Separation of the direct myocardial and vasodilator actions of milrinone administered by an intracoronary infusion technique

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ABSTRACT To determine the relative contributions of milrinone’s positive inotropic and vasodilator actions in patients with severe congestive heart failure, the drug was administered by constant infusion directly into the left main coronary artery of 11 patients with New York Heart Association functional class III or IV heart failure. Intracoronary infusion of milrinone at rates up to 50 μg/min had no effect on mean arterial pressure or systemic vascular resistance but resulted in dose-related increases in peak positive dP/dt (+21%), stroke volume index (+18%), and stroke work index (+21%) and decreases in heart rate (−3%), mean right atrial pressure (−25%), and left ventricular end-diastolic pressure (−17%). In eight patients, intravenous administration (75 μg/kg) after the intracoronary infusion resulted in significant decreases in mean arterial pressure (−14%) and systemic vascular resistance (−40%), further increase in stroke volume index compared with intracoronary administration, and further decreases in mean right atrial and left ventricular end-diastolic pressures compared with intracoronary administration. These data indicate that milrinone exerts both positive inotropic and vasodilator actions that contribute significantly to the drug’s overall hemodynamic effect. Circulation 73, No. 1, 130–137, 1986.

IN PATIENTS WITH HEART FAILURE, the cardiac bipyridines, including milrinone, reduce cardiac filling pressures and systemic vascular resistance and increase cardiac output.1–5 These agents exert both positive inotropic and direct vasodilator properties in vitro.6–11 However, considerable controversy exists as to whether their hemodynamic effects in patients are due primarily to an increase in the myocardial inotropic state, to peripheral vasodilation, or to a combination of these actions.12–16 This issue has been difficult to address because of the difficulty of distinguishing the hemodynamic actions of positive inotropic and vasodilator agents in patients.17 Both types of agents can reduce filling pressures and systemic vascular resistance and increase cardiac output.

The purpose of this study was to determine whether milrinone exerts a direct positive inotropic action in patients with severe congestive heart failure, and if so, whether this action contributes importantly to the drug’s overall hemodynamic effects. To delineate the relative contributions of milrinone’s inotropic, vascular, and chronotropic properties, two basic strategies were used. First, milrinone was administered directly into the left main coronary artery, thereby minimizing any direct peripheral vascular action of the drug. Second, the hemodynamic effects of intravenous and direct intracoronary administration of milrinone were compared. This approach allowed for delineation of milrinone’s direct cardiac and peripheral vascular actions and avoided many of the problems inherent in evaluating the effects of systemic administration of agents with both positive inotropic and vasodilator actions.17

Methods

Patients. The study population consisted of 11 consecutive patients with New York Heart Association functional class III or IV congestive heart failure despite optimal standard therapy with digitalis, diuretics, and vasodilators in all cases (table I). The cause of congestive heart failure was coronary artery disease in six patients and dilated cardiomyopathy in five. No patient had significant symptomatic angina, documented myo-
The following standard formulas were used for derived hemodynamic variables: systemic vascular resistance (SVR, dyne-sec-cm⁻²) = 79.9 (MP - RA)/CO; pulmonary vascular resistance (PVR, dyne-sec-cm⁻²) = 79.9 (PA - PCW)/CO; stroke volume index (SVI, ml/beat/m²) = CI/HR; and stroke work index (SWI, g-m/m²) = SVI (MP - LVEDP) (0.0136), where MP = mean arterial pressure, PA = mean right atrial pressure, PCW = mean pulmonary arterial pressure, LVEDP = left ventricular end-diastolic pressure (all pressures reported in mm Hg), HR = heart rate, CO = cardiac output (liters/min), and CI = cardiac index (liters/min²).

**Study protocol.** Baseline hemodynamics were established as the mean of two sets of measurements separated by at least 10 min and differing by less than 10%. All measurements were taken as the average of 30 consecutive cardiac cycles. After baseline hemodynamic measurements, 5% dextrose in water (D₅W), the vehicle for milrinone, was infused into the left main coronary artery at a rate of 4 ml/min (Harvard pump) and measurements were repeated at 4 to 6 min. In no case did infusion of D₅W cause a significant change from the baseline hemodynamic measurements. To demonstrate adequate myocardial contractile responsiveness, patients were pretested with an intracoronary infusion of dobutamine. In all cases, dobutamine elicited an increase in +dP/dt of at least 30% over baseline. Hemodynamic measurements were allowed to return to the same baseline over at least 30 min before a repeat intracoronary infusion of D₅W to establish baseline conditions for the infusion of milrinone. The premilinone D₅W baseline measurements differed by less than 10% from the original baseline. Milrinone (Sterling-Winthrop Drug, Inc., Rensselaer, NY) diluted in D₅W was then infused by the intracoronary route according to the following schedule with upward titration of the infusion rate at 5 min intervals: 1.5, 3, 6, 12.5, 25, 50, 100, 200, and 400 μg/min. Hemodynamic measurements were made at the end of each infusion rate. All 11 patients received at least the six doses ranging from 6 to 200 μg/min. After the highest intracoronary infusion rate in eight consecutive patients, an intravenous bolus dose (75 μg/kg) of milrinone was administered over 1 min and measurements repeated at 10 min. Oxygen consumption index was measured over 5 to 10 min at control, peak milrinone effect, and study termination (133 ± 6, 136 ± 6, and 136 ± 6 ml/min/m², respectively) and the mean of these values was used for calculation of cardiac output by the Fick method.

The serial intracoronary infusion rates were divided into two groups. The lower infusion rates of 1.5, 3, 6, 12.5, 25, and 50 μg/min were selected, assuming a left coronary arterial blood flow of approximately 125 ml/min,18 to result in a coronary arterial concentration of milrinone that would be similar to the systemic levels achieved during intravenous or oral administration (i.e., 12 to 400 ng/ml).5,19,20 Higher intracoronary infusion rates of 100, 200, and 400 μg/min resulted in predicted coronary arterial milrinone concentrations above 400 ng/ml and, in addition, resulted in significant systemic drug levels of 100 to 400 ng/ml similar to those achieved by systemic administration. Serum arterial milrinone concentration determined by the method of Edelson et al.21 was measured at all control points and at the time of all hemodynamic measurements. Blood samples for determination of plasma norepinephrine concentration were drawn into chilled tubes containing reduced glutathione in ethylene glycol tetraacetic acid, placed on ice, centrifuged, and stored at −70°C until measured by a radioenzymatic technique.22

**Statistical methods.** All data are presented as the mean ± 1 SEM. Significant changes among multiple observations for each variable were detected by Wilcoxon's nonparametric test
using Bonferroni’s method for multiple simultaneous comparisons so that statistical significance was assumed if the null hypothesis could be rejected at the .05/n probability level (where n = number of comparisons).23 Significant changes among two observations for one variable within the same group were determined by a two-tailed paired t test.23

Results

Relationship between intracoronary infusion rate and hemodynamic effects of milrinone (Figures 1 and 2). Baseline hemodynamic measurements reflected severe hemodynamic impairment consistent with the clinical diagnosis of congestive heart failure in all patients. Infusion of D5W, the vehicle for milrinone, had no effect on any of the hemodynamic measurements. The effects of intracoronary infusion of milrinone were compared with those obtained during infusion of D5W.

The first significant hemodynamic effects of intracoronary milrinone were decreases in pulmonary capillary wedge (D5W, 29 ± 2; milrinone, 27 ± 2 mm Hg; p < .05) and left ventricular end-diastolic pressures (D5W, 29 ± 2; milrinone, 28 ± 2 mm Hg; p < .05) at the 3 μg/min infusion rate. Peak positive dP/dt became significantly increased at the 6 μg/min infusion rate and increased further in a dose-related manner to a maximum increase of 45% (D5W, 709 ± 48; milrinone, 1027 ± 103 mm Hg/sec; p < .001). Pulmonary arterial pressure and heart rate also decreased significantly at 6 μg/min. As the infusion rate was increased, additional hemodynamic effects became significant, including an increase in stroke work index at 12.5 μg/min, a decrease in right atrial pressure at 25 μg/min, and an increase in cardiac index at 50 μg/min. Heart rate decreased or remained unchanged at all infusion rates.

Systemic and pulmonary vascular resistances were decreased only at infusion rates of 200 μg/min and greater, which were associated with significant peripheral serum milrinone levels of 199 ± 18 and 373 ± 50 ng/ml for the 200 and 400 μg/min infusions, respectively. Mean arterial pressure did not change at any intracoronary infusion rate. At the 400 μg/min infusion rate, right atrial pressure decreased from 12 ± 2 to 7 ± 1 mm Hg (p < .001), and left ventricular end-diastolic pressure decreased from 29 ± 2 to 19 ± 2 mm Hg (p < .001). Cardiac index, stroke volume index, and stroke work index all increased in a dose-related manner, and at the 400 μg/min infusion rate cardiac index increased from 2.0 ± 0.1 to 2.9 ± 0.2 liters/min/m² (p < .001), stroke volume index increased from 22 ± 2 to 32 ± 3 ml/beat/m² (p < .001),

FIGURE 1. Relationship between the intracoronary infusion rate of milrinone and peak positive dP/dt (n = 11). Baseline dP/dt was determined during infusion of D5W, the vehicle for milrinone. * = p < .006 vs D5W.

FIGURE 2. Hemodynamic effects of intracoronary infusion rates of milrinone from 6 to 50 μg/min, which were estimated to produce coronary arterial drug levels comparable to systemic drug administration. LVEDP = left ventricular end-diastolic pressure. * = p < .01 vs D5W.
and stroke work index rose from 14 ± 2 to 23 ± 2 g-m/m² (p < .001).

Peripheral serum milrinone concentration was undetectable at intracoronary infusion rates of 1.5 and 3 μg/min and was 7 ± 1, 15 ± 1, 30 ± 3, and 52 ± 5 ng/ml at intracoronary infusion rates of 6, 12.5, 25, and 50 μg/min, respectively.

Hemodynamic effects of intracoronary infusion of milrinone at 50 μg/min (figure 3). The 50 μg/min intracoronary infusion of milrinone was selected to result in a coronary arterial concentration of approximately 400 ng/ml,¹⁰ comparable to the systemic levels achieved with intravenous administration of the drug (75 μg/kg).⁵, ¹⁹, ²⁰ At this intracoronary infusion rate, serum milrinone concentration reached 52 ± 5 ng/ml at the end of the 5 min infusion period. Intracoronary infusion of milrinone at a rate of 50 μg/min resulted in no significant change in mean arterial pressure (D,W, 73 ± 2; milrinone, 73 ± 3 mm Hg; p = NS), systemic vascular resistance (D,W, 1472 ± 126; milrinone, 1435 ± 112 dyne-sec-cm⁻⁵; p = NS), or pulmonary vascular resistance (D,W, 261 ± 27; milrinone, 270 ± 27 dyne-sec-cm⁻⁵; p = NS). However, mean right atrial pressure decreased from 12 ± 2 to 9 ± 2 mm Hg (p < .01), mean pulmonary capillary wedge pressure decreased from 29 ± 2 to 23 ± 2 mm Hg (p < .01), and left ventricular end-diastolic pressure decreased from 29 ± 2 to 24 ± 1 mm Hg (p < .01). Although heart rate decreased from 93 ± 6 to 90 ± 6 beats/min (p < .02), cardiac index increased from 2.0 ± 0.1 to 2.2 ± 0.2 liters/min/m² (p < .01) because of an increase in stroke volume index (22 ± 2 to 26 ± 3 ml/beat/m²; p < .01). Peak positive left ventricular dP/dt increased from 709 ± 48 to 859 ± 66 mm Hg/sec (p < .005) and was accompanied by an increase in stroke work index from 14 ± 2 to 17 ± 2 g-m/m² (p < .001) despite the significant decrease in left ventricular filling pressure.

Comparative hemodynamic effects of intracoronary and intravenous administration of milrinone (figure 4). To determine the contribution of milrinone’s vasodilator action to the drug’s overall effect, eight consecutive patients received an intravenous dose of milrinone of 75 μg/kg after the intracoronary infusion. The resulting mean serum milrinone level was 372 ± 50 ng/ml. The effects of this intravenous administration were compared with those of the 50 μg/min intracoronary infusion, which, based on an assumed left main coronary arterial blood flow of 125 ml/min,¹⁸ we calculated to result in a coronary arterial concentration of approximately 400 ng/ml, a level comparable to that achieved by this intravenous dose. As noted above, mean arterial pressure and systemic and pulmonary vascular resistances were unchanged, left and right heart filling pres-

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**FIGURE 3.** Hemodynamic effects of intracoronary infusion of milrinone at a rate of 50 μg/min (n = 11). The baseline hemodynamic values during infusion are shown. HR = heart rate (beats/min); MAP = mean arterial pressure (mm Hg); SVR = systemic vascular resistance (dyne-sec-cm⁻⁵); LVEDP = left ventricular end-diastolic pressure (mm Hg); +dP/dt = left ventricular peak positive dP/dt (mm Hg/sec); SVI = stroke volume index (ml/beat/m²); SWI = stroke work index (g-m/m²).
pressures were decreased, heart rate was slowed, and peak positive left ventricular dP/dt, stroke volume index, stroke work index, and cardiac index were increased with this dose of the drug administered by the intracoronary route. In contrast, intravenous infusion of milrinone caused a 14% decrease in mean arterial pressure (D5W, 72 ± 1; milrinone, 62 ± 4 mm Hg; p < .01) without change in heart rate (D5W, 93 ± 7; milrinone, 96 ± 6 beats/min; p = NS). Although unchanged by intracoronary infusion of the drug, systemic and pulmonary vascular resistances were lowered significantly by the intravenous drug from baseline (D5W) values of 1587 ± 151 and 271 ± 36 dyne-sec-cm⁻² to 947 ± 91 and 195 ± 26 dyne-sec-cm⁻², respectively (p < .001, p < .05). Filling pressures decreased markedly beyond the decreases with the intracoronary infusion, with additional decreases in right atrial pressure from 9 ± 2 to 5 ± 1 mm Hg (p < .001), in pulmonary arterial pressure from 35 ± 2 to 25 ± 3 mm Hg (p < .001), in mean pulmonary capillary wedge pressure from 24 ± 2 to 13 ± 2 mm Hg (p < .01), and in left ventricular end-diastolic pressure from 24 ± 2 to 14 ± 3 mm Hg (p < .01). Likewise, compared with intracoronary infusion, intravenous infusion caused further increases in stroke volume index from 25 ± 3 to 31 ± 4 ml/beat/m² (p < .05), in stroke work index from 16 ± 2 to 21 ± 3 g-m/m² (p < .05), and in cardiac index from 2.1 ± 0.1 to 2.9 ± 0.2 liters/min/m² (p < .05). Based on the relative magnitudes of the vectors describing the shift in the relationship between left ventricular end-diastolic pressure and stroke work index, intracoronary infusion of milrinone at a rate of 50 μg/min caused an improvement in left ventricular function that was approximately 38% of that caused by intravenous infusion (figure 5). Intravenous infusion of milrinone caused no further significant increase in peak positive dP/dt compared with intracoronary administration at an infusion rate of 50 μg/min. Arterial plasma norepinephrine concentration was elevated at baseline (540 ± 101 ng/liter), decreased with intracoronary milrinone at 50 μg/min (423 ± 90 ng/l; p < .001 vs D5W), and remained reduced after intravenous administration (452 ± 75 ng/l; p < .05 vs D5W).

Discussion

Milrinone causes a substantial increase in myocardial contractility in vitro,⁸,⁹ and consequently it has been assumed that a positive inotropic action is at least partially responsible for the marked beneficial hemodynamic effects of this agent in patients with severe congestive heart failure. However, recent studies in vitro with ventricular muscle from patients with New York Heart Association functional class III congestive heart failure showed no direct increase in myocardial contractile force with the related bipyridine, amrinone.¹⁴ In addition, milrinone,¹⁰,¹¹ like amrinone,⁷ is a potent direct vascular smooth muscle relaxing agent in vitro. In patients with congestive heart failure, milrinone causes lowering of left and right ventricular filling pressures, systemic vascular resistance, and mean arterial pressure in excess of that expected for a pure inotropic agent.³⁻⁵ Recent studies of amrinone alone, and comparative studies with dobutamine or nitroprusside.⁶,²⁻¹⁰
side, demonstrated no positive inotropic action, leading to the conclusion that the hemodynamic effects of amrinone were due to direct vasodilation alone.\textsuperscript{12-16} The purpose of this study was to determine whether an increase in inotropic state contributes significantly to milrinone’s overall hemodynamic effect in patients with severe congestive heart failure. Intracoronary infusion of milrinone was used to achieve an effective coronary arterial concentration of the drug in the absence of significant serum levels, thereby allowing evaluation of milrinone’s direct myocardial effects in the absence of direct drug effects on the peripheral vasculature. It is important to emphasize that the purpose of this short-term hemodynamic study was not to determine the clinical efficacy or safety of this agent.

Intracoronary infusion of milrinone, resulting in coronary arterial drug levels estimated to have been comparable to those achieved with systemic drug administration, caused a significant dose-related increase in peak positive dP/dt indicative of increased myocardial contractility. Based on the significant reductions in right and left heart filling pressures that occurred with intracoronary infusion of milrinone, it is very likely that both preload and afterload decreased. In addition, heart rate was unchanged or decreased, and therefore the observed increase in dP/dt was not secondary to changes in loading conditions or heart rate, which if anything would have tended to reduce the magnitude of the increase in dP/dt.\textsuperscript{17, 24} A limitation of this study was that coronary arterial concentration of milrinone was not measured directly. Several factors, including the variability of coronary blood flow among patients, regional inequalities in flow, and streaming effects, preclude an exact estimate of coronary arterial concentration of milrinone.

Although increases in peak positive left ventricular dP/dt have been observed previously with milrinone and amrinone,\textsuperscript{1, 3, 5} at least in the case of amrinone this finding has been controversial.\textsuperscript{12-16} Wilmshurst et al.\textsuperscript{13} observed that the intravenous administration of amrinone in doses that caused nearly a 50% increase in cardiac index resulted in significant decreases in right and left heart filling pressures, a 12% fall in mean arterial pressure, and a 35% decrease in systemic vascular resistance, but no significant change in any of several isovolumic measures of inotropic state, including peak positive dP/dt. Likewise, Firth et al.,\textsuperscript{15} using graded-dose infusions of amrinone in patients with a range of left ventricular function, demonstrated only a lowering of left heart filling pressure without a significant change in cardiac output, mean arterial pressure, or positive dP/dt. Recent data obtained from isolated human ventricular myocardium from patients with congestive heart failure also demonstrated no positive inotropic effect of amrinone,\textsuperscript{14} and it was concluded that amrinone, and perhaps the cardiac bipyridines in general, act only as vasodilators in most patients with congestive heart failure.

These discrepant observations may be secondary to basic differences in the ratio of positive inotropic to vasodilator actions of amrinone and milrinone, or alternatively, may be due to the substantially lower left heart filling pressures in the studies failing to find an increase in dP/dt.\textsuperscript{13, 15, 16} Baseline left ventricular filling pressures (mean pulmonary capillary or left ventricular end-diastolic pressures) were substantially lower (range 15 to 22 mm Hg) than those in our patients. We have observed that an excessive reduction in left heart filling pressure with intravenous administration of milrinone can result in a marked attenuation of the drug’s apparent positive inotropic effect as reflected by peak positive dP/dt.\textsuperscript{25} Thus an excessive reduction in preload caused by the intravenous administration of a cardiac bipyridine, particularly in a patient whose initial filling pressures are not elevated, could obscure the drug’s positive inotropic action. With regard to the few patients who did demonstrate an apparent positive inotropic response in the study of Wilmshurst et al., the study was postulated that increased contractility was the result of an indirect effect of the drug to increase sympathetic tone.\textsuperscript{16} This mechanism cannot explain the positive inotropic effects of intracoronary infusion of milrinone in the present study because there were significant decreases in both heart rate and norepinephrine levels, suggesting that sympathetic tone was actually reduced, most likely due to reflex withdrawal. Because milrinone can cause coronary vasodilation,\textsuperscript{26} it is possible that a reduction in myocardial ischemia contributed to improved pump function. However, this seems unlikely because the patients with coronary artery disease whom we studied exhibited no evidence of ischemia at the time of study, and similar effects occurred in the patients with idiopathic cardiomyopathy without coronary disease.

The results of this study indicate that milrinone’s systemic vasodilator action also contributes importantly to the drug’s effects. Although coronary arterial milrinone levels were not measured, based on an assumed left main coronary blood flow of 125 ml/min,\textsuperscript{18} the 50 μg/min infusion would have resulted in coronary arterial levels of approximately 400 ng/ml, comparable to the systemic levels achieved with the dose (75 μg/kg) used for intravenous administration. However, intravenous infusion caused significant further
increases in stroke work and stroke volume when compared with those seen with the intracoronary infusion (50 μg/min). Likewise, intravenous infusion caused substantial further decreases in left and right heart filling pressures and in arterial pressure. The percentage of overall improvement in ventricular function due to direct myocardial effects of milrinone can be estimated by comparing the hemodynamic changes resulting from the intravenous bolus (75 μg/kg) with those resulting from the intracoronary infusion (50 μg/min) (figure 5). Approximately one-third of milrinone’s effect on pump function can be attributed to its direct myocardial action.

The first significant hemodynamic changes during intracoronary infusion of milrinone were decreases in mean pulmonary capillary wedge and left ventricular end-diastolic pressures. Since this effect occurred at a very low intracoronary infusion rate of only 3.0 μg/min, resulting in undetectable serum milrinone levels, it is unlikely that this reduction in left heart filling pressure was caused by a direct peripheral vascular action of the drug. This finding is consistent with the suggestion that milrinone may act directly on the myocardiun to enhance diastolic relaxation.27 Alternatively, although it is possible that the early reduction in left ventricular end-diastolic pressure may have been caused by improved pump function or by a withdrawal of sympathetic vasoconstriction due to drug-induced hemodynamic improvement, this seems unlikely because the reduction in left heart filling pressure preceded other overt evidence of an improved hemodynamic status, including an elevation of dP/dt.

The decreases in heart rate and plasma norepinephrine with intracoronary infusion of milrinone suggest that there was a withdrawal of sympathetic tone. Systemic drug administration results in an increase in heart rate in excess of that caused by an equihypotensive infusion of nitroprusside,5 suggesting that milrinone exerts a direct positive chronotropic action. However, because the artery to the sinoatrial node arises from the right coronary artery in the majority of patients, the negative chronotropic action of infusion of the drug into the left coronary artery is most likely mediated indirectly. Mechanisms possibly involved in such a reflex withdrawal of sympathetic tone include a direct, digitalis-like sensitizing effect on myocardial mechanoreceptors,28 activation of arterial baroreceptors due to an increase in pulse pressure,29 or stimulation of cardiac receptors due to an increase in contractile state.29

In summary, direct intracoronary infusion of milrinone caused a dose-dependent increase in left ventricular peak positive dP/dt in the absence of peripheral vascular effects and resulted in significant hemodynamic effects, including an increase in stroke work index and decreases in left and right heart filling pressures. The decrease in left heart filling pressure at very low infusion rates may be caused by improved diastolic relaxation properties. Additional important hemodynamic effects attributable to direct peripheral vasodilation were noted with systemic administration of milrinone. These data support the hypothesis that milrinone exerts a direct positive inotropic effect in patients with severe myocardial failure and that this action contributes importantly to the overall hemodynamic effects of the drug. The intracoronary infusion technique can provide useful information in evaluating the myocardial and peripheral vascular effects of drugs with both positive inotropic and vasodilator actions.

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References
THERAPY AND PREVENTION—CONGESTIVE HEART FAILURE


29. Longhurst JC: Cardiac receptors: their function in health and disease. Prog Cardiovasc Dis 27: 201, 1984
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