Journal of Cardiovascular Pharmacology
11:258–269 © 1988 Raven Press, Ltd., New York

Short-Term Assessment of Left Ventricular Function, Coronary Hemodynamics, and Catecholamine Balance in Severe Congestive Heart Failure After a Single Oral Dose of Milrinone

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Summary: Systemic and coronary hemodynamics were measured before and every 10 min after oral milrinone (10 mg) administration for 50 min, together with the drug plasma level in 14 patients with congestive heart failure. Left ventricular pressure (tip manometry), volume (angiography), and derived indexes were simultaneously assessed before and 60 min after milrinone treatment. Peak positive dP/dt, V_{max}, and peak velocity of contractile element significantly increased 30 min after milrinone administration by 15%, 37%, and 30%, respectively. An increase in cardiac output (25%) with a consistent decrease in systemic vascular resistance (20%) occurred after 40 min without major changes in heart rate and aortic pressure. Right atrial pressure and minimal and end-diastolic left ventricular pressures decreased significantly after 50 min, by 30%, 25%, and 20%, respectively. Peak $-dP/dt$ increased despite a slight change in end-systolic pressure. The time constants of relaxation, τ_1 and τ_2, significantly decreased by 15% after 50 min and by 16%. A transient but significant increase of 40% in coronary sinus blood flow was observed after 30 min, while myocardial oxygen consumption was unchanged 50 min after milrinone treatment. No changes were observed in catecholamine balance with milrinone. Ejection fraction increased significantly (22%) after milrinone administration, as well as the net work of left ventricle (27%). The increase of inotropism in failing hearts with a parallel reduction in preload and afterload makes milrinone a drug potentially useful in the oral treatment of severe heart failure. **Key Words:** Milrinone—Congestive heart failure—Left ventricular function—Coronary circulation—Catecholamines.

Multiple studies have demonstrated the safety and efficacy of intravenous and oral milrinone in humans. Intravenous milrinone increased the end-systolic wall stress versus fractional shortening relationship without adverse effects in normal subjects (1). Intravenous milrinone led to decreases in right and left ventricular filling pressures accompanied by significant increases in the maximal rate of left ventricular pressure rise and cardiac index in patients with class III or IV congestive heart failure (2,3). Oral milrinone led to significant increases in exercise duration and maximal exercise oxygen consumption in patients with congestive heart failure (4). Furthermore, an acute improvement in indexes of diastolic performance in patients treated with intravenous milrinone has been recently reported (5). No significant adverse effects have been reported with either intravenous or oral milrinone (2–9).

Our study was undertaken to assess invasively the short-term effects of a single oral dose of milrinone on the central and coronary hemodynamics as well as on the myocardial catecholamine and hypoxanthine metabolism. Furthermore, we evaluated the left ventricular global performance using angiography and pressure recordings which allow a detailed analysis of isovolumic contraction and relaxation and of early filling phase.

Received February 5, 1986; revision accepted May 27, 1987.
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METHODS

Study population

Fourteen patients with severe congestive heart failure entered the study. There were 10 men and four women, ranging in age from 49 to 71 years (mean, 59 ± 6 years). The chronic congestive heart failure was related to coronary artery disease in 12 individuals and was of idiopathic etiology in the remaining two. Patients with valvular heart disease, hypertension, angina, or other evidence of active myocardial ischemia were excluded from the study.

Eleven patients were in sinus rhythm, with minor intraventricular conduction disturbances in five cases; three patients were in chronic atrial fibrillation. A previous myocardial infarction had occurred in 10 patients and two of them had undergone surgical revascularization of myocardium. All patients were treated with digoxin and diuretic therapy, and most received vasodilator drugs such as nitrates or angiotensin-converting enzyme inhibitors. Based on the symptomatology and the New York Heart Association classification, 12 patients were functional class III and two patients were functional class IV. After the approval of the Ethics Committee of Erasmus University, informed written consent was obtained.

Study protocol

All patients underwent right and left heart catheterization in the morning and were in the fasting state. All vasodilators were discontinued for at least 24 h prior to the study, while diuretics were continued until the evening preceding the day of the study. A potential rebound phenomenon after discontinuation of vasodilators has been reported, particularly regarding nitrates withdrawal (10), but the clinical stability of our patients after discontinuing the drug militates against this possibility. To avoid a high heart rate at the time of the study, which could have precluded reliable evaluation of isovolumic contraction and relaxation, digoxin treatment was maintained but not given on the morning of the study.

The parameters used to evaluate the hemodynamic changes were obtained as follows: (a) triple-lumen Swan Ganz thermodilution catheter (7F) in the pulmonary artery for recording of pulmonary artery pressure, right atrial pressure, and cardiac output by thermodilution; (b) coronary sinus thermodilution catheter of Webster for measurement of coronary blood flow and atrial pacing, advanced into coronary sinus from a right antecubital vein. The catheter position was ascertained by initial contrast injection and subsequent fluoroscopy; (c) either (i) double micromanometer-tipped catheter (8F) in the left ventricle for measurement of left ventricle and central aortic pressures and administration of contrast for left ventricular angiogram, (MTC-2P8L; Honeywell) or (ii) angio microtip pigtail catheter (MTC-P8L; Honeywell) in the left ventricle and separate tip manometer in the aorta (MTC P5; Honeywell).

All catheters were inserted via a femoral approach.

Heart rate, pulmonary artery and right atrial pressures, aortic and left ventricular pressures, pressure-derived indexes of isovolumic relaxation (see below), coronary sinus flow, and simultaneous arterial and coronary sinus oxygen saturation could thus be measured. After a baseline hemodynamic measurement, the following protocol was started:

(a) Left ventricular cineangiography at atrial paced heart rate 15 beats more 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), which has been shown to have no hemodynamic effect (11). Care was taken to have the patient in a uniform position relative to roentgenogram equipment during angiogram, which was performed with the breath in shallow inspiration. Simultaneous beat-to-beat analysis of left ventricular pressure and its derived indexes was carried out during cineangiography.
(b) At least 15 min after angiography and when spontaneous heart rate and pressure values had returned to control, 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 oxygen saturation, catecholamines, and hypoxanthine.
(c) Milrinone, 10 mg, was given orally.
(d) Every 10 min during the following 50 min, the measurements were repeated as in protocol b. Blood samples to determine the plasma concentration of milrinone were withdrawn every 10 min. Blood samples to determine oxygen saturation, catecholamines, and hypoxanthine were withdrawn after 50 min.
(e) Left ventricular cineangiography at matched atrial paced heart rate with simultaneous beat-to-beat left ventricular pressure recording was repeated 60 min after drug administration. The three patients with atrial fibrillation were not paced and heart cycles of similar length were selected to compare the sequential left ventricular angiograms.

Analysis of left ventricular pressure–derived indexes

Pressure measurements and left ventricular angiograms suitable for analysis of the parameters indicated below were available in each of the 14 patients.

Left ventricular pressure was digitized at 250 samples/s. Peak left ventricular pressure, minimal diastolic and end-diastolic left ventricular pressures, peak positive and peak negative dP/dt, the relation between dP/dt pressure and total pressure linearly extrapolated to pressure 0 (V_{max}), and the peak velocity of contractile element (V_{ce}) were computed on-line after data acquisition of 20 s.

For off-line analysis of left ventricular pressure relaxation an updated version of the beat-to-beat program described previously (12) was used with the following definitions: (a) pressure at the beginning of isovolumic relaxation (P_b) is the pressure at the point at which dP/dt is minimal (maximum negative dP/dt); and (b) 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.

Two techniques were implemented for the off-line

beat-to-beat calculation of the relaxation parameters (13,14). All required a minimum of eight samples (>32 ms) between P_b and P_e. No other computations were attempted.

Semilogarithmic model. The semilogarithmic model used was $P(t) = P_o e^{-t/\tau}$; where P is pressure, and P_o is equivalent to P_b when a true exponential decay is present starting from the time of peak negative *dP/dt*. The P_o and T parameters were estimated from a linear least squares fit on ln in $P = -t/\tau + \ln P_o$. 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), τ_1; and the fit after the first 40 ms, τ_2 (14).

Exponential model. The exponential model used was $P(t) = P_o e^{-t/\tau} + P_1$, with a nonlinear least squares fit of P, for P_o, P_1, and T. P_1 represents the offset pressure the system relaxes to for t infinitely greater than T. The isovolumic relaxation period is modelled only as a monoexponential.

Hemodynamic measurements

Right heart and aortic pressures were recorded directly and expressed as mean pressures; cardiac output was determined in triplicate by thermodilution and expressed as cardiac index. Systemic vascular resistance and stroke volume index were calculated from standard formulae.

Coronary blood flow measurements

In 13 patients coronary sinus flow was measured by the continuous thermodilution method of Ganz (15). Coronary vascular resistance was derived from the ratio of mean aortic pressure to coronary sinus blood flow. Myocardial oxygen consumption (MVO_2) was measured as the product of coronary blood flow and arterial–coronary venous oxygen content differences. Myocardial oxygen extraction was calculated as the difference between aortic and coronary sinus oxygen content divided by arterial oxygen content and was expressed as a percentage. During the hemodynamic monitoring MVO_2 was calculated indirectly from the equations of Rook and Feigl (16) and Bretschneider (17).

Catecholamine measurements

Adrenaline, noradrenaline, and dopamine were measured in duplicate with the radioenzymatic technique of Peuler and Johnson (18) with slight modifications. Normal basal values in our laboratory are as follows: adrenaline and dopamine, 10–110 pg/ml; noradrenaline, 100–500 pg/ml. The transmyocardial noradrenaline release was calculated as follows: arterial − coronary sinus noradrenaline × coronary blood flow (expressed as pg/min).

Analysis of global systolic and diastolic left ventricular function during angiography

From both cineangiograms, a complete cardiac cycle was analyzed frame by frame. Films were projected with a 35-mm film projector and converted into video format with a videocamera (Philips, Eindhoven, The Netherlands). The ventricular contour was detected automatically with a dedicated hard-wired system, the Contouromat (19). All contour data were coded in a special interface and stored with a PDP 1134 minicomputer onto a Rk-05 disk (Digital Equipment Co., Waltham, MA, U.S.A). For each analyzed cineframe, left ventricular volume was computed according to Simpson's rule, where each videoline in the right anterior oblique (RAO) image is taken to represent a circular slice of the left ventricular lumen. After the end-diastolic and end-systolic frames were determined, ventricular volumes and global ejection fraction were calculated. End-diastole was defined with reference to the point in the pressure trace at which the derivative of left ventricular pressure first exceeded 200 mm Hg/s and in all cases coincided with the maximal measured left ventricular volume (12). End-systole was defined with reference to the pressure tracing at the occurrence of the incisura of the central aortic pressure. The net work performed by the left ventricle ($\oint$ PdV) was calculated as the pressure × volume product from a complete cardiac cycle. Left ventricular wall stress, assuming a relatively thin wall, was calculated according to the following formula:

$$\sigma = \frac{p \cdot b}{h} \cdot \left(1 - \frac{b^2}{2a^2}\right)$$

where p is the intraventricular pressure, a and b are the major and minor hemiaxis, respectively, h is the wall thickness, and σ is the wall stress.

Drug level measurements and statistics

Plasma levels of milrinone were measured using a validated high-performance liquid chromatography procedure (20). An isocratic pressure liquid chromatographic system was used for estimation of hypoxanthine in blood (21). Results during hemodynamic monitoring are given as means ± SD after analysis of variance for repeated measurements. When overall significance was found, multiple comparisons were used to delineate which paired comparisons were significantly different at the 0.05 level. Data before and after milrinone administration were compared by paired Student's *t* test. All the results are expressed as means ± SD.

RESULTS

Measurements during hemodynamic monitoring

Of the 14 patients studied, three had serum levels of milrinone <50 ng/ml after 50 min. Table 1 summarizes the changes in central hemodynamics following milrinone treatment. The heart rate as well as pulmonary and aortic mean pressures remained unchanged over the study period. The peak systolic left ventricular pressure also did not change. Cardiac index showed a progressive increase which was significant after 40 min (from 2.0 ± 0.6 to 2.5 ± 0.7 L/min/m^2; $p < 0.05$). Concomitantly, systemic vascular resistance decreased from 1,680 ± 400 to 1,408 ± 600 dyne s cm^{-5} ($p < 0.05$) (Table 1 and Fig. 1). Stroke volume index increased from 23 ± 9 to 27 ± 9 ml/m^2 ($p < 0.05$) after 40 min and to 28 ± 9 ml/m^2 ($p < 0.05$) after 50 min (Table 1 and Fig. 1). Right atrial pressure also showed a progressive decrease during the first 30 min (from 9 ± 5 to 7 ± 7 mm Hg; $p < 0.05$), remaining stable during the following 20 min (Table 1).

The isovolumic phase indexes (peak $+dP/dt$, V_{max}, and V_{ce}) increased early and significantly (Fig. 2). In fact, peak $+dP/dt$ (control value, 917 ±

TABLE 1. *Time course of changes in central hemodynamics after oral milrinone*

	Control	10 min	20 min	30 min	40 min	50 min
HR (beats/min)	92 ± 18	89 ± 18	92 ± 18	94 ± 17	94 ± 17	94 ± 18
CI (L/min/m²)	2 ± 0.6	1.9 ± 0.6	2 ± 0.6	2.3 ± 0.7	2.5 ± 0.7[a]	2.5 ± 0.7[a]
SVR (dyne s cm^{-5})	1,680 ± 400	1,736 ± 480	1,600 ± 480	1,480 ± 608	1,408 ± 600[b]	1,384 ± 702[b]
SV (ml/m²)	23 ± 9	22 ± 9	23 ± 9	26 ± 8	27 ± 9[b]	28 ± 9[b]
PAP (mm Hg)	36 ± 14	37 ± 14	35 ± 14	31 ± 14	33 ± 14	33 ± 14
AoP (mm Hg)	83 ± 13	82 ± 13	82 ± 16	79 ± 17	81 ± 19	79 ± 20
LVSP (mm Hg)	109 ± 28	106 ± 22	102 ± 18	103 ± 19	101 ± 17	100 ± 19
RAP (mm Hg)	9 ± 5	9 ± 6	9 ± 7	7 ± 7[b]	6 ± 6[a]	6 ± 6[a]

HR, heart rate; CI, cardiac index; SVR, systemic vascular resistance; SV, stroke volume index; PAP, mean pulmonary artery pressure; AoP, mean aortic pressure; LVSP, left ventricular systolic pressure; RAP, mean right atrial pressure.

[a] $p < 0.01$.

[b] $p < 0.05$.

222 mm Hg/s) increased progressively, reaching the maximal value (1,119 ± 385 mm Hg/s; $p < 0.01$) after 50 min, as did the peak V_{ce}. Both parameters were already significantly elevated 30 min after drug administration (Fig. 2). V_{max} increased significantly after 30 min (from 28 ± 7 to 35 ± 9 s^{-1}; $p < 0.05$), remaining elevated over the study period (Fig. 2). As shown in Fig. 3, peak negative *dP/dt*

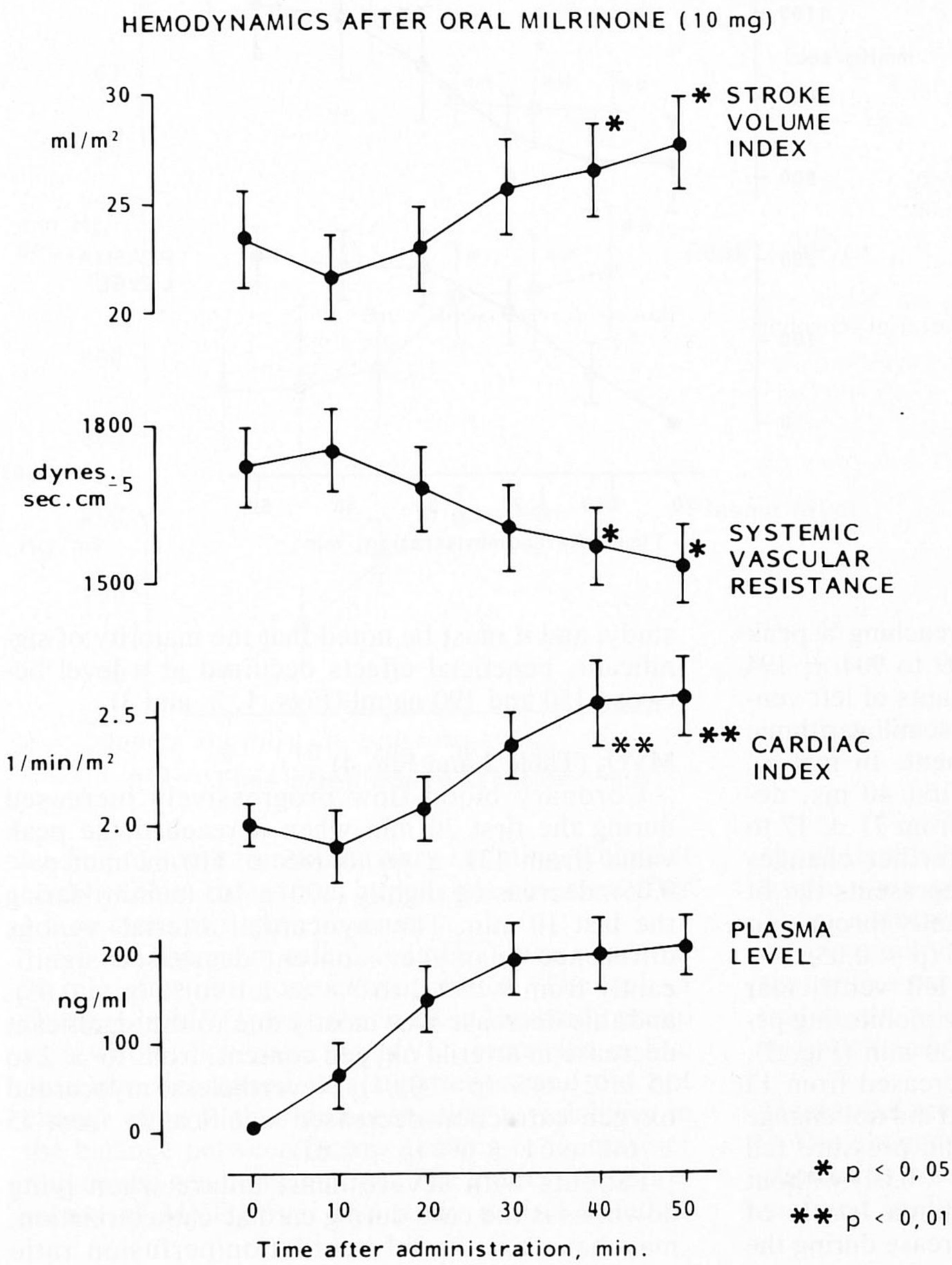


FIG. 1. Time course of hemodynamic responses to oral milrinone over 50 min. Significant changes in cardiac index, systemic vascular resistance, and stroke volume occurred within 40 min. The curve of milrinone plasma level shows a progressive increase throughout the study. Mean (SEM) values are shown.

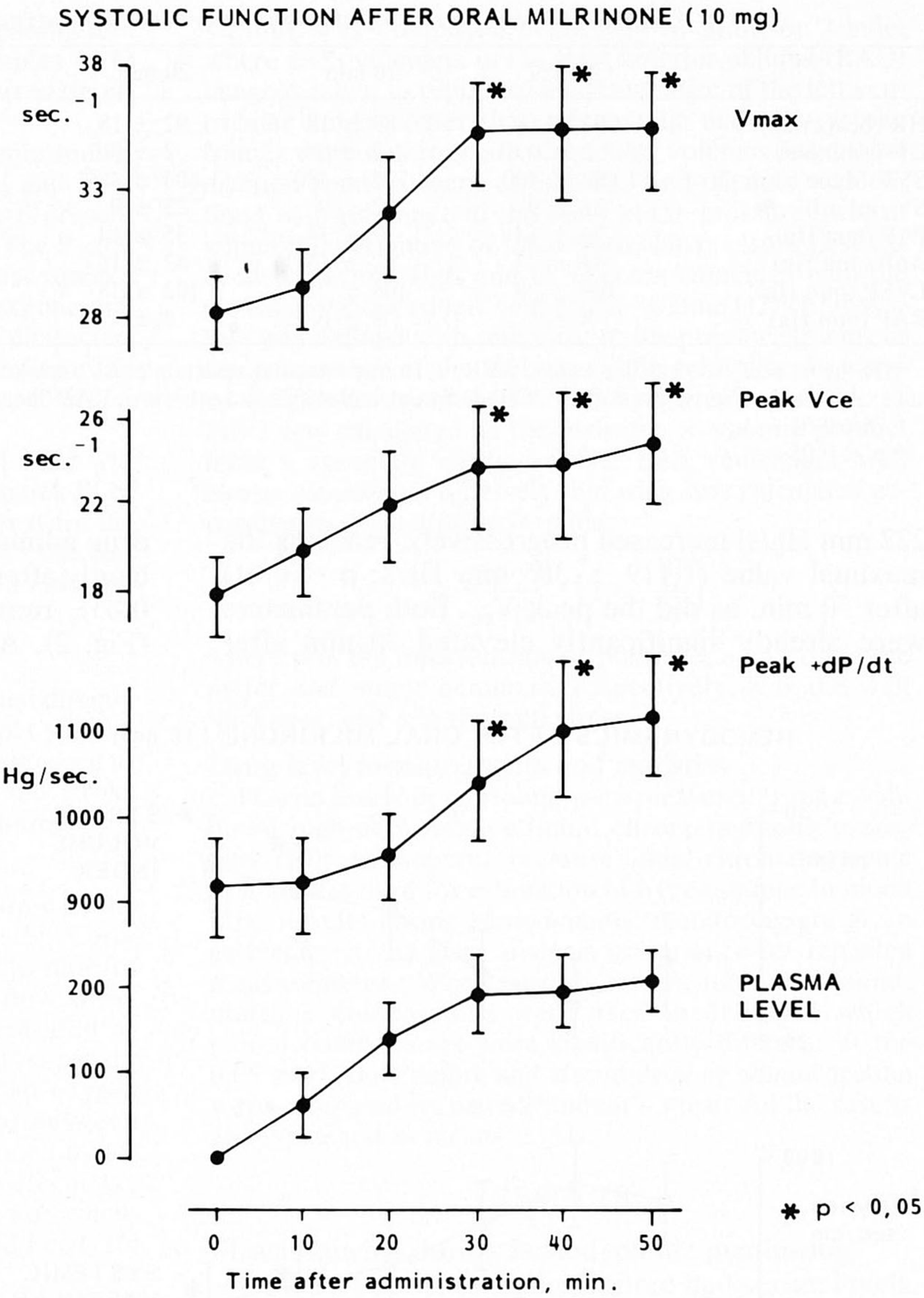


FIG. 2. Time course of changes in left ventricular isovolumic phase indexes [peak $+dP/dt$, peak velocity of contractile element (V_{ce}), and V_{max}] over 50 min after oral milrinone treatment. Within 30 min all the parameters were significantly increased, remaining significantly higher than the basal values during the last 20 min. The curve representing the time course of milrinone plasma level increase is also shown. Mean (SEM) values are shown.

increased over the study period, reaching a peak value after 50 min (from 827 ± 209 to 904 ± 194 mm Hg/s; $p < 0.01$); the time constants of left ventricular relaxation measured by the semilogarithmic model showed a similar improvement. In fact τ_1, which represents the fit for the first 40 ms, decreased significantly after 30 min (from 71 ± 17 to 59 ± 14 ms; $p < 0.01$) without further changes during the last 20 min; τ_2, which represents the fit after 40 ms, also decreased significantly throughout the study, from 54 ± 14 to 45 ± 16 ($p < 0.05$).

The minimal and end-diastolic left ventricular pressures both decreased during the monitoring period, reaching the minimum after 30 min (Fig. 3). The minimal diastolic pressure decreased from 13 ± 4 to 10 ± 7 mm Hg ($p < 0.05$) and did not change in the last 20 min; the end-diastolic pressure fell from 25 ± 6 to 20 ± 10 mm Hg ($p < 0.01$) without further significant changes. Plasma levels of milrinone showed a progressive increase during the study, and it must be noted that the majority of significant, beneficial effects occurred at a level between 150 and 190 ng/ml (Figs. 1, 2, and 3).

MVO_2 (Table 2 and Fig. 4)

Coronary blood flow progressively increased during the first 30 min when it reached the peak value (from 131 ± 66 to 185 ± 110 ml/min; $p < 0.05$), decreasing slightly (170 ± 105 ml/min) during the last 10 min. The myocardial arterial–venous difference in oxygen content decreased significantly from 9 ± 1.2 to 7.8 ± 1.1 vol% ($p < 0.05$), and this decrease was mostly due to the significant decrease in arterial oxygen content, from 16 ± 2 to 15 ± 2 vol% ($p < 0.01$). Nevertheless, myocardial oxygen extraction decreased significantly from 55 ± 6% to 51 ± 6% ($p < 0.05$).

Patients with severe heart failure when lying down, as is the case during cardiac catheterization, may have an altered ventilation/perfusion ratio

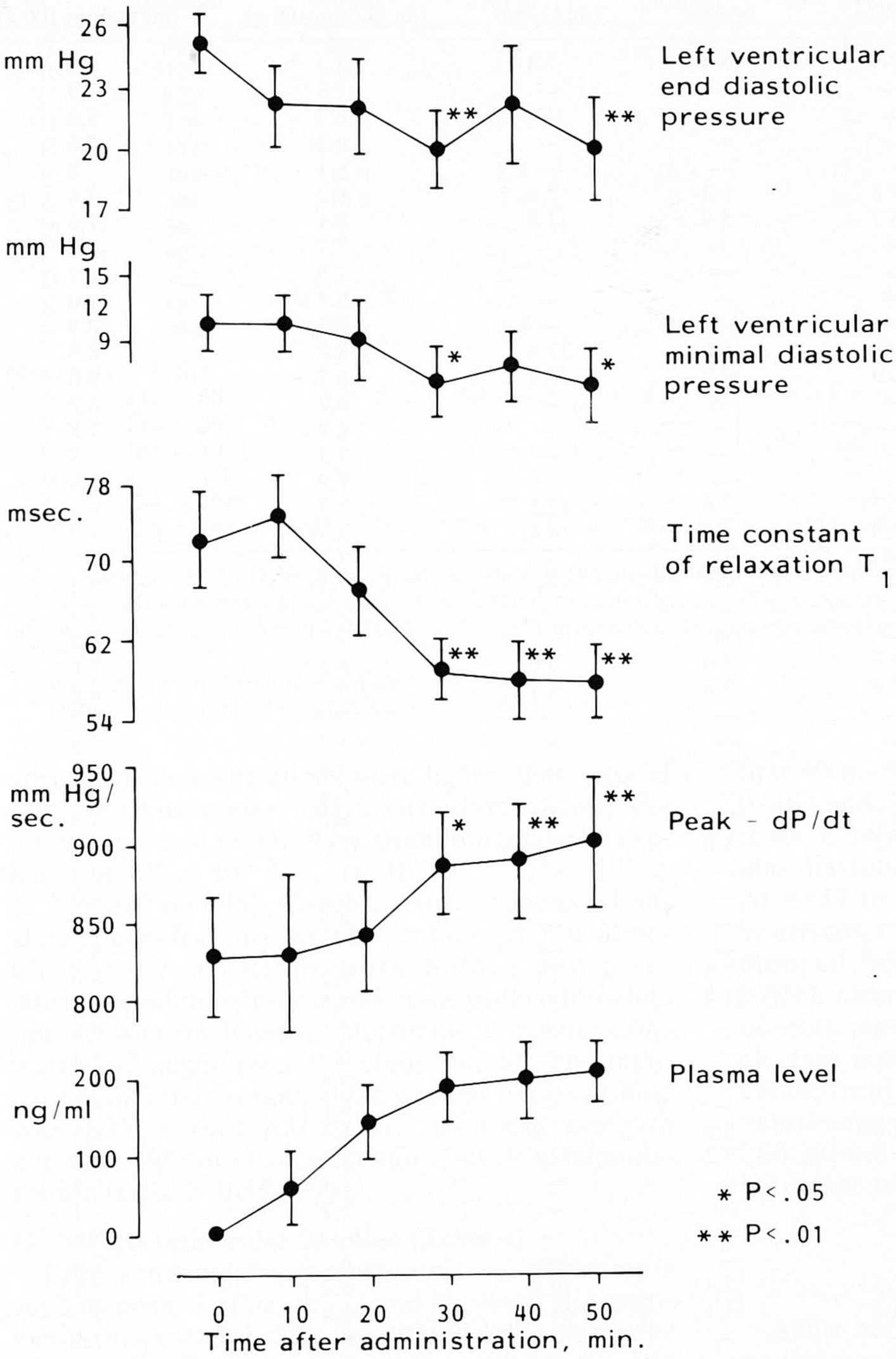


FIG. 3. Time course of changes in parameters of left ventricular diastolic performance after oral milrinone administration. The peak $-dP/dt$ significantly increased within 30 min and the time constant of relaxation (τ_1) decreased. Both left ventricular minimal diastolic and end-diastolic pressures dropped significantly at the same time interval. Mean (SEM) values are shown.

leading to some transpulmonary shunting. This fact could explain the arterial hypoxemia observed after 1 h or more of supine position.

No net change in calculated MVO_2 was observed 50 min after milrinone administration. The lack of changes in MVO_2 was observed in the study group as a whole; however, the MVO_2 increased in five patients, decreased in six patients, and did not change in two, thus demonstrating a variability in the balance between factors tending to increase or reduce oxygen consumption. The indirect measurements of MVO_2 over the study period failed to show significant change despite an increased inotropic state of the failing myocardium (Table 2). Thus, a decrease in arterial–venous difference in oxygen content with no change in MVO_2 is consistent with a primary increase in coronary blood flow and is not related to an increased myocardial oxygen demand.

Myocardial metabolism

The changes in arterial and coronary sinus catecholamine concentrations after milrinone are summarized in Table 3. Coronary sinus venous nor-

TABLE 2. *Time course of coronary hemodynamics after oral milrinone*

Case	CSBF (ml/min)	AO_2 (vol%)	VO_2 (vol%)	$A-VO_2$ (vol%)	MVO_2(1) (ml O_2/ml)	MVO_2(2) (ml O_2/min/100 g)	MVO_2(3) (ml O_2/min/100 g)
1 A	88	16.3	7.9	8.4	7.3	7.4	8.0
B	48	—	—	—	—	7.3	7.9
C	46	—	—	—	—	6.7	8.2
D	37	—	—	—	—	6.2	7.8
E	41	—	—	—	—	6.1	7.8
F	41	14.2	7.8	6.4	2.6	6.2	7.6
2 A	134	15.6	6.7	8.9	11.8	8.1	11.4
B	121	—	—	—	—	7.7	9.3
C	125	—	—	—	—	7.9	11.2
D	320	—	—	—	—	9.4	11.0
E	268	—	—	—	—	8.5	10.9
F	293	12.3	6.3	6.0	17.4	8.8	8.9
3 A	73	15.8	6.9	8.9	12.4	6.7	8.0
B	78	—	—	—	—	6.7	8.2
C	—	—	—	—	—	6.9	7.8
D	178	—	—	—	—	7.5	7.8
E	179	—	—	—	—	7.9	7.8
F	161	15.3	7.7	7.6	12.2	7.7	8.3
4 A	154	18.6	9.3	9.3	14.4	8.3	8.2
B	114	—	—	—	—	7.7	7.7
C	164	—	—	—	—	7.5	8.4
D	—	—	—	—	—	7.5	8.4
E	104	—	—	—	—	7.7	8.0
F	113	17.3	9.7	7.6	8.6	8.3	8.3
5 A	90	17.7	7.9	9.8	8.7	6.2	6.0
B	96	—	—	—	—	6.0	6.2
C	99	—	—	—	—	5.7	5.9
D	109	—	—	—	—	5.8	6.0
E	105	—	—	—	—	6.4	6.1
F	78	15.9	6.5	9.4	7.3	6.2	5.5
6 A	95	15.2	7.2	8.0	7.6	12	10.2
B	109	—	—	—	—	11	10.0
C	—	—	—	—	—	6.6	9.0
D	104	—	—	—	—	8.7	8.6
E	—	—	—	—	—	—	8.6
F	—	15.0	7.7	7.3	7.6	9.5	8.6
7 A	115	15.2	3.9	11.3	13	6.5	11.3
B	110	—	—	—	—	5.8	8.6
C	124	—	—	—	—	6	8.3
D	130	—	—	—	—	6.4	8.6
E	130	—	—	—	—	6.5	8.6
F	130	14.2	5.6	8.6	11.2	6.3	8.3
8 A	139	16.0	6.8	9.2	12.8	5.4	6.9
B	149	—	—	—	—	5.1	6.9
C	168	—	—	—	—	5.7	7.1
D	256	—	—	—	—	—	5.8
E	263	—	—	—	—	6	7.6
F	264	14.6	7.3	7.3	19.3	6.2	7.7
9 A	216	21.5	10.4	11.1	24	6.4	7.9
B	206	—	—	—	—	6.1	7.5
C	328	—	—	—	—	6.6	7.8
D	290	—	—	—	—	6.7	7.8
E	236	—	—	—	—	7.4	8.2
F	217	19.0	10.6	8.4	18.2	7.8	8.5
10 A	140	14.8	6.0	8.8	12.3	9.9	11.1
B	139	—	—	—	—	9.1	10.6
C	162	—	—	—	—	9.2	10.7
D	178	—	—	—	—	9.0	10.7
E	281	—	—	—	—	9.1	10.9
F	115	13.3	5.9	7.4	8.5	9.7	9.9
11 A	55	13.1	6.4	6.7	3.7	5.5	6.6
B	56	—	—	—	—	5.7	6.7
C	50	—	—	—	—	5.8	6.8
D	54	—	—	—	—	5.9	7.9
E	55	—	—	—	—	5.8	7.8
F	61	12.7	4.9	7.8	4.7	5.8	7.8

TABLE 2—(*Continued*)

Case	CSBF (ml/min)	AO_2 (vol%)	VO_2 (vol%)	$A-VO_2$ (vol%)	$MVO_2^{(1)}$ (ml O_2/ml)	$MVO_2^{(2)}$ (ml O_2/min/100 g)	$MVO_2^{(3)}$ (ml O_2/min/100 g)
12 A	107	20.0	9.2	7.8	11.7	8.0	9.3
B	128	—	—	—	—	6.9	8.2
C	123	—	—	—	—	9.6	11.0
D	170	—	—	—	—	10.3	11.8
E	159	—	—	—	—	9.9	9.8
F	169	18.8	8.5	10.3	17.3	10	11.3
13 A	304	16.6	7.4	9.2	28	6.7	9.7
B	364	—	—	—	—	6.3	10.8
C	407	—	—	—	—	6.6	10.9
D	392	—	—	—	—	7.0	11.0
E	386	—	—	—	—	6.6	10.9
F	393	15.8	7.6	8.2	32	6.8	10.9
Mean values ± SD							
A	131 ± 66	16 ± 2	7.4 ± 1.6	9 ± 1.2	13 ± 6	7.5 ± 1.8	8.9 ± 1.8
B	132 ± 80	—	—	—	—	7.0 ± 1.6	8.3 ± 1.4
C	163 ± 10	—	—	—	—	6.9 ± 1.2	8.6 ± 1.7
D	185 ± 110[b]	—	—	—	—	7.5 ± 1.4	8.7 ± 1.9
E	184 ± 104[b]	—	—	—	—	7.3 ± 1.3	8.7 ± 1.5
F	170 ± 105	15 ± 2[a]	7.4 ± 1.6	7.8 ± 1.1[b]	13 ± 8	7.5 ± 1.6	8.6 ± 1.5

A = baseline; B, C, D, E, F = 10, 20, 30, 40, and 50 min after milrinone administration.

CSBF, coronary sinus blood flow; AO_2, arterial oxygen content; VO_2, coronary sinus oxygen content; $A-VO_2$, arterial–venous difference in oxygen content; $MVO_2^{(1)}$, calculated myocardial oxygen consumption; $MVO_2^{(2)}$, indirect $MVO_2^{(15)}$; $MVO_2^{(3)}$, indirect $MVO_2^{(16)}$.

[a] Difference from baseline significant at $p < 0.01$ level.

[b] Difference from baseline significant at $p < 0.05$ level.

adrenaline concentrations were higher than arterial noradrenaline values. There was no statistically significant change in net myocardial noradrenaline release ($-4.8 \times 10^3 \pm 5.7 \times 10^3$ vs. $-7.7 \times 10^3 \pm 11.3 \times 10^3$ pg/min). Coronary sinus venous adrenaline concentrations were lower than arterial adrenaline concentrations both before and after milrinone administration and myocardial adrenaline uptake was unchanged. Dopamine concentrations were unchanged over the study period. The myocardial arterial–venous difference of hypoxanthine was 0.35 ± 0.21 μ*M* before milrinone and, on average, did not change 50 min after drug administration (0.62 ± 0.45 μ*M*).

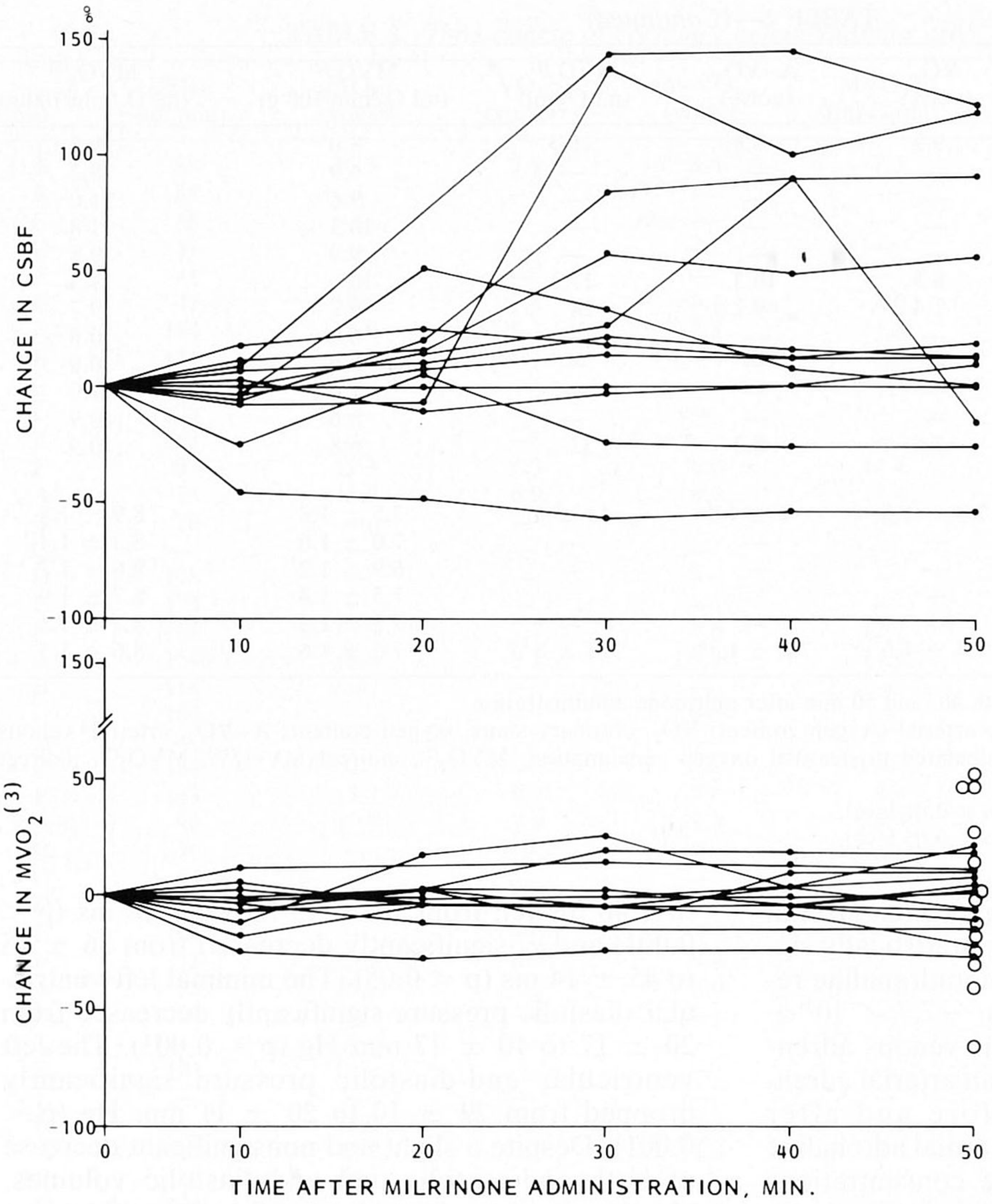
Global left ventricular function (Table 4)

Left ventricular pressure–derived parameters such as peak $+dP/dt$, V_{max}, and V_{ce} were all significantly increased during the second left ventricular angiogram. The net work performed by the left ventricle, expressed as the pressure × volume product from a complete cardiac cycle ($\oint$ PdV), showed a significant increase from 2,222 ± 1,099 to 2,814 ± 1,439 g m/m² beat ($p < 0.01$). The analysis of isovolumic relaxation before and after milrinone administration showed a significant increase in peak negative dP/dt (from 824 ± 216 to 959 ± 304 mm Hg/s; $p < 0.001$), still present even after normalization for end-systolic pressure. We observed a concomitant, significant decrease in the constant of relaxations τ (global time constant measured from the "semilogarithmic" model), which decreased from 68 ± 21 to 58 ± 21 ms ($p < 0.001$); τ_1 fit of the first 40 ms fell from 70 ± 15 to 60 ± 18 ms ($p < 0.001$) and τ_2 significantly decreased from 56 ± 15 to 45 ± 14 ms ($p < 0.05$). The minimal left ventricular diastolic pressure significantly decreased from 20 ± 17 to 10 ± 17 mm Hg ($p < 0.001$). The left ventricular end-diastolic pressure significantly dropped from 29 ± 10 to 20 ± 11 mm Hg ($p < 0.001$). Despite a slight and nonsignificant decrease of both end-systolic and end-diastolic volumes, ejection fraction showed a small but significant increase from 18 ± 8% to 22 ± 12% ($p < 0.01$). Left ventricular wall stress was unchanged, being 696 ± 260 g/cm² before and 711 ± 323 g/cm² after milrinone treatment.

DISCUSSION

Acute administration of milrinone in severe congestive heart failure results in substantial increases in cardiac output accompanied by large reductions in pulmonary wedge pressure, systemic vascular resistance, and right atrial pressure, without significant changes in heart rate or arterial blood pressures (2,3,5–9).

An associated increase in cardiac contractility has been demonstrated, but there is still disagreement as to whether the inotropic or the vasodilatory effects of milrinone predominate. Our study was undertaken to assess the short-term effects of a single oral dose of milrinone on the central and coronary hemodynamics, as well as on the left ventricular global performance, as evaluated by means of



Flg. 4. Top: Percent change in coronary sinus blood flow (CSBF) caused by oral milrinone in individual patients. Although in the majority of patients CSBF rose throughout the study, the magnitude of increase ranged widely and generally plateaued after 30 min. **Bottom:** Percent change in myocardial oxygen consumption (MVO_2), calculated according to the Bretschneider equation (17), caused by oral milrinone in individual patients. No major variations occurred throughout the study, even though a wide range of individual changes (decrease or increase) were observed. The open circles represent the percent change in the measured MVO_2 at the end of the study.

angiography and pressure recordings. To assess the positive inotropic effect of milrinone, we used the isovolumic phase indexes.

In the case of combined vasodilator and inotropic agents, decreases in both preload and afterload from the vasodilator component of the drug will result in a decrease in peak positive *dP/dt*. Therefore, as found in this study, an increase in *dP/dt* and derived parameters such as V_{max} and V_{ce} gives strong evidence for a positive inotropic effect.

The angiographic ejection fraction—a parameter never used before in the evaluation of milrinone—despite a severely low basal value, showed a consistent and significant increase (22%) despite the small changes in end-systolic and end-diastolic volumes. The analysis of the left ventricular pressure × volume product during a complete cardiac cycle, reflecting the net work of the left ventricle, also confirmed the improvement in contractility caused by milrinone. In fact, it has been demonstrated that such an index should be considered a reliable parameter of contractile efficiency unless major changes in left ventricular end-diastolic volume take place (22). That milrinone should be

TABLE 3. *Catecholamines balance before and 50 min after oral milrinone (M)*

	Before M		After M	
	Aorta	Coronary sinus	Aorta	Coronary sinus
Noradrenaline (pg/ml)	620 ± 117	988 ± 183	622 ± 93	954 ± 168
Adrenaline (pg/ml)	168 ± 26	123 ± 14	127 ± 21	89 ± 15
Dopamine (pg/ml)	167 ± 27	153 ± 20	146 ± 17	143 ± 19

TABLE 4. *Left ventricular performance, at matched paced heart rate, before and 60 min after oral milrinone*

	Control	Milrinone
RR (ms)	613 ± 122	628 ± 147
Peak $+dP/dt$ (mm Hg/s)	1,014 ± 365	1,164 ± 388[a]
$\dot{V}_{max}$ (s^{-1})	27 ± 8	36 ± 11[b]
Peak V_{ce} (s^{-1})	18 ± 5	27 ± 10[b]
ESP (mm Hg)	70 ± 19	63 ± 13
ESVI (ml/m²)	145 ± 55	139 ± 58
EF (%)	18 ± 8	22 ± 12[b]
∮PdV (gm/m² beat)	2,222 ± 1,099	2,814 ± 1,439[b]
Peak $-dP/dt$ (mm Hg/s)	824 ± 216	959 ± 304[c]
Peak $-dP/dt$/ESP/s	12 ± 2	15 ± 4[a]
T(ms)	68 ± 21	58 ± 21[c]
τ_1 (ms)	70 ± 15	60 ± 18[c]
τ_2 (ms)	56 ± 15	45 ± 14[a]
P_{min} (mm Hg)	20 ± 17	10 ± 17[c]
LVEDP (mm Hg)	29 ± 10	20 ± 11[c]
EDVI (ml/m²)	175 ± 55	169 ± 61

RR, cycle length; V_{ce}, velocity of contractile element; ESP, end-systolic left ventricular pressure; ESVI, end systolic volume index; EF, ejection fraction; ∮PdV, net work of left ventricle; τ, global time constant from the "semilogarithmic" model; τ_1 and τ^2, biexponential fitting: τ_1, fit of first 40 ms; τ_2, fit after 40 ms; P_{min}, minimal left ventricular diastolic pressure; LVEDP, left ventricular end-diastolic pressure; EDVI, end-diastolic volume index.

[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

considered an inotropic drug with combined vasodilatory action seems to be confirmed by a recent report of Jaski et al. (3), who compared intravenous milrinone to nitroprusside at doses producing similar falls in mean aortic pressure. This study demonstrated that, at an equivalent level of afterload and despite a lower preload, milrinone induced greater improvement in myocardial performance than nitroprusside.

Furthermore, more recently, Ludmer et al. (23) clearly demonstrated that intracoronary administration of milrinone leads to a dose-related increase in inotropic state of failing myocardium in the absence of concomitant changes in either loading conditions or heart rate. Thus, even if our study was not designed to assess the relative inotropic and vasodilator components of milrinone's action, our results suggest that oral administration of this agent caused a positive inotropic action as well as a vasodilator action in patients with severe congestive heart failure.

Isovolumic relaxation

A previous study reported altered early relaxation in patients with congestive cardiomyopathy and heart failure (24). Furthermore, in patients with chronic ischemia the resting alteration in left ventricular relaxation is probably due to the presence of fibrotic scar tissue within still viable myocardium affecting the biochemical processes of activation-contraction-relaxation (25). In our study, despite a severe resting abnormality in isovolumic relaxation, we observed a consistent improvement, toward normal, of such parameters. These results suggest an important, and probably still underscored, component of improved early diastolic function in the overall hemodynamic improvement observed in patients with congestive heart failure treated with milrinone.

We evaluated the isovolumic relaxation period by using a biexponential model. The oral administration of milrinone shortened quickly and significantly some of the most sensitive indexes of left ventricular pressure decay, such as the time constant for the first 40 ms of the relaxation phase (τ_1). It has been postulated that an improvement in left ventricular systolic function could lead to an improved relaxation which is an active process energized by the preceding systole (26). Recently, it has been demonstrated that an increase in contractility does not necessarily lead to improved myocardial relaxation (27), so that contraction and relaxation are not necessarily coupled processes. Thus, it seems conceivable that the improvement observed in isovolumic relaxation is due to a direct, although still undefined, effect of milrinone on the intracellular biochemistry rather than to the effect of milrinone on left ventricular loading.

Coronary hemodynamics

Together with global hemodynamic improvement, we observed throughout the study a significant increase in coronary blood flow peaking at 30 min. Furthermore, a decrease in aortic–coronary sinus difference in oxygen constant, occurring together with a decrease in myocardial oxygen extraction, appeared to be the result of primary rather than secondary vasodilation. Such a vasodilating effect on the coronary circulation in patients with a chronic coronary artery disease as a cause of heart failure could lead to an inappropriate flow distribution with a consequent coronary steal phenomenon. We did not record any clinical or electrocardiographic evidence of possible drug-related ischemia during the study period, and the myocardial arterial–venous difference of hypoxanthine was on average unchanged 50 min after milrinone administration.

The effect of an inotropic agent on myocardial oxygen demand depends on its effects on the heart rate, contractile state, and left ventricular wall stress (a function of chamber size, intracavitary pressure, and wall thickness). It has been demonstrated that among these three major determinants of MVO_2, contractile state contributes to a lesser extent to left ventricular oxygen requirements (28). We did not observe any change in heart rate, and wall stress remained unchanged 60 min after milrinone administration. In our patients with severe heart failure, milrinone caused, on average, no increase in MVO_2 either calculated or measured.

These findings suggest that the drug improved cardiac performance without worsening the balance between myocardial oxygen supply and demand, although some individual variability in response is evident (29).

In other words, this beneficial effect of milrinone possibly depends on its vasodilator action which tends to reduce myocardial oxygen demand, thereby counterbalancing the expected increase caused by an augmented contractility.

Myocardial catecholamines balance

In patients with heart failure an enhanced systemic and cardiac sympathetic tone associated with low cardiac output has been documented (30). Arterial noradrenaline concentrations reflect systemic activity, whereas changes in net myocardial noradrenaline release can be used to assess cardiac sympathetic activity (31). In our patients both parameters were elevated, thus demonstrating a heightened systemic and cardiac sympathic activity. After milrinone treatment, no changes occurred either in arterial noradrenaline concentration or in net myocardial noradrenaline release, despite a marked improvement in left ventricular function. Since increased sympathetic activity has been regarded as a reflex response to impaired left ventricular function in patients with heart failure, the improvement observed after milrinone would have decreased sympathetic activity in our patients. However, despite the marked increase in cardiac output and the lack of change in arterial pressure, no changes were observed in parameters reflecting both systemic and cardiac sympathetic activity.

These findings suggest that an acute improvement in left ventricular function after oral milrinone treatment is not immediately associated with reflex decrease in systemic or cardiac sympathetic activity.

Conclusions

Potential limitations of our study should be taken into account. First of all, hemodynamic measurements at rest do not reflect the actual myocardial function, and exercise hemodynamics are a more reliable way to measure improvement in cardiac function. However, the severity of symptoms in our patients precluded exercise testing.

The majority of our patients were coronary patients and therefore the global measurements of coronary blood flow and oxygen content in the coronary sinus, as well as, of course, the calculation of global MVO_2, do not reflect what happened in different myocardial regions.

In summary, a single oral dose (10 mg) of milrinone produced in patients with severe congestive heart failure an evident global improvement of systolic and diastolic myocardial function without positive chronotropic effects and/or reduction in mean aortic pressure—effects typical of a pure or predominant vasodilator agent which often limits its use in patients already in a compromised hemodynamic state. A primary coronary vasodilator action of milrinone was evident, although further studies are needed to more accurately investigate the continuous balance between myocardial oxygen supply and demand, particularly in patients with evidence of ischemia.

Acknowledgment: The authors thank Susan Veldhof for her careful review of the manuscript and Anja van Huuksloot and Gusta Koster for expert and patient preparation of the manuscript. Dr. Piscione is supported by CNR-NATO research fellowship no. 216.1095. Dr. Jaski is supported by National Institutes of Health training grant 5-T32-HLO-7049.

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