrial pressures (7, 8). It is thus highly likely that milrinone exerts vasodilatory effects in patients with heart failure, and that a reduction in left ventricular afterload contributes significantly to the drug's overall action to increase stroke volume.

The major purpose of this study was to test the hypothesis that an increase in inotropic state contributes to milrinone's overall hemodynamic effects in patients with congestive heart failure. To do this, the effects of milrinone were compared to those of nitroprusside, a vasodilator without known inotropic action. By design, several doses of nitroprusside were administered so that it was possible to select for analysis in each patient a dose of nitroprusside that caused a fall in mean arterial pressure that was closely matched to the fall in mean arterial pressure produced by milrinone. Thus, although it was not possible to assess directly the level of left ventricular afterload or systolic wall stress, it was possible to compare the effects of milrinone and nitroprusside in each patient for a closely matched reduction in mean arterial pressure, an important determinant of afterload that can be measured directly (11). The data were also analyzed by matching the two drugs with regard to their effects on systemic vascular resistance and cardiac index.

Milrinone caused a significant increase in peak positive  $dP/dt$ , whereas nitroprusside had no effect. This isovolumic phase measure of inotropic state can be influenced by both loading conditions and heart rate. Decreases in preload and afterload may both result in decreases in peak positive  $dP/dt$ , whereas an increase in heart rate can cause an increase in  $dP/dt$  (10, 16–19). Based on the significant reductions in right and left heart-filling pressures and mean arterial pressure with milrinone, it is highly likely that both preload and afterload fell. Therefore, the observed increase in  $dP/dt$  could not be related to the changes in loading conditions, which should have decreased  $dP/dt$ . As previously noted, at the milrinone dose used for comparison in this study, heart rate was significantly increased by 8%, and could have potentially contributed to the increase in  $dP/dt$ . However, in previous studies of the relationship between heart rate and  $dP/dt$ , heart rate increases of 10% caused little or no change in  $dP/dt$  (16, 17, 19). It is therefore unlikely that this small increase in heart rate could

account for the 32% increase in  $dP/dt$  observed in this study. This conclusion is further supported by the fact that both  $dP/dt$  and stroke volume index were increased at the lowest dose of milrinone administered, whereas heart rate was unchanged. Finally, in one patient in our study with a fixed-rate ventricular pacemaker, milrinone increased  $dP/dt$  by 31% despite the absence of a change in heart rate.

Although increases in peak positive  $dP/dt$  have been seen previously with milrinone (3) and amrinone (20), at least in the case of amrinone, this finding has been controversial (21). Wilmhurst et al. (21, 22) observed that intravenous administration of amrinone in doses that caused an almost 50% increase in cardiac index, resulted in a 9-mmHg fall in mean arterial pressure, a 35% decrease in systemic vascular resistance and significant decreases in both right and left heart filling pressures. However, these hemodynamic changes were not accompanied by significant changes in any of several isovolumic indices of inotropic state. Based on these data, it was concluded that amrinone acted only as a vasodilator. These discrepant findings may be due to basic differences in the actions of amrinone and milrinone, or alternately, may be due to the substantially lower left ventricular end-diastolic pressures in the study of Wilmhurst et al.

Three observations indicate that the increase in inotropic state reflected by an increase in  $dP/dt$  contributes significantly to milrinone's overall hemodynamic effects. First, despite matched mean arterial pressures and a significantly lower left ventricular end-diastolic pressure, milrinone caused a significantly greater increase in stroke work index than nitroprusside. When the data are plotted in the format of a ventricular function curve, it is thus readily apparent that milrinone caused a more leftward and upward shift than did nitroprusside. As discussed by Sarnoff (9) and others (23), a change in stroke work at any given left ventricular end-diastolic pressure can be a useful measure of a change in inotropic state, and previously has been used to demonstrate a positive inotropic action of digitalis in patients with heart failure (24). Stroke work is not specific for inotropic state since it can also be influenced by changes in ventricular loading conditions (23). However, in this study, by design arterial pressure was similarly affected by milrinone, and left ventricular end-diastolic pressure was lower with milrinone. The greater increase in stroke work caused by milrinone cannot be therefore attributed to loading conditions, and most likely reflects a direct positive inotropic action. Second, when the hemodynamic effects of nitroprusside and milrinone were matched for equal increases in cardiac index, left ventricular end-diastolic pressure was lowered equally by both drugs, but mean arterial pressure was significantly higher with milrinone. Milrinone thus increased cardiac index to the same degree as nitroprusside, but did so with a 42% smaller reduction in mean arterial pressure. Third, analysis of the dose-response relationships for milrinone's effects on  $dP/dt$ , systemic vascular resistance and stroke volume index indicate that milrinone caused a significant increase in both stroke volume index and  $dP/dt$  at the lowest concentration examined, whereas there was no significant change in systemic vascular resistance. Milrinone thus exerts a significant hemodynamic and positive inotropic effect at concentrations that have no appreciable vasodilator action.

A potential limitation of this comparison between milrinone

and nitroprusside is that left ventricular afterload was not directly measured. Ideally, left ventricular wall stress would have been utilized as a measure of afterload. However, left ventricular wall stress cannot be reliably quantified in patients such as ours with marked regional left ventricular contraction abnormalities and distorted geometry. Mean arterial pressure, rather than systemic vascular resistance, was chosen for analysis because of its primary importance in determining left ventricular wall stress, and because it is directly measurable. In contrast, systemic vascular resistance is derived secondarily from three other measurements, each with its own source of error. Furthermore, it cannot be assumed that systemic vascular resistance and cardiac index are truly independent. Nevertheless, when the hemodynamic effects of milrinone and nitroprusside were analyzed at equivalent levels of systemic vascular resistance, the findings with regard to stroke work index were similar to those observed at equivalent mean arterial pressures, that is, stroke work index was increased to a significantly higher level with milrinone than with nitroprusside.

Based on the fact that milrinone, but not nitroprusside, caused a significant increase in heart rate at equivalent reductions in mean arterial pressure, it appears that milrinone also exerts a modest direct chronotropic effect, at least at higher doses. Since milrinone reduced left ventricular end-diastolic and right atrial pressures at least as much as nitroprusside for equivalent reductions in mean arterial pressure, it also appears that vasodilation contributes significantly to the drug's overall actions, with an apparently balanced effect on arterial and venous vessels. It therefore appears most appropriate to consider milrinone as an agent with both positive inotropic and vasodilator actions.

The combination of vasodilator and positive inotropic actions offers potential advantages for the patient with congestive heart failure, and should prove particularly useful for patients in whom pure vasodilator therapy is limited by hypotension. However, due to milrinone's potent ability to reduce right and left heart filling pressures, it is possible to reduce preload excessively, and thereby cause a reduction in overall left ventricular performance. Similarly, an excessive reduction of preload, or administration of milrinone to a patient who already has a reduced preload, may obscure the drug's positive inotropic action and result in failure to increase cardiac index.

In summary, these data confirm the potent beneficial hemodynamic effects of milrinone in patients with severe congestive heart failure, and provide strong evidence that this agent exerts a positive inotropic action that contributes significantly to the drug's overall hemodynamic effects. In addition, the dose-response comparisons indicate that milrinone is relatively selective for inotropic versus chronotropic actions, and that a hemodynamically-relevant positive inotropic action occurs even at low doses that cause little or no change in heart rate or systemic vascular resistance. This pattern of hemodynamic action should prove useful in the clinical management of patients with severe congestive heart failure, particularly when pure vasodilator therapy is limited by hypotension.

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