

Effect of a Single Oral Dose of Milrinone on Left Ventricular Diastolic Performance in the Failing Human Heart

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In 14 patients with severe congestive heart failure, left ventricular pressure (measured by tip manometer) and derived variables were measured before and every 10 minutes after administration of oral milrinone (10 mg) for 50 minutes along with measurements of coronary sinus blood flow and drug plasma levels. Arterial and coronary sinus catecholamines were measured only before and 50 minutes after milrinone. Left ventricular pressure, volume (as determined by angiography) and derived indexes were simultaneously assessed at matched atrial paced heart rate before and 60 minutes after milrinone. Three patients who did not achieve a therapeutic plasma level (<150 ng/ml) were excluded.

Peak negative first derivative of left ventricular pressure ($-dP/dt$) progressively and significantly increased (10%) together with a decrease in the two exponential time constants of relaxation, namely, τ_1 (19%) and τ_2 (22%), which represent the fit for and after the first 40 ms, respectively. Coronary flow significantly in-

creased by 43% within 30 minutes, whereas the decrease (-13%) in coronary vascular resistance failed to be statistically significant. No change occurred in catecholamine concentrations after milrinone. Peak filling rate significantly increased by 15%. Pressure-volume curves showed a leftward and, in four patients, a downward shift; a significant decrease in minimal left ventricular diastolic and end-diastolic pressures (by 55 and 38%, respectively) and in end-diastolic volume (18%) occurred. The constant of elastic chamber stiffness measured by the simple elastic model tended to decrease, but failed to achieve a statistically significant level.

Thus, oral milrinone improved left ventricular early relaxation and filling as well as chamber distensibility. This global improvement of diastolic function makes milrinone a potentially useful drug in the oral treatment of heart failure.

(*J Am Coll Cardiol* 1987;10:1294-302)

Despite therapy with digitalis, diuretic drugs and arterial and venous vasodilators, patients with congestive heart failure become progressively unresponsive as the severity of the disease progresses. Recently, a new class of cardiac inotropic drugs, the bipyridines, has been tested in animals and humans and has opened new avenues of treatment. The forerunner of these new compounds was amrinone. Intravenous and oral administration of this drug resulted in substantial acute hemodynamic improvement in patients with

congestive heart failure (1-3). However, amrinone therapy may cause thrombocytopenia, fever or major gastrointestinal side effects (2,3). As a result, other compounds with similar chemical structure were investigated, and milrinone has emerged as the most promising (4). In patients with congestive heart failure, milrinone improves left ventricular inotropic state with a concurrent arteriolar vasodilation as demonstrated after intravenous (5-8) and oral (9) administration.

Because it is conceivable that systolic and diastolic function and dysfunction are coupled processes, milrinone may have a major impact on left ventricular relaxation, as recently reported (6). Furthermore an improved diastolic relaxation and distensibility might lead to more effective sarcomere length within the ventricular myocardium and cause the failing myocardium to operate at a more efficient point of sarcomere pressure-length relation. Our study evaluates the effects of a single oral dose of milrinone on multiple variables of left ventricular diastolic function in patients with severe congestive heart failure.

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Manuscript received October 27, 1986; revised manuscript received May 28, 1987, accepted July 6, 1987.

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Methods

Study patients (Table 1). After approval of the study protocol by the Ethics Committee of Erasmus University and informed consent were obtained, 14 patients (10 men and 4 women) entered the study. All patients had severe congestive heart failure (New York Heart Association functional class III or IV), despite optimal conventional therapy with digitalis and diuretic drugs in all patients and nitrates or angiotensin-converting enzyme inhibitors, or both, in eight patients. All patients had undergone cardiac catheterization on a separate occasion during the preceding 2 years, and the diagnosis of ischemic cardiomyopathy in 12 of them was based on the presence of severe multivessel coronary artery disease. One or several previous episodes of myocardial infarction were clinically and electrocardiographically or enzymatically (or both) documented in 10 patients. In the remaining two patients, the presence of an intraventricular conduction disturbance precluded retrospective detection of a silent myocardial infarction. The remaining two patients had idiopathic dilated cardiomyopathy. Patients with symptomatic angina pectoris, myocardial infarction within 3 months or organic valvular heart disease were excluded. Eleven patients had sinus rhythm and three had chronic atrial fibrillation.

Study protocol. All vasodilators were withheld 24 hours before the study. Diuretic drugs were withheld 12 hours before the study, and digoxin was withheld on the morning of study.

A triple lumen 7F balloon-tipped thermodilution catheter was advanced to the main pulmonary artery from the femoral vein. An 8F micromanometer-tipped pigtail catheter was

advanced to the left ventricle from the right femoral artery, and a 5F micromanometer-tipped catheter was placed in the ascending aorta from the left femoral artery to measure the aortic pressure and withdraw blood samples. A Webster coronary sinus thermodilution catheter was advanced to the coronary sinus from a right antecubital vein. The catheter position was ascertained by initial contrast injection and subsequent fluoroscopy. Heart rate, right atrial pressure, cardiac output, aortic and left ventricular pressures and pressure-derived indexes of isovolumic relaxation were then measured. After a baseline hemodynamic measurement, the following protocol was started:

1) *Left ventricular cineangiography at an atrial paced heart rate 15 beats higher than spontaneous heart rate* was performed at 50 frames/s in a 30° right anterior oblique view by injection of nonionic contrast medium (0.7 cc/kg metrizamide [Amipaque]), which has been shown to have no hemodynamic effect (10). Care was taken to maintain a uniform patient position relative to X-ray equipment during angiography, which was performed with the breath held in shallow inspiration. Simultaneous beat to beat analysis of left ventricular pressure and its derived indexes was carried out during cineangiography.

2) *Fifteen minutes after angiography, baseline hemodynamic measurements were repeated.* At the same time, coronary sinus blood flow was measured and arterial and coronary sinus blood samples were withdrawn to determine catecholamine and hypoxanthine concentrations.

3) *Milrinone, 10 mg, was given orally.*

4) *Every 10 minutes for 50 minutes, the measurements were repeated as in protocol 2.* Blood samples for catecholamine and hypoxanthine measurements were withdrawn

Table 1. Clinical and Angiographic Characteristics of 14 Patients

Case	Age (yr) & Sex	Diagnosis/NYHA	Previous MI	EF (%)	Angiography			Coronary Arteriography (%)		
					Hypo	Dys	Aki	LAD	LCx	RCA
1	49F	CMP ischemic/III	+	7	AB,PB	—	AL,AB,IB	100	70	90
2	58M	CMP ischemic/III	—	17	AB,IB,PB	AP	AL	100	—	90
3	59M	CMP ischemic/III	+	20	AB,AL,AP	—	IB,PB	90	60	100
4	51M	CMP ischemic/III	+	39	IB,PB	AP	AL	90	60	—
5	65F	CMP ischemic/III	+	14	IB	AP	AL	100	—	50
6	62M	CMP ischemic/III	+	35	AB,AL,IB,PB	—	AP	90	—	70
7	53M	CMP ischemic/IV	+	23	PB	—	AL+IB	90	—	70
8	64M	CMP ischemic/III	—	24	AB,AL,IB,PB	AP	—	100	70	90
9	58M	CMP ischemic/III	+	8	AB,PB	—	AL,AP,IB	100	—	60
10	65F	CMP idiopathic/IV	—	11	Global	—	—	—	—	—
11	53F	CMP ischemic/III	+	14	AL,IB	—	AP	100	—	70
12	55M	CMP ischemic/III	+	16	AL	—	AP,IB,PB	70	50	100
13	68M	CMP idiopathic/III	—	20	Global	—	—	50	—	70
14	71M	CMP ischemic/III	+	17	AB,AP,IB	AL	PB	90	—	100

AB = anterobasal; AL = anterolateral; Aki = akinesia; AP = apical; CMP = cardiomyopathy; Dys = dyskinesia; EF = ejection fraction; F = female; Hypo = hypokinesia; IB = inferobasal; LAD = left anterior descending artery; LCx = left circumflex artery; LV Angio = left ventricular; M = Male; MI = myocardial infarction; NYHA = New York Heart Association functional class; PB = posterobasal; RCA = right coronary artery.

only at 50 minutes. An additional blood sample was withdrawn every 10 minutes to determine the plasma levels of milrinone.

5) *Left ventricular cineangiography at a matched atrial paced heart rate with simultaneous beat to beat left ventricular pressure recording* was repeated 60 minutes after the drug administration. In the three patients with atrial fibrillation, heart cycles of similar length were selected to compare the sequential left ventricular angiograms.

Analysis of left ventricular pressure-derived indexes. Left ventricular pressure was digitized at 250 samples/s. Minimal diastolic and end-diastolic left ventricular pressures and its peak negative first derivative ($-dP/dt$) were computed on-line after data acquisition for 20 seconds. For off-line analysis of left ventricular pressure decay, an updated version of the beat to beat program described previously (11) was used with the following definitions: 1) pressure at the beginning of isovolumic relaxation (P_b) is the pressure at the point at which dP/dt is minimal (maximal negative dP/dt), and 2) pressure at the end of isovolumetric relaxation (P_e) is the pressure less than or equal to the previous end-diastolic pressure, but no less than 1 mm Hg. Although it is possible that the latter definition may result in P_e being measured just after mitral valve opening, estimation of the time constants by more stringent criteria, such as end-diastolic pressure + 10 mm Hg, did not result in a significantly better estimation and failed to measure pressure during high heart rates (12).

Semilogarithmic model. An off-line isovolumic relaxation was carried out using the following semilogarithmic model: $P(t) = P_0 e^{-t/T}$, where P is pressure and P_0 is equivalent to P_b (pressure at beginning of isovolumic relaxation) when a true exponential decay is present starting from the time of peak negative dP/dt ; the P_0 and T variables were estimated from a linear least-squares fit on $\ln P = -t/T + \ln P_0$. This technique requires a minimum of eight samples (over 32 ms) between P_b and P_e . In addition, a biexponential fit for isovolumic relaxation was determined, characterized by the two exponential time constants; the fit for the first 40 ms ($n = 8$), Tau_1 , and the fit after the first 40 ms, Tau_2 (12).

Mitral valve opening pressure was defined during left ventriculography as occurring in the last frame preceding the entry of nonopacified blood into the left ventricle from the left atrium. The left ventricular pressure corresponding to this frame was considered to reflect left atrial pressure.

Coronary blood flow measurements. In 13 patients, coronary sinus flow was measured by the continuous thermodilution method of Ganz et al. (13). Coronary vascular resistance was derived from the ratio of mean aortic pressure to coronary sinus blood flow.

Analysis of left ventricular diastolic volume and derived variables. A complete cardiac cycle was analyzed on a frame to frame basis from each angiogram. The ven-

Table 2. Time Course of Milrinone Effect on Diastolic Function in 11 Patients

Time	Mil (ng/ml)	HR (beats/min)	MAP (mm Hg)	RA (mm Hg)	CI (liters/min per m ²)	SVR (dynes-s) cm ⁻⁵	Peak + dP/dt	Peak - dP/dt	Tau ₁ (ms)	Tau ₂ (ms)	Pmin (mm Hg)	LVEDP (mm Hg)	CSBF (ml/min)
Mean values													
A	—	91	81	8	2.1	1621	1037	855	68	54	13	26	124
B	101	88	81	9	2.0	1664	1031	856	70	55	12	22	117
C	195	89	79	7†	2.2	1472	1024	869	65	60	10	22	152
D	233	91	76	5*	2.5	1272	1129	922	56*	44*	8*	18*	178†
E	249	92	77	5*	2.8*	1200*	1190†	922	55*	43*	9†	20†	178†
F	251	92	74†	5*	2.8*	1120*	1199*	936*	55*	42*	7*	19*	156
Standard deviation													
A	—	19	12	4	0.6	380	286	221	18	15	4	5	41
B	174	18	12	5	0.6	384	277	228	15	15	5	8	42
C	148	19	13	5	0.6	337	183	187	18	18	8	11	81
D	136	18	13	5	0.6	282	239	197	13	14	6	10	94
E	113	19	12	4	0.5	365	415	189	14	16	7	12	87
F	91	19	9	4	0.5	271	393	187	14	14	6	11	84

A = baseline; B, C, D, E, F = 10, 20, 30, 40 and 50 minutes after milrinone, respectively; CI = cardiac index; CSBF = coronary sinus blood flow; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; MAP = mean aortic pressure; Mil = milrinone; Peak + dP/dt and Peak - dP/dt are calculated as mmHg/sec; Pmin = minimal left ventricular diastolic pressure; RA = mean right atrial pressure; SVR = systemic vascular resistance; Tau₁ = time constant of left ventricular relaxation representing the fit for the first 40 ms; Tau₂ = time constant of left ventricular relaxation representing the fit after 40 ms.

*Differences from control significant at $p < 0.01$; †differences from control significant at $p < 0.05$.

tricular contours were detected using an automated hard-wired system (14) and the volumes, calculated according to Simpson's rule, were graphically displayed as instantaneous volume and its derivative (dV/dt). In this way, end-diastolic and end-systolic volumes, total cardiac index, stroke index and ejection fraction were obtained. Peak filling rate was defined as the greatest volume inflow rate (dV/dt) occurring early after end-systole. The simultaneous recording of pressure and volume during left ventricular angiography allowed us to obtain a pressure-volume curve before and after drug administration in every patient. For the evaluation of global chamber stiffness, the left ventricular pressure (P) and volume (V) data obtained every 20 ms, starting at the lowest diastolic pressure and ending at the end-diastolic pressure, were fitted by a simple elastic model: $P = \alpha e^{\beta V} + C$, where α = intercept (mm Hg), β = constant of elastic chamber stiffness and C = asymptote (mm Hg). The three constants of this equation α , β , C were determined using an iteration procedure until the best nonlinear curve fit was obtained (15).

Metabolic measurements. Plasma levels of milrinone were measured using a validated high performance liquid chromatography procedure (16). An isocratic pressure liquid chromatographic system was used for estimation of hypoxanthine concentrations in blood (17).

Plasma levels of norepinephrine, epinephrine and dopamine were measured in duplicate, both with and without internal standards by the radioenzymatic procedure of Peuler and Johnson (18) with slight modifications. Normal basal values in our laboratory are 100 to 500 pg/ml for norepinephrine and 10 to 110 pg/ml for both epinephrine and dopamine. Assuming that epinephrine and norepinephrine are removed similarly by the heart, the amount of sympathetically mediated norepinephrine release (net myocardial norepinephrine flux) can be estimated by the following formula: (coronary sinus - aorta) norepinephrine \times coronary sinus blood flow \times (1 - hematocrit), where coronary sinus levels are corrected for the amount of norepinephrine extracted by the heart.

Statistical analysis. Results during hemodynamic monitoring are given as mean \pm standard deviation. Analysis of variance for repeated measurements was used for statistical analysis of the data followed by a multiple comparison test, according to methods of Dunnett (19) and Tukey (20). Statistical analysis of measurements during angiography and of catecholamine and hypoxanthine levels was performed using Student's *t* test for paired data.

Results

Measurements of the plasma level of milrinone 50 minutes after drug intake showed that of 14 patients, only 11 had a plasma level >150 ng/ml. Because it has been previously demonstrated (21) that the therapeutic plasma level

of milrinone is approximately 150 ng/ml, we excluded from analysis the three patients with a lower level. One of these three patients had idiopathic dilated cardiomyopathy.

Measurements during short-term monitoring of milrinone effect (Table 2). The heart rate did not change during the study period, and mean aortic pressure decreased slightly but significantly after 50 minutes. Changes observed in right atrial pressure, cardiac output and systemic vascular resistance are reported in Table 2. Both peak positive dP/dt and peak negative dP/dt increased over the study period, reaching a peak value after 50 minutes. The time constants of left ventricular relaxation (Tau_1 , which represents the fit for the first 40 ms, and Tau_2 , which represents the fit after 40 ms) showed similar improvement. The minimal and end-diastolic left ventricular pressures both decreased during the monitoring period.

Coronary blood flow increased progressively during the first 40 minutes, when it reached its peak value and then decreased slightly during the remaining 10 minutes. Concomitantly, coronary vascular resistance showed minimal and insignificant changes during the study. The myocardial arteriovenous difference of hypoxanthine was 0.27 ± 0.64 $\mu\text{mol/liter}$ before milrinone and, on average, did not change 50 minutes after drug administration (0.81 ± 1.4 $\mu\text{mol/liter}$). In two patients (Cases 2 and 4), a negative myocardial arteriovenous difference of hypoxanthine detected in the basal state had subsided by the end of the study. In one

Table 3. Left Ventricular Diastolic Performance at Matched Paced Heart Rate Before and 60 Minutes After Oral Milrinone in 11 Patients

	Before Milrinone	After Milrinone
RR (ms)	613 \pm 122	620 \pm 147
ESP (mm Hg)	71 \pm 20	63 \pm 16
ESVI (ml/m ²)	148 \pm 64	130 \pm 64 [†]
ESP/ESVI (mm Hg/ml per m ²)	60 \pm 45	63 \pm 40
Peak positive dP/dt (mm Hg/s)	1,014 \pm 365	1,164 \pm 388 [†]
Peak negative dP/dt (mm Hg/s)	836 \pm 230	959 \pm 326*
Tau ₁ (ms)	67 \pm 17	57 \pm 19*
Tau ₂ (ms)	58 \pm 17	45 \pm 17*
MVO (mm Hg)	27 \pm 12	22 \pm 10
PFR (ml/s)	282 \pm 96	325 \pm 112 [†]
Pmin (mm Hg)	20 \pm 6	9 \pm 6*
LVEDP (mm Hg)	31 \pm 10	19 \pm 11*
EDVI (ml/m ²)	178 \pm 63	164 \pm 68 [†]
RA (mm Hg)	8 \pm 5	4 \pm 4*
TSG (mm Hg)	22 \pm 9	15 \pm 8 [†]
α (mm Hg)	2.3 \pm 3.3	1.1 \pm 1.4
β	0.026 \pm 0.01	0.020 \pm 0.008
C (mm Hg)	-5.8 \pm 12	-3.3 \pm 9

*p < 0.001 (compared with before milrinone); [†]p < 0.05. α = pressure intercept; β = constant of elastic chamber stiffness; C = asymptote; EDVI = end-diastolic volume index; ESP = end-systolic left ventricular pressure; ESVI = end-systolic volume index; MVO = pressure at mitral valve opening; PFR = peak filling rate; Pmin = minimal left ventricular diastolic pressure; RR = cycle length; TSG = transseptal gradient (LVEDP - RA); other abbreviations as in Table 2.

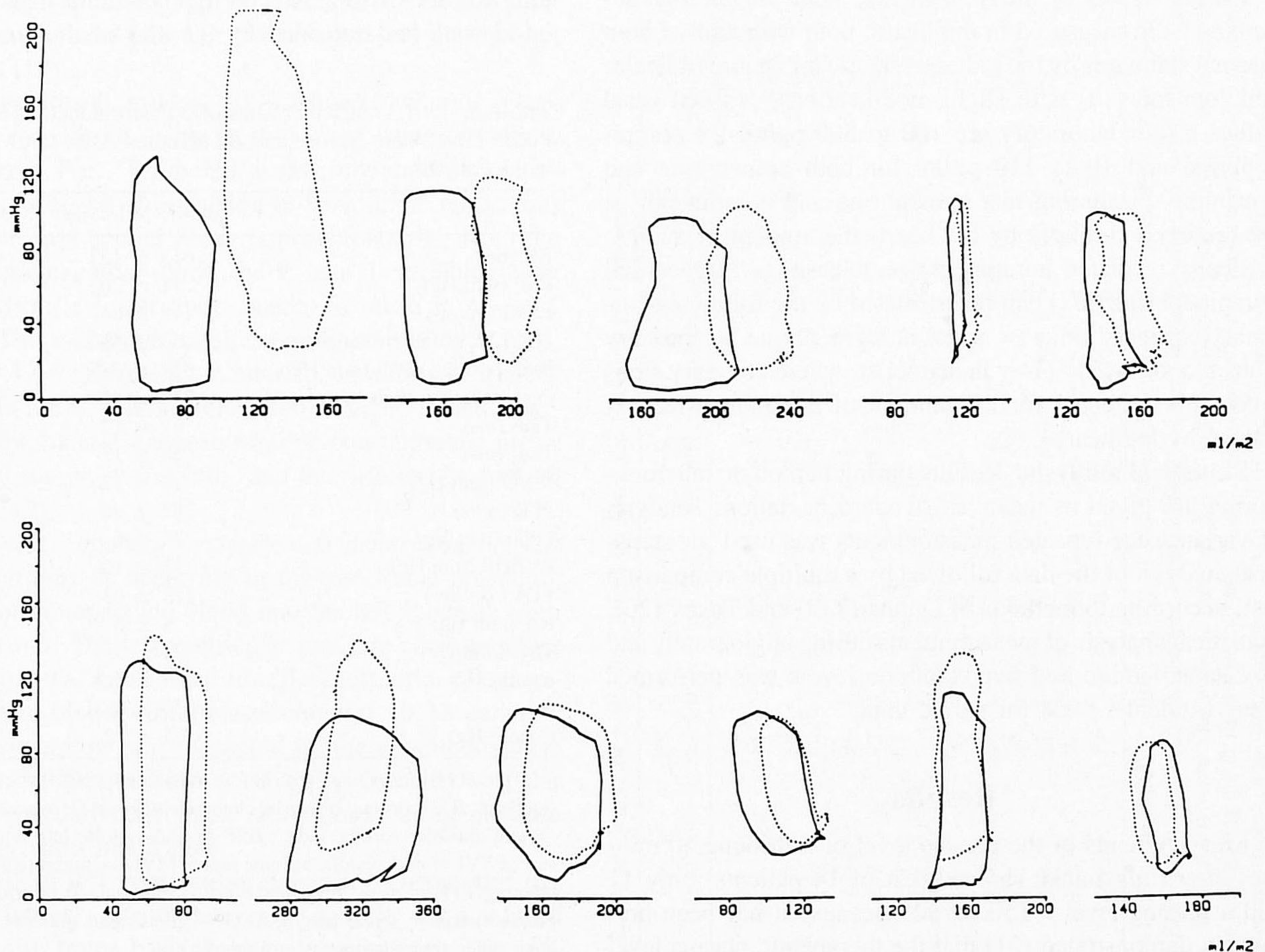
patient (Case 8), a negative balance in myocardial hypoxanthine was observed after milrinone. Nevertheless, none of these patients had clinical or electrocardiographic signs of ischemia and their hemodynamic measurements did not differ from those recorded in the remaining patients.

Measurements during left ventricular angiography (Table 3). End-systolic pressure measured at the occurrence of the dicrotic notch on the aortic pressure tracing did not change, whereas end-systolic volume decreased slightly but significantly ($p < 0.05$). The analysis of isovolumic relaxation before and after milrinone showed a significant ($p < 0.01$) increase in peak negative dP/dt with a concomitant significant decrease in the biexponential time constants of relaxation, Tau_1 ($p < 0.01$) and Tau_2 ($p < 0.01$). The pressure at mitral valve opening, a measure of left atrial driving pressure, increased in four patients, decreased in five patients and showed no change in two patients after milrinone. A significant ($p < 0.05$) increase in peak filling rate occurred. Left ventricular minimal diastolic pressure, end-diastolic pressure and end-diastolic volume decreased significantly ($p \leq 0.05$). The right atrial pressure and the difference between left and right ventricular filling pressures (transseptal gradient), measured as an estimate of average

diastolic force gradient across the interventricular septum, also decreased significantly. In most of the patients, analysis of pressure-volume loops showed a leftward shift after milrinone with a downward shift in four patients (Fig. 1). In this subset of patients, a substantial reduction in pressure throughout a range of volumes common to both pre- and postmilrinone functions reflected a major change in right atrial pressure.

The constant of elastic chamber stiffness, the intercept and the asymptote, failed to show significant changes. Nevertheless, as shown in Figure 2, a dramatic improvement in the slope of the pressure-volume curve was observed in some patients after milrinone, and it is conceivable that if a different dose of milrinone had been used for those patients

Figure 1. Individual pressure-volume curves in 11 patients before (dotted line) and 60 minutes after (solid line) administration of oral milrinone. The concomitant decrease in end-diastolic pressure and volume caused a leftward shift of the curve in most of the patients. In four patients an evident downward shift was observed, indicating improved left ventricular chamber distensibility; in these four patients, a major decrease in right atrial pressure, demonstrating a reduction in pericardial constraint, occurred.



who are at variance with the means observed, our findings would have been more uniform.

Plasma catecholamines. Data suitable for analysis were obtained in 10 patients. As could be expected in these patients with severe heart failure, arterial norepinephrine was markedly elevated in nearly all patients, but in the majority of them arterial epinephrine and dopamine levels were also in excess of the normal range (Fig. 3). Over the coronary vascular bed, extraction of epinephrine occurred, the mean uptake by the heart being $31 \pm 6\%$ (the cardiac venoarterial difference as a percent of arterial levels). In contrast, norepinephrine levels were higher in the coronary sinus than in the aorta, the venoarterial difference being $60 \pm 18\%$. No clear venoarterial difference over the heart was found for dopamine. Milrinone had no effect on the arterial and coronary sinus plasma levels of norepinephrine, epinephrine or dopamine, and sympathetic drive to the heart as estimated

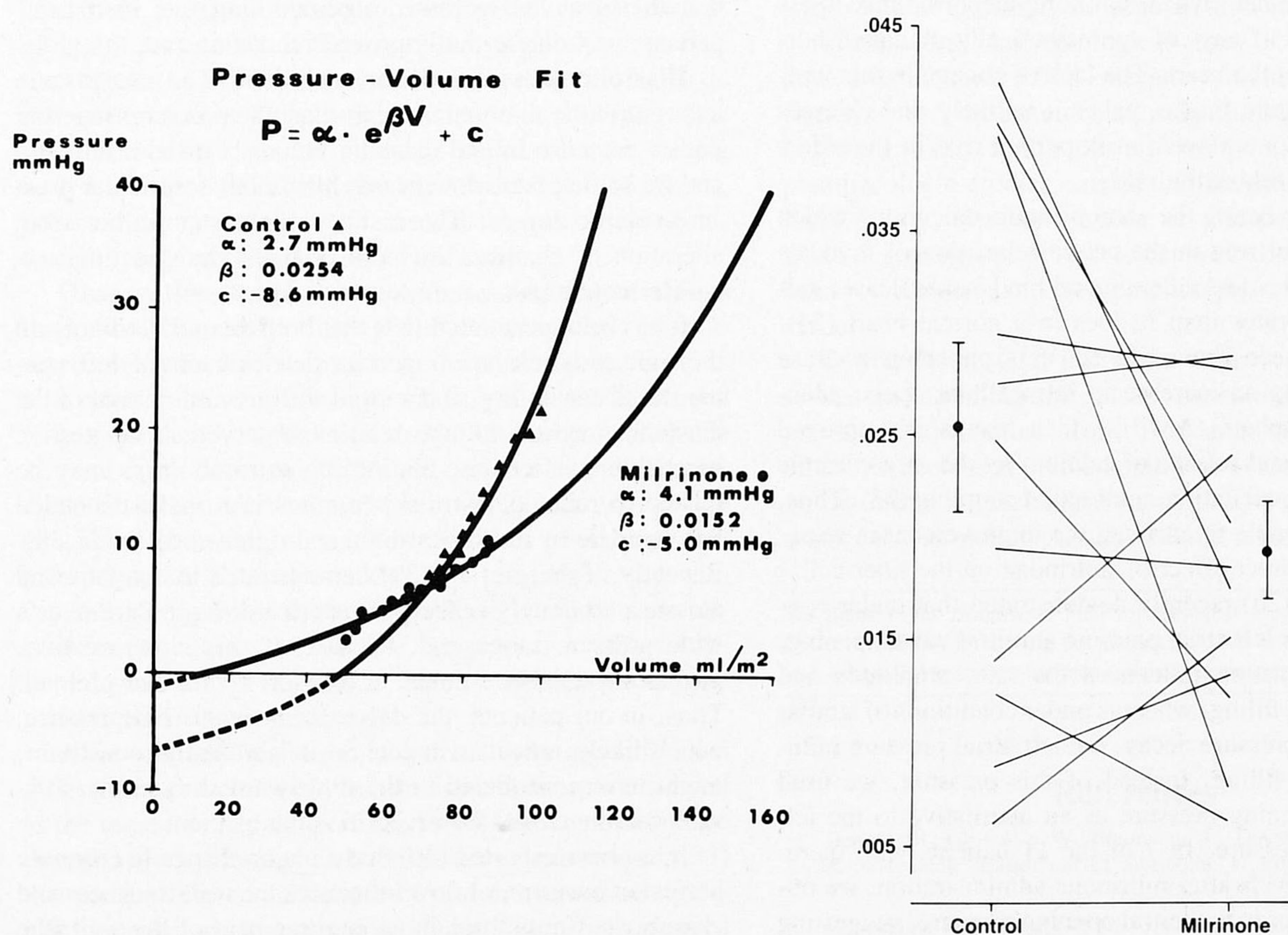
by the net myocardial norepinephrine flux also was not altered by the drug. Before milrinone, it was $43,435 \pm 13,010$ pg/min; after milrinone, it was $49,465 \pm 12,559$ pg/min.

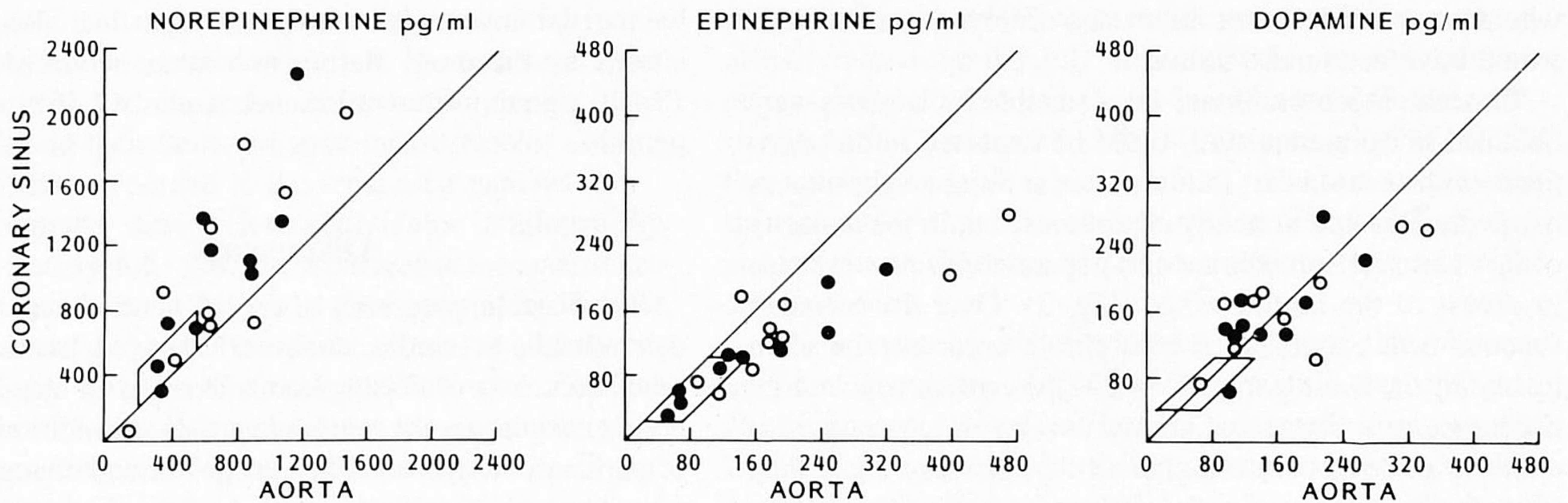
Discussion

The diastolic properties of the left ventricle are important determinants of cardiac function. Delayed left ventricular relaxation, loss of elastic recoil, changes in chamber stiffness, changes in right ventricular loading conditions, effects of pericardium and coronary perfusion and changes in left ventricular shape all may contribute to abnormal diastolic function and the clinical manifestations of congestive heart failure (22). In this study, we evaluated the effect of milrinone on these multiple determinants of left ventricular diastolic function.

Improvement in relaxation and diastolic filling after milrinone: a direct or catecholamine-mediated phenomenon? Before milrinone, the time constants of relaxation in our patients were severely prolonged. Within 30 minutes after oral administration, milrinone consistently improved these variables. Since the two major hemodynamic determinants of left ventricular relaxation rate (end-systolic pressure and heart rate) did not change after administration of milrinone, it seems reasonable to conclude that relaxation

Figure 2. Individual and group mean changes in constant of elastic chamber stiffness after milrinone administration in 11 patients (**right panel**). A definite decrease was observed in only a few patients. In the **left panel**, an example of the beneficial change in the slope of the pressure-volume curve, demonstrating an improved elastic chamber stiffness after milrinone (●), is shown. α = intercept (mm Hg); β = constant of elastic chamber stiffness; c = asymptote (mm Hg).





was improved because of a direct effect of the drug on the failing myocardium.

In the mammalian heart, catecholamines can exert a substantial myocardial relaxing effect by stimulating the calcium uptake by sarcoplasmic reticulum (23). Therefore, Monrad et al. (6) have suggested that the effects of intravenous milrinone on myocardial relaxation could be due to a drug-induced release of endogenous catecholamines. However, no data were provided to validate their hypothesis. In the present study, the plasma levels of norepinephrine, epinephrine and dopamine in both the aorta and the coronary sinus did not change after milrinone. In addition, we measured the net myocardial norepinephrine flux to estimate a release, if any, of sympathetically mediated norepinephrine from the heart. The lack of change in this variable after milrinone intake makes it unlikely that changes in sympathetic tone played an important role in the effect of milrinone on relaxation rate.

In the failing heart, the sarcoplasmic reticulum, which plays an essential role in the active relaxation of myocardium, accumulates less calcium and binds and releases calcium at slower rates than it does in a normal heart (24). Milrinone has been proved to act as a phosphodiesterase inhibitor, causing an increase in intracellular cyclic adenosine monophosphate (AMP), which results in improved uptake, storage and release of calcium by the sarcoplasmic reticulum during excitation-contraction coupling (25). Thus, it seems conceivable to attribute the improvement in relaxation rate to a direct effect of milrinone on the fiber cell.

Ishida et al. (26) recently demonstrated that under conditions of similar left atrial pressure at mitral valve opening, the rate of relaxation influences the rate, amplitude and duration of early filling, whereas under conditions of similar left ventricular pressure decay, the left atrial pressure influences the early filling. Instead of this pressure, we used mitral valve opening pressure as an alternative to the left atrial driving pressure. In 7 of the 11 patients with therapeutic plasma levels after milrinone administration, we observed no changes in the mitral opening pressure, suggesting

Figure 3. Levels of plasma norepinephrine, epinephrine and dopamine measured simultaneously in the aorta and coronary sinus in 10 patients. Note that in most patients values for norepinephrine levels were higher in the coronary sinus than in the aorta. The opposite was found for epinephrine. The **open circles** indicate values before milrinone; the **closed circles** indicate values after milrinone. The normal area is also indicated. Milrinone had no effect on the plasma levels of norepinephrine in the aorta (before 708 ± 388 pg/ml; after 690 ± 611 pg/ml) and coronary sinus (before $1,047 \pm 611$ pg/ml; after $1,038 \pm 552$ pg/ml). Epinephrine and dopamine levels in the aorta and coronary sinus after milrinone also did not change.

that the observed increase in peak filling rate in these 7 patients was due to the improved relaxation rate.

Diastolic pressure-volume relation. The decrease in left ventricular minimal and end-diastolic pressures together with a decrease in end-diastolic volume caused a leftward and, in some cases, downward shift in left ventricular pressure-volume curves. These shifts might stem either from alteration of chamber stiffness or from changes in extracardiac conditions.

It has been postulated (27) that both the pericardium and the right ventricle are important determinants of left ventricular distensibility, and a rapid shift toward normal of the diastolic pressure-volume relation observed in congestive heart failure after vasodilating or inotropic drugs may be related to relief of extrinsic compression of the distended left ventricle by the pericardium and right ventricle (28,29). Recently, Tyberg et al. (29) demonstrated that right atrial pressure accurately reflects intrapericardial pressure over a wide pressure range and, because of this close relation, provides a reliable estimate of true left ventricular preload. Thus, in our patients, the decrease in right atrial pressure, which likely reflects a reduction in pericardial constraint, might have contributed to the downward shift in the pressure-volume curves observed in some of them.

It has been reported (30) that a major change in coronary perfusion pressure, or flow influences the wall thickness and chamber stiffness through an engorgement of the wall (the

so-called erectile or hydraulic effect). Because this effect is greater when the ventricle is stiffer, changes in coronary pressure or flow occurring in patients with volume overload would more severely affect left ventricular diastolic compliance (28).

After milrinone, we observed an increase in coronary blood flow with a minor change in perfusion pressure so that impaired compliance with an increased stiffness due to an erectile effect might have occurred. Although an increase in blood flow might not necessarily be equated with an increase in coronary vascular volume, the actual determinant of the erectile effect (30) (the coronary vasodilation observed after milrinone) might have resulted in a vascular engorgement of the myocardial wall. This latter phenomenon could have affected the pressure-volume relation unfavorably and might have masked a beneficial intrinsic decrease in diastolic myocardial tone.

Chamber stiffness increases in patients with congestive cardiomyopathy, probably because of an increased amount of fibrous tissue within the myocardium (15,22). To characterize the intrinsic diastolic properties of myocardial wall, a viscoelastic rather than a simple elastic stress-strain relation (31) should be used. Our angiographic data do not allow us to quantitate properly strain rates that are essential for determining diastolic viscous effects. Regional wall thickness measurements are needed to characterize the change in myocardial stiffness, but such data cannot be measured accurately at 20 ms intervals from the left ventricular angiogram. As a result of the use of the single elastic model, the constant of stiffness we calculated includes both elastic and viscous forces. Despite these limitations, the high values we observed in diastolic chamber stiffness in the failing heart are in accordance with previous observations (15,22,31). After milrinone, a trend to improvement was observed, although it was not statistically significant.

Observations on pharmacokinetics and potential limitations of the study. In any study where a drug is evaluated, many factors such as dose-response characteristics, pharmacokinetics and concomitant drug administration need to be considered. A previous study (32) demonstrated that 2.5 and 5 mg doses of oral milrinone have minimal hemodynamic effect when administered to patients with severe congestive heart failure and they should be considered subtherapeutic. In the same study (32), patients treated with 7.5 and 10 mg doses showed significant hemodynamic improvement without the adverse hemodynamic effects observed with the 15 mg dose. These observations suggest that 10 mg is the optimal dose.

After oral administration of a drug, there are individual differences in the rate of gastrointestinal absorption as well as the renal and hepatic perfusion rates that could influence the therapeutic plasma levels. It has been demonstrated (33) that the half-life and clearance of oral milrinone are significantly prolonged in patients with heart failure as compared

with values in normal volunteers. Therefore, the variations observed in the improvement of left ventricular diastolic function and central hemodynamics could simply reflect differences in individual clinical status. We observed a plateau in the hemodynamic response to milrinone during the last 20 minutes of the study. This could be explained by the action of milrinone on phosphodiesterase, which does not continue to increase once maximal inhibition is reached, thereby limiting the hemodynamic improvement (34).

An important question is whether the optimal patient population and protocol design were used. The large majority of the patients entered were in New York Heart Association functional class III and had ischemic cardiomyopathy. Although study of patients with milder symptoms would have allowed prolonged hemodynamic monitoring in the supine position, it has been demonstrated (32) that patients with more severe congestive heart failure show a greater hemodynamic improvement after 10 mg of oral milrinone.

In patients with evidence of reduced myocardial blood supply, measurements of coronary hemodynamics and myocardial energetics after administration of a drug with vasodilating and inotropic effects are critical for the evaluation of the drug. A possible deleterious role of milrinone in patients with myocardial ischemia has to be mentioned, because we observed that, in 1 of our 10 patients with ischemic cardiomyopathy, a negative balance in myocardial hypoxanthine occurred 50 minutes after milrinone intake.

The baseline pharmacologic therapy of each patient may have exerted some effect, despite withdrawal, thereby influencing the measurements made during the study. We believe that such limitations are common to the majority of pharmacologic studies carried out in patients with severe heart failure. We were aware of this potential limitation when designing our protocol, but we believe it would have been too dangerous to stop baseline pharmacologic therapy earlier.

Conclusions. Oral milrinone improves left ventricular relaxation and filling and reduces the abnormally high filling pressure of the failing heart. This latter beneficial effect is related to decreased preload and, less evidently, to an effect on the intrinsic mechanical properties of myocardium regulating the diastolic pressure-volume relation.

We thank Frans Boomsma, PhD for technical support and Michael K. Calahan, MD for improving the manuscript. We also thank Gusta Koster and Anja van Huuksloot for preparing the manuscript.

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