Systemic and regional hemodynamic effects of captopril and milrinone administered alone and concomitantly in patients with heart failure

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ABSTRACT  The effects of milrinone and captopril on ventricular performance, renal blood flow, and femoral vein oxygen content were compared in 11 patients with severe chronic heart failure. The increase in stroke volume index was greater with milrinone than with captopril (28 ± 7 vs 24 ± 7 ml/m²; p < .05), while pulmonary capillary wedge pressures fell similarly (19 ± 10 vs 21 ± 7 mm Hg). Mean systemic arterial pressure decreased significantly from 84 ± 10 to 73 ± 11 mm Hg (p < .05) with captopril but did not with milrinone. Neither drug changed heart rate significantly. Although milrinone produced a greater improvement in ventricular performance than captopril, renal blood flow increased similarly with both drugs from 289 ± 78 to 417 ± 111 ml/min (p < .05) and from 278 ± 77 to 441 ± 115 ml/min (p < .05), respectively. Femoral vein oxygen content was increased by milrinone from 7.9 ± 2.6 to 9.8 ± 3.0 ml/100 ml (p < .05) and was not changed by captopril. In seven additional patients, intravenous milrinone, administered at the peak effect of captopril, further augmented stroke volume index from 24 ± 6 to 32 ± 6 ml/m² (p < .05) and tended to reduce pulmonary capillary wedge pressure further from 20 ± 8 to 18 ± 9 mm Hg (p = NS). The addition of intravenous milrinone to captopril did not reduce mean systemic arterial pressure (71 ± 8 vs 71 ± 8 mm Hg) or significantly increase heart rate (89 ± 17 vs 92 ± 18 beats/min) when compared with captopril alone. Although renal blood flow was not further increased by the addition of intravenous milrinone to captopril, femoral vein oxygen content increased from 6.8 ± 1.9 to 9.9 ± 1.8 ml/100 ml (p < .05). Thus simultaneous administration of captopril and milrinone has synergistic effect on cardiac performance and complementary effects on the peripheral circulation.


RECENTLY, angiotensin-converting enzyme inhibition with captopril has been shown not only to improve short-term left ventricular performance but also to enhance long-term exercise tolerance in patients with chronic congestive heart failure during long-term therapy. Accordingly, therapy with captopril has gained wide acceptance for the treatment of congestive heart failure not controlled by digitalis glycosides and diuretics. However, in addition to the fact that some patients fail to benefit or have side effects from long-term captopril therapy that limit its efficacy, some patients with advanced heart failure also become increasingly symptomatic despite this therapy and thus may benefit from further inotropic support. Milrinone, a newly synthesized, selective phosphodiesterase inhibitor that exerts both positive inotropic and vasodilatory properties, can produce sustained improvement in cardiac performance in patients with refractory heart failure. In contrast to its precursor amrinone, milrinone, when administered over the long term, has not been complicated by side effects and thus may be more promising for the treatment of patients with congestive heart failure. This study was undertaken to compare the short-term effects of captopril and milrinone on cardiac performance and regional hemodynamics and to assess the hemodynamic safety and possible synergistic benefits of combined administration of captopril and milrinone in patients with severe heart failure.

Materials and methods

Patients. Sixteen men and two women with severe chronic congestive heart failure were studied (mean age 60 years, range 32 to 79). Ten had ischemic heart disease as documented on the basis of past myocardial infarctions or coronary arteriograms. Eight had cardiomyopathy of unknown origin. No patients had hypertension, recent myocardial infarction, or primary valvular disease.
disease. All patients were restricted in activity by fatigue and/or dyspnea, and not by angina, despite therapy with digitalis, diuretics, and long-acting nitrates. Mean digoxin level was 0.9 ng/ml (range 0.3 to 1.9). All patients were in functional class III or IV of the New York Heart Association for at least 3 months. All were in sinus rhythm except one patient, who was in atrial fibrillation. Their maximal oxygen uptake averaged 9.9 ml/kg/min (range 6.1 to 15.4). Left ventricular ejection fraction measured under resting conditions by gated nuclear scanning was below 20% in all patients.

The patients were admitted to the coronary care unit at least 24 hr before the hemodynamic evaluation. Long-acting nitrates were discontinued and a 2 g sodium diet was prescribed. The patients continued to receive their usual daily doses of digitalis glycosides and diuretics during the study. The nature, potential benefits, and possible risks of the study were explained to all patients, who then gave written informed consent. The study protocol was approved in advance by the Committee on Clinical Investigations of the Albert Einstein College of Medicine.

**Hemodynamic measurements.** After 24 hr of bedrest, patients underwent right heart catheterization performed with flow-directed, balloon-tipped, thermodilution catheters (Edwards Laboratories). Mean pulmonary arterial, pulmonary wedge, and right atrial pressures were recorded on a photographic recorder (Electronics for Medicine). Cardiac output was determined by the thermodilution technique with 5% dextrose in water and obtained in triplicate with less than 10% variation. Systemic arterial pressure was measured via an indwelling artery catheter. Mean systemic arterial pressure was obtained by electronic integration. Derived hemodynamic variables, including cardiac index, stroke volume index, and systemic vascular resistance, were calculated from standard formulas. An electrocardiographic lead was monitored throughout the study.

**Renal blood flow.** Renal blood flow was determined as the left renal venous blood flow by the continuous thermodilution technique and a No. 7F dual thermistor catheter (Webster Laboratories). The injection orifice is located 15 mm proximal to the distal end and on the concavity of the bend to prevent vascular wall contact with the opening obliquely oriented at 30 to 40 degrees against the blood stream to increase turbulence and to ensure optimal indicator/blood admixture. The external “dilution” thermistor is located 10 mm proximal to the injection orifice and the second “indicator” thermistor is within the catheter just proximal to the orifice. The catheter was introduced into the femoral vein via the Seldinger technique and advanced into the left renal vein under fluoroscopy. Optimal positioning within the renal vein was confirmed by injection of meglumine diatrizoate (Renografin) through the catheter, and determination of oxygen saturation of renal vein blood was done with samples withdrawn from the catheter. At the end of the study, the position of the catheter was reconfirmed by fluoroscopy. For each determination of blood flow, 5% dextrose at room temperature was infused through the catheter with a Harvard Pump (Model 921) at a constant rate of 50 ml/min until the resistance deflections of both thermistors were stable. A standard three-channel thermodilution Wheatstone Bridge (Webster Laboratories) was used to convert the resistance changes into calibrated voltages, which were recorded on photographic paper. Blood flow was then calculated with the formula derived by Ganz et al. with a modification to correct for thermodtransport within the Webster catheter at blood flow rate ranging from 300 to 1500 ml/min. Each measurement of left renal vein blood flow was made at least five times, and three determinations within 10% were averaged.

**Femoral vein oxygen content.** Retrograde catheterization of the femoral vein was also performed with an 18 gauge angiographic catheter introduced percutaneously and advanced 10 cm distally into the femoral vein. The catheter was used to withdraw blood samples while the patient was resting in a supine position. All samples were evaluated in triplicate for oxygen content (ml/100 ml) with a Lex O2-Con-TL oxygen analyzer (Lexington Instruments).

**Drug administration.** In the first 11 patients, evaluated in the postprandial state, 7.5 mg of milrinone and 12.5 mg of captopril were administered orally in variable order. Six patients received milrinone and then captopril, and five received captopril and then milrinone. Milrinone or captopril was first administered after two similar sets of control measurements were obtained 30 min apart. Systemic hemodynamic measurements were repeated at 30 min intervals for 2 hr and hourly thereafter until values returned to baseline levels. Renal blood flow and femoral vein oxygen content were measured at 30, 60, and 90 min. One of these measurements corresponded to peak increase in cardiac index in all patients. Two hours after return of the hemodynamic parameters to baseline levels, captopril or milrinone was administered and measurements were repeated as previously described. Renal and femoral vein catheters were removed immediately after completion of the study.

During the first day of the study, the remaining seven patients received an intravenous bolus of 25 μg/kg milrinone. Three patients who failed to demonstrate an increase in cardiac index of at least 20% received a second bolus of 50 μg/kg milrinone administered 3 hr after the initial one. On the second day of the study, captopril was administered after renal and femoral vein catheters had been inserted. Systemic hemodynamic measurements, renal blood flow, and femoral vein oxygen content were measured at 30, 60, and 90 min, with the last measurement corresponding to the peak increase in cardiac index in all patients. Milrinone was then administered intravenously at a dose identical to that given the day before. Ten minutes later, all measurements were repeated and femoral and renal vein catheters were removed.

**Statistical analysis.** The results are expressed as mean ± SD and were considered significant at p < .05. Comparison of the hemodynamic and metabolic effects of milrinone and captopril were made with a two-factor repeated measures analysis of variance. Comparisons of hemodynamic and metabolic parameters under the three treatment conditions (milrinone, captopril, and captopril plus milrinone) were performed with analysis of covariance.

**Results**

Milrinone, which was administered orally to 11 patients at a dose of 7.5 mg, produced a greater improvement in cardiac performance than did 12.5 mg of captopril, as documented by a greater stroke volume index (28 ± 7 vs 24 ± 7 ml/m²; p < .05) and similar decrements in pulmonary capillary wedge pressures (19 ± 10 vs 21 ± 7 mm Hg; p = NS) (figure 1). Mean systemic arterial pressure was significantly reduced by captopril from 84 ± 10 to 73 ± 11 mm Hg (p < .05) but was only modestly decreased by milrinone from 84 ± 10 to 80 ± 10 mm Hg (p = NS). Heart rate tended to decrease after captopril from 94 ± 15 to 91 ± 17 beats/min (p = NS) and was not changed by milrinone (93 ± 15 vs 94 ± 15 beats/min). Systemic vascular resistance significantly decreased with both captopril and milrinone from 1981 ± 416 to 1406 ± 251 dyne-
The increase in blood flow from 278 ± 366 ml/min/m² (p < .05) and from 1926 ± 418 to 1392 ± 362 ml/min/m² (p < .05) increased renal blood flow from 278 ± 77 to 441 ± 115 ml/min (p < .05) (figure 2). Milrinone increased renal blood flow from 289 ± 78 to 417 ± 111 ml/min (p < .05). The increase in renal blood flow after milrinone tended to be lower than that produced by captopril, although it did not reach statistical significance.

Of note was the observation that resting femoral oxygen content was unchanged by captopril (8.0 ± 2.8 vs 8.1 ± 2.4 ml/100 ml) but was increased by milrinone (7.9 ± 2.6 to 9.8 ± 3.0 ml/100 ml; p < .05).

An intravenous bolus of milrinone administered to seven patients at a mean dose of 36 µg/kg (range 25 to 50) increased stroke volume index from 20 ± 4 to 27 ± 4 ml/m² (p < .05) and decreased pulmonary capillary wedge pressure from 26 ± 7 to 20 ± 6 mm Hg (p < .05) (figure 3). Systemic vascular resistance decreased significantly from 1874 ± 389 to 1332 ± 129 dyne-sec-cm⁻⁵ (p < .05). The changes in systemic arterial pressure from 83 ± 12 to 84 ± 13 mm Hg and in heart rate from 89 ± 15 to 94 ± 18 beats/min were not statistically significant. In the same seven patients, captopril at an oral dose of 12.5 mg increased stroke volume index from 19 ± 5 to 24 ± 6 ml/min (p < .05) and decreased pulmonary capillary wedge pressure from 29 ± 9 to 20 ± 8 mm Hg (p < .05). Systemic arterial pressure and vascular resistance decreased significantly from 82 ± 9 to 71 ± 8 mm Hg (p < .05) and from 1926 ± 418 to 1392 ± 362 dyne-sec-cm⁻⁵ (p < .05), respectively. An identical intravenous bolus of milrinone administered at the peak hemodynamic effect of captopril increased stroke volume index further from 24 ± 6 to 32 ± 6 ml/m² (p < .05) and tended to decrease pulmonary capillary wedge pressure further.

**FIGURE 1.** Stroke volume index and pulmonary capillary wedge pressure in 11 patients during the control period (closed circles) and at maximum response (open circles). Values are mean ± SD at an oral dose of 7.5 mg of milrinone and 12.5 mg of captopril. *p < .05.

**FIGURE 2.** Maximal changes in cardiac index and renal blood flow after an oral dose of 7.5 mg of milrinone and 12.5 mg of captopril in 11 patients. Values are mean ± SD. *p < .05.
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FIGURE 3. Maximal changes in stroke volume index and pulmonary capillary wedge pressure during control period (closed circles) and at maximum response (open circles) to 12.5 mg of captopril and to an intravenous bolus of 36 μg/kg milrinone administered alone and at peak hemodynamic effect of captopril in seven patients. Values are mean ± SD. *p < .05.

From 20 ± 8 to 18 ± 9 mm Hg (p = NS). Systemic vascular resistance also decreased further after concomitant intravenous administration of milrinone from 1392 ± 362 to 1071 ± 283 dyne-sec-cm⁻³ (p < .05) when compared with captopril alone. Systemic arterial pressure and heart rate did not change (71 ± 8 vs 71 ± 8 mm Hg and 89 ± 17 vs 92 ± 18 beats/min). When compared with intravenous milrinone alone, the concomitant administration of captopril and intravenous milrinone also resulted in a greater stroke volume index (32 ± 6 vs 27 ± 4 ml/m²; p < .05), while pulmonary capillary wedge pressure tended to be lower (18 ± 9 vs 20 ± 6 mm Hg; p = NS).

Resting femoral vein oxygen content and renal blood flow were measured before oral administration of captopril, at peak effect of captopril, and after intravenous administration of milrinone (figure 4). Femoral vein oxygen content was unchanged by captopril (7.1 ± 1.5 vs 6.8 ± 1.9 ml/100 ml), but was increased by milrinone (9.3 ± 1.8 ml/100 ml; p < .05). Renal blood flow, which was increased by captopril (278 ± 63 to 403 ± 110 ml/min; p < .05), was not further enhanced by concomitant administration of milrinone (437 ± 123 vs 403 ± 110 ml/min; p = NS).

Discussion

In this study, milrinone produced a greater improvement in cardiac performance than captopril for a similar increase in renal blood flow. Resting limb blood flow was increased by milrinone but not by captopril. In addition, concomitant administration of captopril and milrinone was safe and resulted in synergistic effects on cardiac performance and complementary effects on the peripheral circulation.

FIGURE 4. Renal blood flow (RBF) and femoral vein oxygen content (FVO₂) during control, at maximal response to 7.5 mg of captopril, and after concomitant intravenous administration of milrinone at a mean dose of 36 μg/kg in seven patients. Values are mean ± SD. *p < .05.
After administration of 12.5 mg of captopril, our patients demonstrated an improvement in cardiac performance similar to that reported previously.\textsuperscript{2-4} In view of the flat dose-response curve to captopril, administration of higher doses would not have improved ventricular performance further, although the duration of action may have been prolonged.\textsuperscript{15} With oral milrinone, 7.5 mg now represents the starting dose and, as was demonstrated by Kubo et al.,\textsuperscript{16} a dose of 10 or 12.5 mg probably would have produced greater improvement in cardiac performance. Despite the relatively low dose used in this study, milrinone increased stroke volume index substantially more than angiotensin-converting enzyme inhibition with short-term administration of captopril, while left ventricular filling pressures were reduced to a similar extent by both pharmacologic interventions.

Milrinone improves cardiac performance by enhancing myocardial contractility and directly lowering cardiac afterload.\textsuperscript{7, 9, 17} The positive inotropic action of milrinone seems to be mediated by selective inhibition of a fraction III of cardiac phosphodiesterase that is specific for cyclic AMP.\textsuperscript{18} The vasodilating properties of milrinone most probably result from phosphodiesterase inhibition in the smooth muscle. In contrast, captopril improves cardiac performance only by lowering arterial impedance through inhibition of the production of angiotensin II and perhaps by additional mechanisms.\textsuperscript{19} The substantial fall in systemic arterial pressure that was observed only with captopril supports the potent arteriolar vasodilator effects of the latter drug.

The hemodynamic safety of short-term intravenous administration of milrinone at the peak hemodynamic effect of captopril was documented by the absence of further reduction in systemic arterial pressure and by the lack of excessive fall in left ventricular filling pressure when compared with captopril alone. The synergistic hemodynamic effect was demonstrated by the rise in stroke volume index, which was greater than that derived with either drug administered alone. We did not determine whether a similar synergistic effect of captopril and milrinone would have been observed at a higher dose of milrinone. This study has significant implications for the use of inotropic agents vs vasodilators for the treatment of patients with chronic congestive heart failure. Theoretically, enhancing myocardial contractility may have adverse effects on the rate of progression of the underlying disease\textsuperscript{20} and may have the potential for increasing malignant ventricular arrhythmias.\textsuperscript{21} Thus one might prefer to reduce arterial impedance with specific vasodilators such as captopril before mobilizing the entire contractile reserve available with higher doses of milrinone.\textsuperscript{17} In addition, the complementary effects of captopril and milrinone on the peripheral circulation further support combining the two agents.

Captopril did not alter resting femoral oxygen content. In patients lying supine, in whom lower limb oxygen consumption was presumably constant, an increase in femoral oxygen content would have occurred if captopril had increased blood flow to the limbs. Our findings corroborate with those of Faxon et al.,\textsuperscript{22} who found that captopril did not alter calf vascular resistance over the short term. In contrast, milrinone increased femoral vein oxygen content and thus presumably lowered limb vascular resistance flow at rest. Whether milrinone can cause short-term increased limb blood flow during maximal exercise is as yet not known. However, an increase in resting blood flow may have contributed to the delay in anaerobic metabolism induced by short-term administration of amrinone (the precursor of milrinone) during submaximal exercise.\textsuperscript{23} Such short-term improvement in submaximal exercise may explain the immediate clinical benefit noted during therapy with milrinone.\textsuperscript{7}

Both captopril and milrinone increased renal blood flow in our patients. However, the increase tended to be greater with captopril. Thus the ratio of the increase in renal blood flow and cardiac index was substantially higher for captopril as compared with milrinone (2.7 vs 0.9). In experimental preparations, short-term inhibition of the converting enzyme consistently increases renal blood flow.\textsuperscript{19, 24, 25} In patients with chronic congestive heart failure, the results are more controversial. Creager et al.\textsuperscript{26} showed that captopril increased renal blood flow by 60\%, which is identical to our findings. In contrast, Powers et al.\textsuperscript{27} failed to demonstrate an increase, and Mujais et al.\textsuperscript{28} even noted a decrease in renal blood flow at initiation of captopril therapy. As pointed out by Blythe,\textsuperscript{29} an excessive fall in systemic arterial pressure may, in certain instances, be responsible for a fall in renal blood flow. However, a difference in the methods used to determine renal blood flow may also help explain the discrepancy in results. Although the continuous thermodilution technique, as used in this study, allows instantaneous determination, clearance methods are not instantaneous and require a steady hemodynamic state for 60 to 160 min, which may not be present after administration of captopril. The increase in renal blood flow produced by milrinone is consistent with our prior data with amrinone\textsuperscript{20} but is at variance with the lack of changes in renal blood flow measured after 1 month of therapy.
with milrinone.* The lack of additional improvement in renal blood flow despite the further improvement in cardiac performance produced by intravenous administration of milrinone at the peak hemodynamic effect of captopril cannot be readily explained. The renal vasculature, which was already dilated by angiotensin-converting enzyme inhibition, may have been less sensitive to the vasodilating effect of milrinone. Consequently, the increase in cardiac output produced by milrinone may have been shunted to vascular beds where conductance could be improved, i.e., skeletal muscle. Such complementary redistribution of the increased cardiac output may be an important therapeutic benefit of combining therapy with captopril and milrinone.

References


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