Improvement in indexes of diastolic performance in patients with congestive heart failure treated with milrinone

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ABSTRACT To elucidate the mechanisms by which the new bipyridine inotropic agent milrinone improves cardiac function, we examined multiple indexes of left ventricular diastolic function before and after administration of milrinone to patients with advanced (NYHA class III or IV) congestive heart failure. In 13 patients left ventricular pressure measurements were made with a micromanometer to permit assessment of peak negative dP/dt and the time constant of left ventricular isovolumic relaxation, T, before and after milrinone. In nine patients radionuclide ventriculographic studies were performed during left heart catheterization, allowing calculation of left ventricular peak filling rate, volumes, and the diastolic pressure-volume relationship before and after milrinone. After intravenous administration of milrinone, peak negative dP/dt increased (+18%; p < .01) and T decreased (~30%; p < .01), while heart rate increased by only 8% (87 ± 12 to 94 ± 15 beats/min; p < .01), left ventricular systolic pressure did not change, and mean aortic pressure fell by 11% (p < .01). Left ventricular peak filling rate increased (1.2 ± 0.6 to 1.7 ± 0.7 end-diastolic volumes/sec; p ≤ .02) despite a decrease in left ventricular filling pressure (mean pulmonary wedge pressure 27 ± 7 to 18 ± 9 mm Hg; p < .01). There was a fall in left ventricular end-diastolic pressure (28.6 ± 6 to 19 ± 7 mm Hg; p ≤ .01), with no significant change in left ventricular end-diastolic volume. This was associated with a downward shift in the left ventricular diastolic pressure-volume relationship in most cases. These changes in parameters of left ventricular diastolic relaxation and chamber distensibility after administration of milrinone suggest that improved diastolic function may contribute to the beneficial hemodynamic effect of milrinone in patients with congestive heart failure.

_Circulation_ 70, No. 6, 1030-1037, 1984.

MILRINONE, a derivative of the bipyridine inotrope amrinone, has previously been shown to have a profound effect on myocardial contractile function in isolated muscle and animal preparations. The clinical response of patients with congestive heart failure who are treated with this agent has been ascribed to readily demonstrable improvements in indexes of left ventricular systolic function (including increases in peak positive dP/dt and in left ventricular ejection fraction) and concurrent arteriolar vasodilation.

However, possible effects of milrinone on ventricular diastolic function, which might also contribute to the hemodynamic response to this agent, have not been evaluated. In particular, improved diastolic relaxation and distensibility might lead to more effective sarcomere stretch within the ventricular myocardium and to better systolic performance. Thus it is possible that improved systolic pump function in patients with heart failure treated with milrinone might reflect a complex interaction of effects of the drug on systolic and diastolic properties of the ventricular myocardium as well as changes in the peripheral vasculature. In this study we examined the effects of milrinone on multiple indexes of left ventricular diastolic function in patients with advanced congestive heart failure.
Methods

Seventeen patients with advanced congestive heart failure (NYHA class III or IV) refractory to standard medical therapy were studied. The group included patients with ischemic cardiomyopathy (cardiomyopathy associated with extensive prior infarction, n = 10), idiopathic dilated cardiomyopathy (n = 5), dilated cardiomyopathy in association with surgically corrected valvular heart disease (n = 1), and postmyocarditis cardiomyopathy (n = 1) (see Table 1). Informed consent was obtained under a protocol approved by the Human Studies Committees of the Beth Israel Hospital and of the Brigham and Women’s Hospital.

Each of the 17 patients underwent right and left heart catheterization. Right heart studies were done with No. 7F thermistor dilution Swan-Ganz catheters (Edwards Laboratories, Santa Ana, CA). Left heart studies were done with micromanometer catheters (Millar Instruments, Houston) in 13 of the 17 patients. In these patients pressures were differentiated electronically to yield dp/dt, and both left ventricular pressure and dp/dt were recorded on an optical strip chart recorder (Honeywell Electronics for Medicine VR16) at rapid paper speed (≥100 mm/sec) for subsequent computer digitization at 5 msec intervals (Tektronix 4052 graphic computer system). With the digitized pressure waveform data, the time constant, T, of left ventricular pressure fall was calculated from the logarithm of pressure (T₁) after the method initially described by Weiss et al. and from the derivative of pressure (T₂) as described by Raff and Glantz. The pressure asymptote, P₀, was calculated from the equation used to determine T₂. In four of the 17 patients it was not possible to advance a micromanometer into the left ventricle, and pressures were measured with No. 7F fluid-filled catheters connected via manifold to miniaturized low-volume pressure transducers (P50 Micron, Statham Instruments) without intervening tubing. The frequency response of this system has been previously described by us and is flat ±5% to 20 Hz or greater. This system is accurate for measurement of the magnitude of systolic and diastolic pressures in the left ventricle but was not used for calculation of dp/dt and T, which may depend on information whose frequency is in the range of 40 Hz or greater.

In nine patients, radionuclide ventriculographic studies were performed simultaneously with left ventricular pressure measurement as previously described from our laboratory. Each patient was injected with 0.75 GBq (20 mCi) of red blood cells labeled in vitro with technetium-99m. All radionuclide studies were carried out with a mobile Anger camera computer system (Technicare 410 with an on-board VIP computer system). Each gated cardiac blood pool study was obtained with a 30 degree slant-hole collimator to obtain cephalic angulation in the modified left anterior oblique view. The degree of obliquity was individualized in each patient to best visualize the interventricular septum. Neither the patient nor the camera was moved between studies. Gated cardiac blood pool scans were obtained with a 64 × 64 matrix for the full field of view (200 cm). Thirty-two frames per R-R interval were acquired. Acquisition time was from 3 to 5 min. The time of each study was recorded and a blood sample was obtained at the midpoint of each study.

A left ventricular count rate (volume) vs time curve was derived for each scan by an operator-drawn fixed left ventricular region of interest and computer-generated background regions of interest. The operator used the end-diastolic image to identify the septal border of the left ventricle and the stroke volume image to identify the atroventricular and free wall borders of the heart and to confirm the boundaries of the free wall of the

<table>
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CM = cardiomyopathy; CAGB = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MVR = mitral valve replacement.

*Obtained by radionulcide ventriculography.
ventricle. As multiple left ventricular volume vs time curves were obtained for each patient, end-diastolic volume was corrected in each curve for acquisition time, physical decay, and biologic clearance.

Acquisition time for each end-diastolic frame was calculated by multiplying the frame duration (R-R interval/number of frames) by the number of cardiac cycles collected. Loss of counts due to physical decay was calculated from the time at which each study was acquired. Biologic clearance of the tracer was calculated by measuring the changes in the counts obtained in a well counter of a 100 μl sample of blood obtained at the midpoint of each study.

Peak filling rates in each patient were assessed by fitting a third-order polynomial to the rapid diastolic portion of the time-activity curve with a least squares technique and were computed in left ventricular counts per second. Values were normalized for the number of left ventricular counts at end-diastole and expressed as end-diastolic volumes per second (EDV/sec).

Radionuclide pressure-volume diagrams were generated by a method previously described from our laboratory. At the midpoint during each modified left anterior oblique scan, left ventricular pressures were recorded at rapid paper speed. A total of six left ventricular pressure curves were digitized and averaged by a Tektronix 4052 computer. The average left ventricular pressure curve and gated blood pool volume curve were synchronized to end-diastole and digitized, and pressure-volume diagrams were subsequently plotted from 32 pressure-volume coordinates throughout the cardiac cycle.

With the patient in the supine resting state, paired baseline measurements were made of heart rate, cardiac output, and right atrial, pulmonary-capillary wedge, left ventricular, and arterial pressures. Incremental boluses of milrinone were administered, with doses of 12.5, 25, 50, and 75 μg/kg given at 10 min intervals, and the above-described studies were repeated 5 min after each dose was administered.

Baseline data are reported as the mean of the two consecutive hemodynamic measurements, differing by less than 10%. “Postmilrinone” data reported are those obtained 5 min after the final doses of milrinone were administered as described above. Data analysis and statistical comparisons were performed on Analyzer, a Hewlett-Packard 9845-based data-analysis system, with paired t test analysis of measurements obtained before and after administration of milrinone.

Results

Clinical characteristics, baseline left ventricular ejection fraction, and concurrent medical program of the study population are outlined in table 1. Hemodynamic responses (after a mean total intravenous dose of 126 μg/kg milrinone) for the 17 patients are summarized in table 2. The heart rate increased by 8% (87 ± 12 to 94 ± 15 beats/min; p < .01), while significant decreases were seen in mean arterial pressure (−11%), pulmonary capillary wedge pressure (−33%), right atrial pressure (−50%), and left ventricular end-diastolic pressure (−32%). There were no significant changes in left ventricular peak systolic pressure or in the difference between left and right ventricular filling pressures, measured as an estimate of average diastolic force gradient across the interventricular septum.

Results from the measurement of dP/dt and the time constants of left ventricular relaxation for the 13 patients studied with micromanometer catheters are shown in figure 1. As can be seen, T decreased after milrinone, whether calculated by the logarithmic or derivative method. Peak negative dP/dt increased, despite the fall in mean arterial pressure, which would by itself have been expected to cause a fall in peak negative dP/dt. The asymptote, P0, calculated from the equation used to determine T, showed wide variation and no significant change after milrinone. Specifically, P0 ranged from −44 to +12 mm Hg before milrinone (6 ± 15 mm Hg mean ± SD) and ranged from −18 to +9 mm Hg after milrinone (−3 ± 10 mm Hg). P0 increased in seven patients, decreased in four patients, and showed no change in two patients after milrinone.

Peak left ventricular filling rate was measured in the nine patients who underwent radionuclide ventriculographic examinations. The radionuclide time-activity curve for a representative patient is shown in figure 2. There was an increase in the peak left ventricular filling rate for the group as a whole after administration of milrinone (1.2 ± 0.6 to 1.7 ± 0.7 EDV/sec; p ≤ .02), as seen in figure 3. This occurred despite a significant fall in the mean pulmonary capillary wedge pressure (the driving force for left ventricular filling) in these patients (figure 3). Furthermore, this increase in left ventricular peak filling rate was observed in all but one

### Table 2

<table>
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<tr>
<th></th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>PCWP (mm Hg)</th>
<th>RA (mm Hg)</th>
<th>GRAD (mm Hg)</th>
<th>LV (mm Hg)</th>
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<td>Baseline</td>
<td>87 ± 12</td>
<td>84 ± 14</td>
<td>27 ± 7</td>
<td>16 ± 8</td>
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<td>Milrinone</td>
<td>94 ± 15</td>
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<td>18 ± 9</td>
<td>8 ± 6</td>
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<td>NS</td>
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HR = heart rate; MAP = mean arterial pressure; PCWP = mean pulmonary capillary wedge pressure; RA = mean right atrial pressure; GRAD = the difference between left and right atrial pressures (PCWP-RA) for each patient; LV = left ventricular peak systolic/end-diastolic pressures.

aData represent mean ± SD for the 17 patients listed in table 1.
pressure being lower for any given diastolic volume after milrinone. In patients 7 and 8 there was a much smaller end-systolic volume, and a shift of the pressure-volume curve to the left was seen. In these patients, whether the diastolic portions of the two curves represent the same or different curves is uncertain.

Discussion

Congestive heart failure has been shown to be characterized by abnormalities in indexes of both myocardial systolic and diastolic performance. Clinically, this has been reflected in a diminished cardiac output and elevated ventricular filling pressures. Much of the research in heart failure has been directed toward the assessment of left ventricular systolic function, and it is often assumed that the high ventricular filling pressures seen in patients with heart failure are simply the result of impaired systolic ejection of blood with a consequent increase in residual volume, dilatation of the chamber, and passive back-up of blood into the pulmonary and systemic veins. Not surprisingly, clinical therapeutics has focused predominantly on improving ventricular systolic ejection, by diminishing afterload or by increasing myocardial contractility.

It is probable that left ventricular systolic and diastolic function and dysfunction are “coupled” physiologic processes and that the biochemical processes underlying some types of heart failure might affect myocardial relaxation as well as contraction. Furthermore, it is also likely that failure of complete left ventricular myocardial relaxation could contribute to the abnormality seen in left ventricular systolic function.

FIGURE 1. Effect of milrinone on the time constant of left ventricular (LV) relaxation, calculated from the logarithm of left ventricular pressure ($T_L$) or the time derivative of left ventricular pressure ($T_D$) and on peak negative dP/dt.

The patient (figure 3), who demonstrated the greatest fall in the pulmonary capillary wedge pressure. There was no statistically significant change in mean relative left ventricular end-diastolic volume as assessed by radionuclide ventriculography (from control, 100 ± 0% to 104 ± 11% end-diastolic volume; p = NS) after intravenous administration of milrinone.

In figure 4 the left ventricular diastolic pressure-volume relationship is depicted for each of the nine patients studied who underwent radionuclide ventriculography simultaneously with left ventricular pressure measurement. In most patients (e.g., Nos. 1 to 4, 6, and 9) the curve shifted downward, with the diastolic

FIGURE 2. A left ventricular radionuclide time-activity curve from one patient at baseline (PRE) and after intravenous administration of 87.5 μg/kg milrinone (POST). Note the increase in the slope (filling rate) at the inflection point (maximum peak filling rate point, horizontal bar).
tion (e.g., through impairment of the Frank-Starling mechanism at the level of sarcomere stretch).

Milrinone has been shown to have powerful hemodynamic effects when given to patients with congestive heart failure. Analysis of the hemodynamic mechanisms by which milrinone effects this improvement has focused largely on its vasodilative and inotropic effects, i.e., on its role in improving left ventricular systolic ejection. In this study we evaluated the effect of milrinone on multiple indexes of left ventricular diastolic function. We found a consistent improvement toward normal in each of these, suggesting an important component of improved left ventricular diastolic filling in the overall hemodynamic improvement seen in patients with congestive heart failure treated with this agent.

A previous study reported altered early relaxation in patients with congestive (dilated) cardiomyopathy and heart failure, as supported by markedly depressed values for both peak negative dP/dt and velocity of circumferential fiber lengthening in early diastole. In this study three indexes of early diastolic relaxation—maximum negative dP/dt, the time constant (T) of left ventricular isovolumic relaxation, and left ventricular peak filling rate—each showed a significant abnormality in control measurements that improved after administration of milrinone. This was seen despite the absence of a parallel directional change in, or even in the presence of an opposite directional influence of, a major hemodynamic determinant of each of these indexes. Specifically, peak negative dP/dt showed an increase of 18% in the absence of a significant change in peak left ventricular pressure and in association with a fall in mean arterial pressure. A decrease in arterial pressure should have caused a fall in peak negative dP/dt; since we observed a rise in peak negative dP/dt after milrinone, it seems reasonable to conclude that relaxation was improved by the milrinone rather than by some peripheral effect of milrinone on left ventricular loading. This improved relaxation is also suggested by the shortening of the relaxation time (as reflected by the time constant T) after milrinone whether T was calculated by the logarithmic method or the derivative method. Finally, improved relaxation after milrinone is supported by the measurements of peak filling rate. In the nine patients evaluated with simultaneous radionuclide ventriculography and hemodynamic studies, left ventricular peak filling rate showed a 42% increase despite a 33% fall in the left atrial (pulmonary capillary wedge) pressure. A primary fall in filling pressure should have caused a decrease in peak filling rate rather than the increase we noted.

Middle and late diastolic left ventricular filling, as reflected in the left ventricular pressure-volume relationship, showed a similar improvement. There was a 31% fall in left ventricular end-diastolic pressure with-
out any significant decrease, and in some patients even a small increase in left ventricular end-diastolic volume. In most patients there was an evident downward shift in left ventricular diastolic pressure at any given left ventricular volume, indicating improvement in left ventricular chamber distensibility.

There are several possible mechanisms by which milrinone might effect these salutary changes in indexes of left ventricular diastolic relaxation. Milrinone has been shown to have vasodilatory properties, and a reduction in right ventricular filling pressure secondary to venodilation might lead to a downward shift of the left ventricular diastolic pressure-volume relationship through a reduction in transseptally transmitted pressures occurring with ventricular interaction.28-30 In this regard it has been shown previously that vasodilators such as nitroprusside or nitroglycerin can produce a downward shift in the left ventricular diastolic pressure-volume relationship in patients with heart failure.29-31 However, the transatrial pressure gradient (left atrial or pulmonary capillary wedge mean pressure minus right atrial pressure), which presumably reflects the diastolic pressure gradient across the interventricular septum, did not change significantly after administration of milrinone in this study.

Arterial vasodilation with a fall in coronary perfusion pressure might have led to a downward shift in the diastolic pressure-volume relationship through the "erectile" or "hydraulic" effect.32 However, the observed fall in the mean arterial pressure was relatively small (11%) in our patients.

Primary arterial vasodilation with a fall in peak left ventricular systolic pressure would be anticipated33 to lead to a fall in the absolute magnitude of peak negative dP/dt. Since the opposite (an increase in dP/dt) was actually seen, it seems unlikely that vasodilation by milrinone accounted for the changes seen in negative dP/dt. A reflex increase in sympathetic tone after this fall in arterial pressure, with an increase in circulating catecholamines, might have contributed to some of the changes seen, since agonists have been shown to increase the rate of myocardial relaxation. Alternatively, drug-induced release of endogenous catecholamines could have had a similar effect, although we have no evidence to suggest that this occurred.

An increase in the heart rate might also be playing
some role in producing the observed changes in relaxation parameters. Tachycardia has been shown to effect an increase in peak negative dP/dt and a decrease in T in the normal heart.\textsuperscript{33,34} Karliner et al.\textsuperscript{33} in chronically instrumented dogs showed that with an increase in average heart rate from 99 to 162 beats/min (a 64% increase) peak negative dP/dt increased 21% and T decreased 18%. However, since we saw only an 8% increase in the heart rate in our patients after milrinone, it is unlikely that this alone accounted for the changes in peak negative dP/dt and T that were observed after milrinone.

An improvement in left ventricular systolic function may have contributed to the improvement in indexes of early diastolic filling, according to the concept of Gibson et al.,\textsuperscript{35} who suggested that early diastolic relaxation was an active process that was “energized by the preceding systole.”

In animals with normal hearts, other inotropic maneuvers have shown inconsistent effects on parameters of early diastolic function. Isoproterenol\textsuperscript{33} led to a fall in peak negative dP/dt but also to a fall in T. Calcium infusion\textsuperscript{33} led to no significant change in peak negative dP/dt but to a fall in T. Digoxin administration\textsuperscript{36} led to no significant change in peak negative dP/dt. Thus an increase in contractility by itself does not necessarily lead to more rapid myocardial relaxation, and the mechanics of contraction and relaxation are frequently dissociated.\textsuperscript{37} Finally, the potential effects of coronary artery disease and myocardial ischemia on left ventricular relaxation need to be considered.\textsuperscript{38-41} Since 10 of our 17 patients had coronary artery disease, baseline prolongation of T may have somehow reflected resting ischemia or dysynchrony of left ventricular contraction. However, similar findings in T were noted in the patients without coronary disease.

The pressure asymptote, $P_h$, calculated in the patients in whom $T_h$ and $T_i$ were determined, showed wide scatter and no significant change after milrinone. Our control value for $P_h$ ($-6 \pm 15$ mm Hg) was similar to that reported by Carroll et al.\textsuperscript{38} in their “scar group” (five patients with coronary disease and prior infarction) where $P_h$ was $-7 \pm 10$ mm Hg. In their study, $P_h$ showed a significant change only in patients who developed myocardial ischemia with exercise. Thompson et al.\textsuperscript{42} showed a similar wide range of variation in resting values for $P_h$ and point out that the relevance of $P_h$ to diastolic relaxation after mitral valve opening is uncertain. Since the physiologic meaning of $P_h$ is unclear, we cannot interpret its failure to change consistently with milrinone in this study.

Recently\textsuperscript{43} the effects of milrinone on excitation-contraction coupling have been studied in isolated papillary muscles. In association with an increase in contractility, milrinone shortened the duration of tension and produced change in the calcium-tension relationship consistent with inhibition of phosphodiesterase activity, with a resultant increase in cyclic AMP concentration. Generation of cyclic AMP appears to be reduced in heart failure, in association with down-regulation of myocardial β-receptors.\textsuperscript{44} Since cyclic AMP is believed to control the activity of phospholamban, the regulatory protein for sarcoplasmic-reticular-calcium-uptake,\textsuperscript{23} improved relaxation might be expected to result from any agent that increased intracellular cyclic AMP levels (e.g., catecholamines, amrinone, milrinone, etc.), especially if sarcoplasmic reticular calcium uptake was diminished in the baseline state. In this regard, impaired calcium uptake and release by the sarcoplasmic reticulum has been implicated by Schwartz et al.\textsuperscript{45} as a fundamental problem in failing myocardium.

To summarize, we have shown that administration of milrinone in patients with congestive heart failure leads to a significant improvement in indexes of left ventricular diastolic relaxation and filling. Although this improvement in diastolic relaxation and filling may reflect change in mechanical factors influencing left ventricular diastolic properties (e.g., ventricular interaction, loading conditions), the findings are more consistent with a fundamental influence of milrinone on relaxation at the level of the myocardial cell. Whatever its mechanism, it is likely that this improvement in diastolic function contributes to the overall hemodynamic improvement seen with this agent in these patients. To what extent this improvement in diastolic function contributes to the more vigorous myocardial systolic performance seen with this agent remains to be investigated.

We are indebted to the technical and nursing staffs of the Cardiac Catheterization Laboratory and the Nuclear Radiology Division, to Dr. Shin-ichi Monomura for his assistance with the data analysis, to Dr. Bernard J. Ransil for his assistance with the statistical analysis, and to Ms. Patricia Allen for typing the manuscript.

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Vol. 70, No. 6, December 1984

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Circulation. 1984;70:1030-1037
doi: 10.1161/01.CIR.70.6.1030

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