Identification of the direct vasodilator effect of milrinone with an isolated limb preparation in patients with chronic congestive heart failure

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ABSTRACT   We developed an isolated limb preparation to evaluate the direct vasoactive properties of cardioactive drugs on the forearm vasculature in patients with congestive heart failure. Using this model, we infused milrinone in subsystemic doses (1, 10, and 20 μg/min per 100 ml forearm volume [FAV]) into the brachial artery of 13 patients with moderate-to-severe congestive heart failure. We monitored forearm hemodynamics, systemic hemodynamics, and milrinone plasma concentration from both the forearm venous effluent and pulmonary artery. This preparation enabled us to assess the direct forearm vascular response to milrinone. Compared with baseline forearm blood flow (2.46 ± 1.37 ml/min/100 ml FAV), the three doses of milrinone resulted in increases in forearm blood flow to 2.66 ± 1.43, 4.21 ± 1.79, and 6.73 ± 3.69 ml/min/100 ml FAV. This was associated with a reduction of forearm vascular resistance from the baseline value of 52 ± 38 U to 47 ± 36, 25 ± 13, and 17 ± 10 U. The p value for the difference in response of flow and resistance after the 10 and 20 μg doses vs that at baseline was .05. This forearm vasodilatation occurred without change in systemic hemodynamics or therapeutic milrinone plasma concentrations in the pulmonary artery. In five patients, we compared the response to intra-arterial milrinone with that of nitroprusside. At a dose of 10 μg/min/100 ml FAV, the response to nitroprusside (7.20 ± 3.24 ml/min/100 ml FAV) was greater than that to milrinone (4.65 ± 2.18 ml/min/100 ml FAV) (p < .05). When milrinone was administered by a systemic intravenous route, the magnitude of forearm vasodilatation was not as great as that with intra-arterial milrinone, suggesting different sensitivities of vasodilatation in alternate vascular beds or the influence of baroreceptor autoregulation. Thus, this study identifies direct vasodilator properties of milrinone that are independent of its inotropic activity.
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THE DEVELOPMENT of milrinone is a potential new therapy of chronic congestive heart failure. The inotropic activity of this bipyridine compound has been identified in laboratory and clinical studies,[1-2] but the observed reduction in calculated systemic vascular resistance noted in clinical trials[2-5] suggests an additional direct vasodilator effect. The systemic administration of milrinone does not provide a means to directly analyze a vasodilator effect, since the reduction in calculated systemic vascular resistance could also be an indirect reflex response to the increase in cardiac output. The present study describes the application of an isolated limb preparation to the direct assessment of vascular tone in patients with chronic congestive heart failure. With this technique, we have identified the direct vasodilator effect of the cardiotonic compound milrinone.

Methods

Patient population. The study group consisted of 13 patients with chronic congestive heart failure and included 10 male and three female patients, ranging from 29 to 75 years of age. The cause of congestive heart failure was ischemic in nine patients and nonischemic in four. All patients were admitted to the Clinical Research Center of New York Hospital–Cornell University Medical College. Any previous therapy with vasodilators was discontinued before, or at the time of, admission. Patients were stabilized in the hospital on their long-term regimens of digoxin and diuretics for at least 3 days before participation in this protocol, and digoxin and diuretic therapy were withheld for the 24 hr before this study. All patients gave written in-

formed consent and this protocol was approved by the Committee on Human Rights in Research.

Isolated limb preparation. The elements of the isolated model used in this study are shown in figure 1. A right heart catheter was passed percutaneously through an introducer sheath from a basilic vein for measurement of cardiac output, right atrial pressure, pulmonary arterial pressure, and pulmonary capillary wedge pressure. The distal port of the catheter was connected to a three-way stopcock for intermittent sampling of blood from the pulmonary artery for measurement of plasma concentration of milrinone. The sidearm of the introducer sheath was used for intermittent sampling of forearm venous blood for measurement of plasma concentration of milrinone. An arterial cannula was placed in the brachial artery of the same arm, and was connected to a three-way stopcock for pressure monitoring and for the infusion of milrinone via a constant infusion pump. The study arm was supported in a comfortable position, at a level slightly higher than the level of the heart, in a position of approximately 30 degrees of abduction. Forearm blood flow was measured using venous occlusion plethysmography.[6] A mercury-in-rubber strain gauge was placed around the mid forearm for measurement of forearm blood flow. The strain gauge was connected to an electronically calibrated plethysmograph (Hokanson EC-4).

A venous occlusion cuff was placed on the upper arm, proximal to the brachial artery catheter. Venous occlusion was achieved by inflating the cuff to 30 mm Hg by a rapid cuff

inflator (Hokanson E-10). A pediatric blood pressure cuff was placed around the wrist and inflated to a pressure of 30 to 40 mm Hg above the systolic blood pressure to exclude the hand circulation from the measurements, thereby excluding the influence of shunting in the microcirculation of the hand. The wrist cuff was inflated 30 sec before each measurement and throughout measurement of forearm flow. The forearm blood flow output signal was transmitted to an Electronics for Medicine VR-12 recorder. A 1% volume calibration signal was recorded before each set of forearm blood flow determinations. Five consecutive flow curve recordings were obtained for each measurement of forearm blood flow, with each recording lasting 10 sec. All forearm blood flow curves were analyzed by computer, with the use of a digital bit pad for entry of data into the computer, which provided a mean value for each set of recordings. The computer program is based on a standard technique for strain-gauge plethysmographic forearm flow calculations, which includes determination of the calibration signal, time factor, and slope of the forearm blood flow curve. Forearm volume (FAV) was measured by water displacement[7] and forearm blood flow was expressed as milliliters per minute per 100 ml FAV. Forearm vascular resistance was calculated by dividing mean arterial pressure by forearm blood flow, and was expressed in resistance units. Heart rate and all pressures were also recorded on the Electronics for Medicine VR-12. Mean pressures were determined by electronic damping. Cardiac output was determined by thermodilution, in triplicate. Derived hemodynamic indexes were by standard formulae.[8]

With this preparation, milrinone was administered by the constant-infusion pump into the brachial artery in subsystemic doses, that is, doses that could potentially increase forearm flow without having any effect on the heart or on the systemic circulation after passage through the left heart. We were able to document that the doses of milrinone infused were subsystemic in two ways. First, by measurement of systemic hemodynamics during the infusion, we were able to demonstrate the presence or absence of changes in cardiac filling pressures, cardiac output, and calculated systemic vascular resistance. Second, we obtained simultaneous blood samples from the brachial vein and the pulmonary artery. Thus, we were able to assess the effluent venous drainage from the forearm under study for plasma milrinone concentrations for comparison against concentrations known to cause favorable hemodynamic effects.[9]

Protocol for intra-arterial administration of milrinone. All studies were performed in the morning, after subjects had fasted overnight, and in a room of constant temperature (22° C). After placement of the catheter, the patients were allowed to rest for at least 60 min. We then obtained baseline measurements of both forearm and systemic hemodynamics, as well as blood samples for determination of forearm and pulmonary arterial plasma milrinone concentrations. These measurements were repeated 30 min later to ensure a stable baseline. Milrinone was diluted in 5% dextrose solution and was infused into the brachial artery with the constant-rate infusion pump. Milrinone was administered to all patients in three stepwise increments of 1, 10, and 20 μg/min/100 ml FAV for a duration of 1 min per dose. This was achieved by increasing the volume of infusion, and the total volume infused in all patients was less than 2 ml. In the first seven patients, the incremental of milrinone included an infusion dose of 0.1 μg/min/100 ml FAV. When it became clear that both 0.1 and 1 μg/min/100 ml FAV were both no-response doses, then the 0.1 μg infusion rate was deleted from the protocol. Each dose of milrinone was infused for a total of 1 min. Forearm hemodynamics and simultaneous plasma milrinone concentrations from the forearm vein and pulmonary artery were obtained at 1 and 10 min after each infusion. At approximately 3 to 5 min after each infusion, we also measured system-
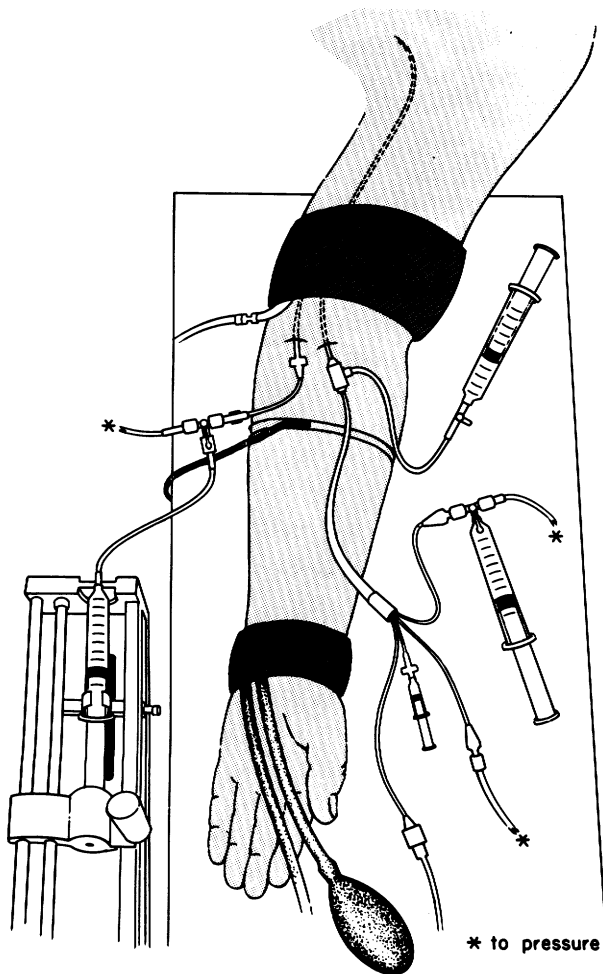

FIGURE 1. Schema of the isolated limb preparation that was developed to evaluate the vasodilator properties of milrinone.

✻ to pressure

ic hemodynamics to document the presence or absence of systemic response to the intra-arterial administration of milrinone. After the 10 min measurement, we did not proceed to the next dose of milrinone until forearm blood flow had returned to within 10% of the baseline value.

To assess the effects of the infusion of the 5% dextrose solution vehicle, determinations of forearm blood flow were obtained in five patients after the infusion of the vehicle alone. The 5% dextrose solution vehicle was infused in the same manner as the 10 μg/min/100 ml FAV milrinone infusion, and consisted of a volume of approximately 0.5 ml given over 1 min. Forearm blood flow determinations were obtained by the same method as that used after administration of milrinone.

To compare the changes in forearm blood flow induced by milrinone with a standard vasodilator, five patients also received an intra-arterial infusion of nitroprusside. Nitroprusside was chosen because of its potent direct vasodilator effect and was diluted in 5% dextrose solution and administered into the brachial artery in successive doses of 1 and 10 μg/min/100 ml FAV. Measurement of forearm and systemic hemodynamics were obtained at 1 and 10 min after each dose.

After the intra-arterial administration of milrinone, we allowed a 45 min equilibration period of systemic and forearm hemodynamic parameter values to return to baseline. To compare the vasodilator effects of intra-arterial milrinone with those of systemically administered milrinone, we then administered milrinone as an intravenous bolus of 12.5 and 75 μg/kg after the equilibration period. We chose these doses since the 12.5 μg/kg dose has minimal systemic effects, whereas the 75 μg/kg dose has been reported to result in significant hemodynamic improvement.[10] After each dose of intravenous milrinone, systemic and forearm hemodynamics were measured at 5, 15, and 30 min. In addition, blood samples for determination of plasma milrinone concentration were simultaneously obtained from the forearm vein and pulmonary artery at baseline and 5, 15, and 30 min after each intravenous dose of milrinone. The peak hemodynamic effect occurred 5 min after drug administration, so that these values were used for analysis. All hemodynamic parameter values had returned to within 10% of baseline by 30 min after the 12.5 μg/kg dose and the 75 μg/kg dose was not administered until the establishment of this baseline. Blood samples for plasma milrinone concentration were analyzed by liquid chromatography as previously described[9] and expressed as nanograms per millimeter plasma.

Statistical analysis. Evaluation of the response of intra-arterial milrinone and the response to intravenous milrinone were by analysis of variance. All values are expressed as mean ± SD. Changes were considered statistically significant if a p value of <.05 was achieved.

Results

The response to the intra-arterial administration of milrinone is summarized in figure 2. In the baseline state, forearm blood flow was 2.46 ± 1.37 ml/min/100 ml FAV and forearm vascular resistance was 52 ± 38 U. The plasma concentration of milrinone in both the forearm vein and the pulmonary artery was undetectable. Calculated systemic vascular resistance was 1775 ± 577 dynes·sec·cm^{-5}. Additional baseline hemodynamics included a heart rate of 89 ± 18 beats/min, mean arterial pressure of 83 ± 13 mm Hg, right atrial pressure of 9 ± 8 mm Hg, pulmonary wedge pressure of 23 ± 12 mm Hg, and cardiac index
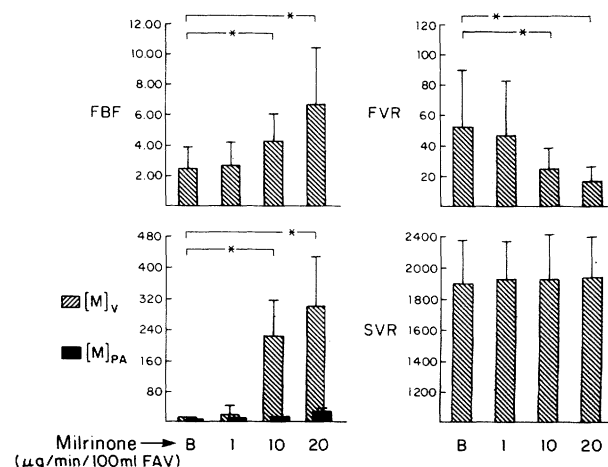

FIGURE 2. The direct vasodilator response to intra-arterial infusion of milrinone. FBF = forearm blood flow (ml/min/100 ml FAV); FVR = forearm vascular resistance (units); [M]v = forearm venous plasma milrinone concentration (ng/ml); [M]pa = pulmonary arterial plasma milrinone concentration (ng/ml); SVR = systemic vascular resistance (dynes·sec·cm^{-5}). All values are mean ± 1 SD.

of 1.84 ± .30 liters/min/m^2. After the administration of milrinone in a dose of 1 μg/min/100 ml FAV, there was no significant change of forearm blood flow (2.66 ± 1.43 ml/min/100 ml FAV) or forearm vascular resistance (47 ± 36 U). The concentration of milrinone in both the forearm vein and pulmonary artery remained negligible. After the 10 μg/min/100 ml FAV infusion of milrinone, forearm blood flow increased to 4.21 ± 1.79 ml/min/100 ml FAV and forearm vascular resistance decreased to 25 ± 13 U (both p < .05 compared with their respective baseline values). With this response, plasma milrinone concentration in the forearm vein was 223 ± 96 ng/ml (p < .05 compared with baseline), while the pulmonary arterial milrinone plasma concentration was only 8 ± 4 ng/ml. The milrinone concentration noted in the forearm vein is the same as those associated with systemic hemodynamic effects when milrinone is given either orally or intravenously.

Further incremental response to milrinone was noted after the 20 μg/min/100 ml FAV infusion. Forearm blood flow increased to 6.73 ± 3.69 ml/min/100 ml FAV and forearm vascular resistance decreased to 17 ± 10 U (both p < .05 compared with their respective baseline values). The forearm hemodynamic changes were associated with a further increase of milrinone concentration in the forearm vein to 298 ± 135 ng/ml (p < .05 compared with baseline); however, pulmonary arterial milrinone concentration was only 25 ± 12 ng/ml. Despite these dose-related changes in forearm hemodynamics, systemic hemodynamics were unchanged. Compared with the baseline value,

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systemic vascular resistance was 1850 ± 550, 1838 ± 593, and 1963 ± 571·sec·cm^{-5} for the three milrinone infusions. These values were not significantly changed compared with baseline. With the three successive infusions of milrinone, the following additional hemodynamic values were recorded: heart rate, 84 ± 18, 86 ± 18, and 87 ± 20 beats/min; mean arterial pressure, 85 ± 13, 85 ± 12, and 86 ± 20 mm Hg; right atrial pressure, 9 ± 8, 9 ± 8, and 9 ± 8 mm Hg; pulmonary wedge pressure, 24 ± 13, 22 ± 12, and 22 ± 13 mm Hg; cardiac index, 1.84 ± .27, 1.83 ± .31, and 1.81 ± .26 liters/min/m². As with systemic vascular resistance, none of these systemic hemodynamic parameters were significantly changed compared with baseline values.

Forearm blood flow did not change when the 5% dextrose vehicle was administered (1.66 ± 1.38 vs 1.73 ± 1.52 ml/min/100 ml FAV). In addition, systemic hemodynamics were the same before and after this infusion, including heart rate (95 ± 22 vs 92 ± 22 beats/min), mean arterial pressure (99 ± 13 vs 100 ± 9 mm Hg), right atrial pressure (11 ± 7 vs 11 ± 11 mm Hg), pulmonary wedge pressure (24 ± 11 vs 23 ± 11 mm Hg), cardiac index (1.52 ± .20 vs 1.60 ± .20 liters/min/m²), and systemic vascular resistance (2541 ± 635 vs 2449 ± 510 dynes·sec·cm^{-5}) (all p = NS).

The comparison of the response of forearm blood flow to intra-arterial administration of milrinone and nitroprusside is shown in figure 3. The baseline forearm blood flow values after milrinone (1.83 ± 1.40 ml/min/100 ml FAV) and nitroprusside (2.09 ± 1.21 ml/min/100 ml FAV) were not significantly different. With infusion of milrinone, forearm blood flow was 1.80 ± 1.16, 3.35 ± 1.89, and 4.65 ± 2.18 ml/min/100 ml FAV with successive doses of 1, 10, and 20 µg/min/100 ml FAV. After nitroprusside, forearm blood flow increased to 3.09 ± 1.58 and 7.20 ± 3.24 ml/min/100 ml FAV with successive doses of 1 and 10 µg/min/100 ml FAV. Comparing the 10 µg/min/100 ml FAV infusion, the response of intra-arterial nitroprusside was significantly greater than that to milrinone (p < .05). There were no changes in systemic hemodynamics observed during the infusion of nitroprusside in a dose of 10 µg/min/100 ml FAV. The following hemodynamics data were recorded before and after the infusion of nitroprusside: heart rate, 94 ± 18 vs 92 ± 18 beats/min; mean arterial pressure, 104 ± 11 vs 101 ± 11 mm Hg; right atrial pressure, 10 ± 9 vs 9 ± 9 mm Hg; pulmonary wedge pressure 24 ± 11 vs 25 ± 13 mm Hg; cardiac index, 1.52 ± .16 vs 1.55 ± .23 liters/min/m²; and systemic vascular resis-
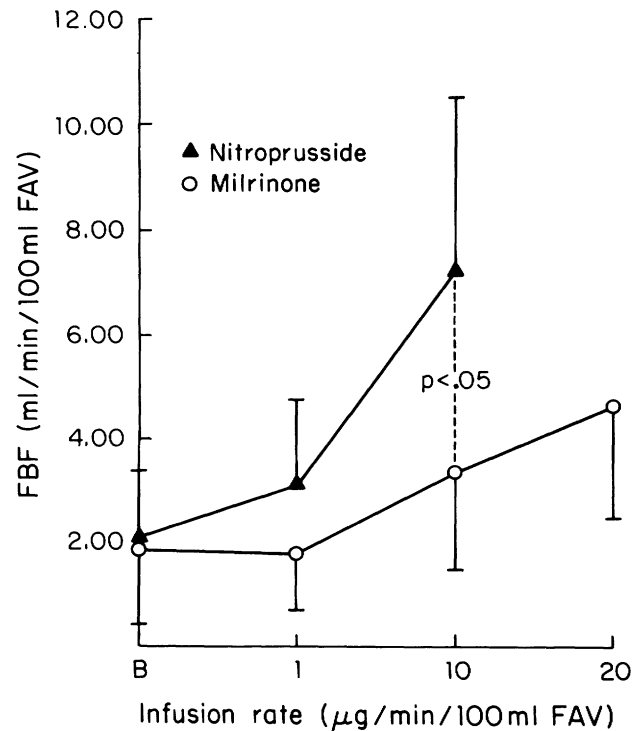

FIGURE 3. Comparison of the forearm blood flow response to the intra-arterial administration of milrinone and nitroprusside in five patients. There was a statistically significant difference between nitroprusside and milrinone at the infusion rate of 10 µg/min/100 ml FAV. All values are mean ± 1 SD.

tance, 2708 ± 550 vs 2607 ± 644 dynes·sec·cm^{-5} (all p = ns).

The peak responses to the intravenous administration of milrinone are shown in table 1. For comparison, the column on the left provides the peak changes after intra-arterial administration of 20 µg/min/100 ml FAV milrinone, as well as the subsequent return to baseline, before intravenous administration of milrinone. After the 12.5 µg/kg bolus of milrinone, there were no significant hemodynamic changes. The plasma concentrations of milrinone achieved in the forearm vein and pulmonary artery were 79 ± 18 and 98 ± 70 ng/ml, respectively. After the 75 µg/kg intravenous dose of milrinone, significant hemodynamic improvement was observed. While mean arterial pressure and right atrial pressure were not significantly changed, cardiac index increased to 2.54 ± 43 liters/min/m², which was associated with the reduction of calculated systemic vascular resistance to 1227 ± 344 dynes·sec·cm^{-5} (both changes p < .05 compared with their respective baselines). Accompanying this hemodynamic improvement was the reduction of pulmonary wedge pressure to 14 ± 10 mm Hg (p < .05 compared with baseline). Forearm blood flow increased from 2.98 ± 1.76 to 4.01 ± 2.00 ml/min/100 ml FAV, but

TABLE 1
Hemodynamic response to intravenous milrinone

	Intra-arterial milrinone (20 μg/min/ 100 ml FAV)	Baseline	Intravenous milrinone	
			12.5 μg/kg	75 μg/kg
MAP (mm Hg)	86 ± 20	85 ± 15	82 ± 11	76 ± 14
CI (l/min/m²)	1.81 ± 0.26	1.83 ± 0.28	2.09 ± 0.31	2.54 ± 0.43^A
SVR (dynes·sec·cm⁻⁵)	1863 ± 571	1852 ± 665	1596 ± 533	1227 ± 344^A
RAP (mm Hg)	9 ± 8	8 ± 8	7 ± 7	5 ± 5
PWP (mm Hg)	22 ± 13	23 ± 12	22 ± 11	14 ± 10^A
FBF (ml/min/100 ml FAV)	6.73 ± 3.69	2.98 ± 1.76	3.59 ± 2.03	4.01 ± 2.00
FVR (U)	17 ± 10	44 ± 34	34 ± 27	26 ± 18
$[M]_V$	298 ± 135	32 ± 34	79 ± 18	374 ± 79^A
$[M]_{PA}$	25 ± 12	10 ± 6	98 ± 70	388 ± 64^A

MAP = mean arterial pressure; CI = cardiac index; SVR = systemic vascular resistance; RAP = right atrial pressure; PWP = pulmonary wedge pressure; FBF = forearm blood flow; FVR = forearm vascular resistance; $[M]_V$ = forearm venous plasma milrinone concentration; $[M]_{PA}$ = pulmonary arterial plasma milrinone concentration.

$^A p < .05$ compared with baseline.

this change was not statistically significant. The reduction of forearm vascular resistance from 44 ± 34 to 26 ± 18 U was only of borderline significance ($p < .08$). The absence of a greater response of forearm hemodynamics to intravenous milrinone could not be attributed to an insufficient plasma milrinone concentration since the plasma concentrations were 374 ± 79 and 388 ± 64 ng/ml, respectively, in the forearm vein and pulmonary artery and both were greater than the venous concentration of milrinone after intra-arterial administration.

Discussion

This isolated limb preparation provides a means to measure forearm and systemic hemodynamics during intra-arterial drug administration, and thus can directly assess the vasoactive properties of newer therapeutic modalities such as the cardiotonic agents. This preparation excludes the effects of cardiac performance, and also the influence of reflex autoregulatory response that may occur when drugs are given systemically. Since calculated systemic vascular resistance may change in response to direct vasodilator effects, increases in cardiac output, and reflex autoregulatory compensation, it is necessary to separate these various influences as much as possible when assessing the response to drug therapy, and also the response to physiologic maneuvers.

Using this isolated limb preparation, we have identified the direct vasodilator properties of milrinone, a cardiotonic agent currently under evaluation for use in patients with congestive heart failure. Administration of milrinone in subsystemic doses into the brachial artery resulted in a dose-dependent increase in forearm blood flow and reduction in forearm vascular resistance. This occurred in the absence of changes in systemic hemodynamic parameters. The infusion of 1.0 μg/min/100 ml FAV was a no-response dose, while the infusions of 10 and 20 μg/min/100 ml FAV resulted in significant increases in forearm blood flow. It is conceivable that further incremental infusions of milrinone may have increased forearm blood flow and decreased forearm vascular resistance to greater degrees, but we wished to avoid the possibility of systemic hemodynamic effects that could occur if larger doses of milrinone resulted in therapeutic systemic plasma concentrations.

To place the response to milrinone in the context of a standard vasodilator, we compared it with nitroprusside, since this is one of the most potent parenteral vasodilators. While milrinone resulted in a direct vasodilator effect, the magnitude of this response was not as potent as that of nitroprusside on a microgram per microgram basis, since there was a significant difference between the forearm blood flow response to milrinone and nitroprusside at an infusion rate of 10 μg/min/100 FAV. The systemic intravenous administration of milrinone (75 μg/kg) produced only a small increase in forearm blood flow and a small reduction of forearm vascular resistance that were much less than those seen with intra-arterial administration. The absence of a greater response of forearm hemodynamics to intravenous milrinone was not due to differences in plasma milrinone concentration.

It is possible that an alternate vascular bed could vasodilate with a greater sensitivity after the short-term

intravenous administration of milrinone, so that there was relatively less immediate vasodilatation of the forearm vessels. In contrast, a study by Cinquergrani et al.[11] has shown that the change in forearm blood flow and forearm vascular resistance do achieve statistical significance with a prolonged intravenous infusion of milrinone. It is also possible that reflex circulatory autoregulation may blunt the forearm vascular response to systemically administered milrinone, while intra-arterial milrinone administration is independent of compensatory reflex autoregulation. Finally, it is possible that, despite similar venous milrinone concentrations, the intra-arterial administration of milrinone resulted in a higher peak tissue concentration, thereby leading to a greater vasodilator effect.

Therefore, it would not appear appropriate to consider the bipyridine compounds, such as milrinone, to be purely inotropic agents. These compounds, which appear to be phosphodiesterase inhibitors, have both vasodilator and inotropic properties. A recent study by Borow et al.[12] has suggested both inotropic and vasodilator properties of milrinone in a group of normal volunteers in whom echocardiographic determinations were obtained. More recently, Colucci et al.[13] have attempted to separate the inotropic and vasodilator effects of milrinone in a group of patients with congestive heart failure. They found that the intracoronary administration of milrinone resulted in significant increases in dP/dt, without systemic effects. When milrinone was given intravenously, there was significant changes in systemic vascular resistance and forearm vascular resistance. When the direct vasodilator properties identified in the present study are taken together with these additional two reports, the bipyridine class of cardiotonic agents appear to be a unique class of therapeutic agents for the treatment of congestive heart failure. It remains to be determined whether there is a threshold for these two mechanisms of action, since the relative sensitivity of vascular smooth muscle (vasodilatation) and cardiac muscle (positive inotropy) to milrinone is not known.

In summary, the present study describes an isolated limb preparation for the assessment of the direct vascular effects of vasoactive compounds in patients with congestive heart failure. With this preparation we have

demonstrated the direct vasodilator effects of the bipyridine milrinone. When milrinone is administered in subsystemic doses into the brachial artery, there is a dose-dependent increase of forearm blood flow and reduction of forearm vascular resistance. However, the effect of milrinone on forearm hemodynamics was not as potent as that of nitroprusside. While intravenous milrinone improved systemic hemodynamics, its effects on forearm hemodynamics were less apparent than those of the intra-arterial drug.

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