Importance of Venodilatation in Prevention of Left Ventricular Dilatation After Chronic Large Myocardial Infarction in Rats: A Comparison of Captopril and Hydralazine

Thomas E. Raya, Richard G. Gay, Maria Aguirre, and Steven Goldman

In rats with large myocardial infarctions, we compared the effects of captopril, a presumed arterial and venous vasodilator, with hydralazine, which is thought primarily to be an arterial vasodilator. To determine if the effects of captopril were dependent on the pathophysiological consequences of heart failure, we also studied a group of noninfarcted rats treated with captopril. In noninfarcted rats treated with captopril, left ventricular (LV) systolic and mean aortic pressures decreased from 132±12 to 107±15 mm Hg and 122±1 to 100±2, respectively (p<0.01). In noninfarcted rats, captopril decreased LV weight, LV weight/body weight, and total heart weight/body weight but produced no effects on the peripheral venous circulation. Rats subjected to coronary artery ligation were selected by ECG criteria to have large myocardial infarctions and were treated for 4 weeks with captopril (n=8), hydralazine (n=5), or placebo (n=9). In infarcted rats treated with captopril, LV systolic, mean aortic pressures and LV end-diastolic pressure (LVEDP) decreased (p<0.01) from 115±4 to 86±3 mm Hg, 106±4 to 74±3 mm Hg, and 23±2 to 11±2 mm Hg, respectively. Mean circulatory filling pressure decreased (p<0.05) from 11.2±0.6 to 8.7±0.8 mm Hg and venous compliance increased (p<0.05) from 2.04±0.07 to 2.70±0.20 ml/mm Hg/kg. Blood volume decreased (p<0.05) from 67.3±0.9 to 58.2±1.8 ml/kg. At LVEDP recorded during the hemodynamic study, LV end-diastolic volume ("operating" LV end-diastolic volume) decreased (p<0.01) from 2.64±0.15 to 1.88±0.12 ml/kg. Hydralazine treatment decreased (p<0.01) LV systolic (91±3 mm Hg) and mean aortic (86±2 mm Hg) pressures, increased (p<0.05) LVEDP (27±2 mm Hg) but did not change mean circulatory filling pressure, venous compliance, blood volume, or operating LV end-diastolic volume. We conclude that in rats with heart failure, captopril, in addition to being an arterial vasodilator, produced venodilatation and decreased blood volume. Operating LV end-diastolic volume and LVEDP were decreased. These changes appear to be caused by the decrease in blood volume and venodilatation in combination with afterload reduction because hydralazine which has no effect on the venous circulation did not alter LVEDP or operating LV end-diastolic volume. (Circulation Research 1989;64:330–337)

The pathophysiology of heart failure includes activation of neurohumoral systems that produce alterations of the peripheral circulation.1–3 Recent data suggest that the renin-angiotensin axis, and possibly the sympathetic adrenergic nervous system, contribute to the increased systemic vascular resistance of heart failure.4–8 The magnitude of activity of these systems is related to the extent of left ventricular (LV) dysfunction.6 Vasodilator therapy is useful for the treatment of heart failure because antagonism of these vasoconstrictor responses leads to more favorable cardiac loading conditions and thus increased stroke volume and ejection fraction.9–14 In addition, LV dilation may be prevented, which could be the most important factor responsible for the beneficial effects of vasodilator drugs in heart failure. Several vasodilators have been shown to have beneficial effects on cardiac performance in patients with heart failure; these include captopril, hydralazine, prazosin, and combined hydralazine-isosorbide.
These drugs produce favorable effects on LV performance, in part, by their vasodilating actions in the arterial circulation. Arterial vasodilators reduce systemic vascular resistance and increase cardiac and stroke volume index.

These agents may also have effects in the venous circulation. The fact that captopril decreases LV end-diastolic pressure (LVEDP) has been offered as evidence of the effects of captopril on the venous circulation. The beneficial effects resulting from the addition of nitrates to arterial vasodilators has also been attributed to the effects of nitrates on the venous circulation. Definition of the effects of vasodilators on the venous circulation in terms of changes in LVEDP can result in confusion. For example, hydralazine, which presumably has no effect on the venous circulation, has been reported to decrease LVEDP and LV end-diastolic volume in patients with heart failure. Are these changes caused by effects of hydralazine on the venous circulation or does the decrease in afterload that results from hydralazine treatment produce a decrease in LVEDP and LV end-diastolic volume independent of effects on the venous circulation?

We have studied the chronic effects of captopril and hydralazine on the venous circulation by measuring mean circulatory filling pressure (MCFP) and venous compliance in rats with heart failure induced by myocardial infarction. LV pressures and volumes were also determined. We hypothesized that by comparison of the effects of treatment with captopril with the effects of treatment with hydralazine, we could demonstrate that the venodilating properties of captopril are primarily responsible for decreasing LVEDP and LV end-diastolic volume.

Materials and Methods

Myocardial infarction was produced in male Sprague-Dawley rats (175-275 g) with techniques similar to those described previously. In brief, the rats were anesthetized with methoxyflurane, and a left thoracotomy was performed. The heart was expressed from the thorax, and a ligature was placed around the proximal left coronary artery. After 3-5 weeks, rats were anesthetized with ether, and a micromanometer-tipped catheter (Millar Instruments, Houston, Texas) was inserted into the right carotid artery. The catheter was advanced into the aorta and then into the left ventricle for recording of pressures. With the rat lightly anesthetized and breathing spontaneously, recordings were made on a physiological recorder (model 2400, Gould Instruments Co, Cleveland, Ohio). This catheter was then exchanged for the polyethylene (PE) catheter described below.

Venous Compliance

MCFP and venous compliance were measured with techniques previously described. A tracheostomy was performed, and the rats were ventilated with a volume cycled respirator (Harvard Apparatus, South Natick, Massachusetts). The right carotid artery was cannulated with PE tubing, (0.58 mm i.d.) that was advanced to the region of the thoracic vena cava. Both catheters were fluid filled and connected to a solid state pressure transducer (Millar). A balloon-tipped catheter, prepared by connecting a latex balloon to PE tubing (0.58 mm i.d.), was inserted into the right atrium from the right external jugular vein.

Arterial and venous pressures were recorded and the means determined by electronic averaging. Heart rate was determined from the arterial pressure tracing. To measure plasma volume, a 0.5% (wt/vol) solution of Evans blue dye in a volume of 0.10-0.15 ml was injected via the venous catheter. Ten minutes later, a 0.3-ml arterial blood sample was obtained, and after centrifugation, the Evans blue dye concentration in the plasma was spectrophotometrically determined.

After the measurement of plasma volume, two or three determinations of the baseline MCFP were made. To measure MCFP, the balloon was inflated for 6-8 seconds to transiently arrest the circulation while arterial and venous pressures were recorded. The venous pressure reached a plateau pressure within 5-6 seconds of the inflation of the balloon, and the arterial pressure fell to a constant level in the same period.
To determine the MCFP-blood volume relation, MCFP was measured immediately after an increase or decrease in blood volume of 10% (6.2 ml/kg). Blood volume changes of 10%, rather than larger changes, were used to construct the MCFP-blood volume curves to limit the influences of reflex changes in venous tone, stress relaxation/reverse stress relaxation, and transcapillary fluid changes caused by the blood volume changes. Blood volume was immediately returned to baseline by reinfusion or withdrawal after the determination of MCFP. Blood volume changes were accomplished by rapid transfusion of fresh donor blood from another rat or bleeding through the arterial catheter and were completed so that MCFP was determined within 10 seconds of the initiation of the blood volume change. The order of blood volume change was random and two measurements of MCFP were made at each blood volume. The average value of MCFP at each blood volume was used for construction of the MCFP-blood volume curve for each rat. Effective vascular compliance was defined as the change in blood volume divided by the change in MCFP and therefore is equal to the reciprocal of the slope of this curve. The V0 was obtained for each rat by linear extrapolation of the MCFP-blood volume curve to MCFP=0. Between each determination of MCFP at least 7 minutes was allowed for pressures and heart rate return to baseline. Because arterial compliance is negligible relative to venous compliance in the rat, effective vascular compliance is essentially equal to venous compliance.

Isolated Left Ventricular Pressure-Volume Relation

Pressure-volume data were recorded with methods described previously. After completion of the venous compliance studies, potassium chloride was injected via the femoral venous catheter to arrest the heart in diastole. The heart was rapidly removed and the right ventricle was incised. A double lumen catheter, attached to a pressure transducer (Statham 23Id, Gould) and an infusion pump (Sage 341, Orion Research, Cambridge, Massachusetts), was passed into the left ventricle. The atrioventricular groove was identified, and a ligature was passed around the heart and tied to isolate the left atrium from the left ventricle. After gentle aspiration of the LV cavity to remove any residual blood and to reduce the pressure to -5 mm Hg, normal saline was infused at 0.70 ml/min into the suspended left ventricle, and pressures were recorded simultaneously. Saline was infused until the suspended left ventricle within 10 minutes after cardiac arrest. The remaining stiffness constants were determined by methods described previously. Pairs of simultaneous pressure-volume points (15 pairs for each pressure interval) were recorded, digitized, and stored. For pressures from 0 to 3 mm Hg, the relation between pressure and volume was linear and the slope of this relation was designated as K1. The stiffness constants K2 (2.5 to 30 mm Hg), the overall chamber stiffness constant; K3 (3 to 10 mm Hg); K4 (10 to 20 mm Hg); and K4 (20 to 30 mm Hg) were thus derived.

Statistical Analysis

All results are presented as mean±SEM. Statistical comparisons were made with unpaired t tests or Dunnett’s test for multiple comparisons against a single control after an analysis of variance demonstrated significant differences, as appropriate. Venous compliance and values for LV chamber stiffness constants were determined by regression analysis using the method of least squares.

Results

Forty-nine rats were studied. There were 10 rats in the noninfarcted group, 10 rats in the noninfarcted group treated with captopril, and seven rats in the group with small to moderate infarction.
Table 1. Heart Rate; Mean Aortic, Left Ventricular, and Right Atrial Pressures; and Indexes of Venous Tone in Noninfarcted Rats, Rats With Small to Moderate-Sized Infarctions, and Rats With Large Infarctions

<table>
<thead>
<tr>
<th></th>
<th>Noninfarcted (n=10)</th>
<th>Moderate infarcts (n=7)</th>
<th>Large infarcts (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>369±6</td>
<td>372±10</td>
<td>390±18</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>122±1</td>
<td>114±3*</td>
<td>106±4*</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>4±1</td>
<td>13±1*</td>
<td>23±2*</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>132±12</td>
<td>110±7*</td>
<td>115±4*</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>1.5±0.4</td>
<td>2.4±0.9</td>
<td>3.6±0.5†</td>
</tr>
<tr>
<td>Mean circulatory filling pressure (mm Hg)</td>
<td>6.8±0.9</td>
<td>8.2±0.5†</td>
<td>11.2±0.6*</td>
</tr>
<tr>
<td>Venous compliance (ml/mm Hg/kg)</td>
<td>3.3±0.34</td>
<td>2.63±0.58†</td>
<td>2.04±0.07*</td>
</tr>
<tr>
<td>Unstressed vascular volume (ml/kg)</td>
<td>33.7±5.1</td>
<td>37.0±6.1*</td>
<td>43.2±2.6*</td>
</tr>
<tr>
<td>Blood volume (ml/kg)</td>
<td>55.4±3.3</td>
<td>60.6±5.9†</td>
<td>67.3±0.9*</td>
</tr>
<tr>
<td>Plasma volume (ml/kg)</td>
<td>33.5±2.0</td>
<td>37.3±0.6†</td>
<td>42.3±0.5*</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>47±1</td>
<td>48±1</td>
<td>47±1</td>
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Values are mean±SEM. Rats were selected for small to moderate and large myocardial infarctions using ECG criteria. LVEDP, left ventricular end-diastolic pressure; LVSP, left ventricular systolic pressure.

*p<0.01 compared with noninfarcted rats.
†p<0.05 compared with noninfarcted rats.

Among rats selected for large infarction, there were nine rats in the control group, eight rats in the captopril-treated group, and five rats in the hydralazine-treated group. Histologically, all rats selected for small to moderate myocardial infarctions had histological evidence of infarction. Average infarction size was 30±4% (range 12-40%). Average infarction size in the three groups with large infarctions was 49±2%, 48±2%, and 50±3% in the control, captopril-treated, and hydralazine-treated groups, respectively.

Table 1 shows pressures and measurements of venous tone for noninfarcted rats and rats with two sizes of infarcts. There were no changes in heart rate, but as the size of the infarction increased, there were progressive decreases in LV systolic pressure and increases in LV end-diastolic and right atrial pressures. MCFP increased and venous compliance significantly decreased. Unstressed vascular volume, blood volume, and plasma volume all increased as the size of the infarct increased.

The hemodynamics, cardiac, and body weights for rats with large infarctions are shown in Table 2. There were no significant differences in heart rate among the three groups (control, captopril-treated, and hydralazine-treated). Mean aortic pressure and LV systolic pressure were decreased in both treatment groups. LVEDP was decreased in the captopril-treated group but was slightly increased in the hydralazine group. Right atrial pressure was decreased in the captopril-treated rats compared with control but not changed in the hydralazine-treated rats.

Body weight and LV weight were slightly increased in the hydralazine-treated group, but the LV weight-to-body weight ratio was not changed. Body weight, LV weight, and the LV weight-to-body weight ratio of captopril-treated rats were unchanged. However, total heart weight-to-body weight ratio was decreased in the captopril-treated group. Right ventricular weight was decreased in the captopril-treated group and unchanged by hydralazine treatment.

Table 3 summarizes the data derived from the ex
vivo LV pressure-volume relations in the noninfarcted rats, in rats with small to moderate infarctions, and in rats with large infarctions. In rats with small to moderate infarctions, \(K_0\), \(K_1\), and \(K_2\) were decreased, and LV end-diastolic volume was increased when compared with noninfarcted rats. In rats with large infarctions, \(K_0\) and \(K_1\) were decreased and LV end-diastolic volume was increased compared with noninfarcted rats. Captopril had no effect on any chamber stiffness constant or LV end-diastolic volume in noninfarcted rats (data not shown).

The data derived from the ex vivo LV pressure-volume relations in control and treated groups of rats with large infarctions are shown in Table 4. The stiffness constants in the captopril-treated rats with large infarctions demonstrated a tendency to decrease; however, the difference did not reach statistical significance. Left ventricular end-diastolic volume at the operating LVEDP was decreased 29% by captopril treatment. This reduction in LV end-diastolic volume was primarily the result of a decrease in LVEDP (Figure 1) since captopril treatment did not appear to shift the LV pressure-volume relation. These results are quantitatively similar to those of a recent study which examined the effects of captopril on the pressure-volume relation in rats with extensive (greater than 45% of the left ventricle) myocardial infarctions. Left ventricular end-diastolic volume at LVEDP was not changed by hydralazine treatment. There were no differences in any of the stiffness constants in the hydralazine-treated group compared with untreated rats.

The effects of captopril and hydralazine on venous tone and blood volume in rats with large infarctions are shown in Table 5. MCFP was decreased in the captopril-treated group, but there was no change in MCFP in the hydralazine-treated rats. Venous compliance was increased 32% in the captopril-treated group but was unchanged in the hydralazine-treated group. Blood volume was decreased approximately 14% in the captopril-treated rats but was unchanged by hydralazine therapy. Unstressed vascular volume was decreased proportionally to the decrease in blood volume in the captopril-treated group. These results show that the reduction in MCFP in the captopril-treated rats was a result of both a decrease in blood volume and an increase in venous compliance (Figure 2).

In noninfarcted rats treated with captopril (n=10), mean aortic and LV systolic pressures were decreased to 100±2 and 107±15 mm Hg, respectively (p<0.001). Heart rate (370±6 beats/min), LV end-diastolic pressure (3±1 mm Hg), and right atrial pressure (1.8±0.4 mm Hg) did not change. Captopril also produced a decrease in LV weight to 529±32 mg (p<0.05), a decrease in LV weight-to-body weight ratio to 1.71±0.28 mg/g (p<0.01), and a decrease in total heart weight-to-body weight ratio to 2.21±0.08 mg/g (p<0.01). Captopril treatment did not change MCFP (6.9±1.2 mm Hg), venous compliance (3.36±0.56 ml/mm Hg/kg), unstressed vascular volume (33.6±5.9 ml/kg), blood volume (54.6±1.1 ml/kg), plasma volume (32.6±0.7 ml/kg), or hematocrit (47±1). These data show that, in noninfarcted rats, captopril produced afterload reduction but had no effect on the venous circulation.

**Discussion**

The results indicate that captopril treatment decreased MCFP and blood volume while venous
compliance increased in rats with chronic LV dysfunction after myocardial infarction. These effects were associated with a significant reduction in LVEDP and LV end-diastolic volume. In hydralazine-treated rats, reduction of mean aortic pressure to a similar degree as with captopril treatment was not associated with decreased LVEDP or LV end-diastolic volume. Hydralazine treatment also failed to alter MCFP, blood volume, or venous compliance. In noninfarcted rats, captopril decreased mean arterial pressure but had no effect on LVEDP, LV end-diastolic volume, blood volume, or the venous circulation. These data suggest that the venodilating effects of captopril are apparent only in the pathophysiological state of heart failure.

Systemic venoconstriction has been previously demonstrated in this model of heart failure in which rats with large infarctions were used. It is now apparent the decrease in venous compliance is a continuum and appears to be related to the degree of LV dysfunction that occurs in this model of heart failure. The mechanism(s) whereby captopril increases venous compliance and decreases blood volume are not known. Since the renin-angiotensin-aldosterone axis is activated in heart failure, especially under conditions of advanced LV dysfunction, one mechanism whereby captopril might increase venous compliance may be related to its antagonism of the effects of angiotensin. Angiotensin is a potent arterial and venous vasoconstrictor. However, the circulatory responses that have been demonstrated with captopril may not be solely dependent on continuous inhibition of converting enzyme production of angiotensin. For example, it has been shown that brief restoration of the integrity of the renin-angiotensin system is not accompanied by a deterioration of hemodynamic effects in patients with heart failure. Converting enzyme inhibitors may increase circulating levels of bradykinin, by inhibition of the enzyme kinase II, which would result in venodilatation. It is also possible that captopril prevents sodium and water retention that is characteristic of advanced heart failure. The decrease in total body sodium may prevent accumulation of sodium and water in vessel

<table>
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<th>TABLE 5. Indexes of Venous Tone in Control, Captopril-, and Hydralazine-Treated Rats With Large Myocardial Infarctions</th>
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<tr>
<td>Control (n=9)</td>
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<tr>
<td>Mean circulatory filling pressure (mm Hg)</td>
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<td>Venous compliance (ml/mm Hg/kg)</td>
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<td>Unstressed vascular volume (ml/kg)</td>
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<td>Hematocrit</td>
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Values are means±SEM.
*p<0.05 compared with control rats.

FIGURE 1. The left ventricular pressure-volume relation of rats after large myocardial infarctions treated with captopril (○) and control (●). The captopril pressure-volume relation is shifted leftward toward the pressure axis, *p<0.01. The absolute operating volume shifted was 0.6–0.7 ml/kg.

FIGURE 2. Mean circulatory filling pressure (MCFP)-blood volume relation of rats after large myocardial infarctions treated with captopril (○) and control (●). In the captopril-treated rats, the MCFP-blood volume relation is shifted toward the pressure axis because of a decrease in blood volume and unstressed vascular volume. The slope of the line is decreased compared to the controls indicating increased venous compliance.
walls, a process that is felt to contribute to increased wall stiffness and decreased vascular compliance in chronic heart failure. In addition, the interaction between the renin-angiotensin system and the sympathetic nervous system, which results in a decrease in peripheral sympathetic tone, could also produce changes in venous compliance. Whatever the precise mechanism of action of captopril may be, these effects in the venous circulation lead to decreased LV volumes. A review of Figure 1 demonstrates that the operating LV end-diastolic volume is significantly decreased in captopril-treated rats, largely due to decreased LVEDP. A decrease in operating LVEDP in heart failure can lead to a decrease in wall tension developed in systole and to a subsequent decline in myocardial oxygen consumption.

Even though hydralazine has been shown to decrease systemic vascular resistance and increase stroke volume in heart failure, decreases in LV filling pressure have not been consistently demonstrated in either acute or chronic studies. There are few studies available that have explored the mechanism or extent of action of hydralazine on veins. In noninfarcted rats, hydralazine has no effect on the venous circulation. Hydralazine failed to inhibit portal vein tone even in high concentrations. When hydralazine is infused into the brachial artery and its effects on resistance and capacitance are measured by plethysmography, its predominant effect is to increase forearm blood flow while it produces smaller increments in forearm volume when compared with sodium nitrite. Our study shows that systemic venous compliance is likewise unchanged by hydralazine. In the model of heart failure used in the present study, hydralazine produced no discernible effects on the venous circulation. We attribute the failure of hydralazine to lower LV end-diastolic pressure or volume to the absence of any effect of hydralazine on the venous circulation.

The explanation for the differences between hydralazine and captopril on operating LV end-diastolic volume and LVEDP is complex. If hydralazine and captopril have similar effects on the arterial circulation and LV outflow impedance, then the differences that occurred in operating LVEDP and LV end-diastolic volume could have resulted because of changes in the venous circulation. For example, since venous compliance and total blood volume are unchanged with hydralazine, any increase in stroke volume will be shifted to the central blood volume and not stored in the venous circulation. Thus, ventricular filling will be increased. This was reflected in the increased LV end-diastolic pressure and volume found in the hydralazine-treated animals. In contrast, the decrease in blood volume and increased venous compliance found with captopril may result in a different response to any potential increase in stroke volume with captopril. A decrease in circulating blood volume would be expected to have a direct effect on LV diastolic volume if blood volume was not redistributed and was reduced throughout the entire circulation, proportionally. If the decrease in total blood volume was responsible for the change in LV end-diastolic volume, then we would have expected the operating volume to decrease approximately 0.37 ml/kg. The observed decrease in operating LV end-diastolic volume (0.6–0.7 ml/kg) was nearly twice greater. This suggests that half of the decrease in operating volume was not caused by the decrease in total blood volume. The decrease in the slope of the total vascular pressure-volume relation indicates that venous capacitance was increased. Therefore, the decline in LV end-diastolic volume and LVEDP can be attributed not only to decreased total blood volume but also to redistribution of blood volume, possibly to the venous reservoir.

There are limited data available that have directly measured changes in the systemic venous circulation produced by those vasodilator drugs that also have important effects on the arterial circulation. This is due in large part to the technical difficulties in measuring changes in the venous circulation. For example, when external reservoirs and open-chest preparations are used to document changes in the venous circulation, it is not possible to study lightly sedated or conscious animals. In addition, in the presence of cardiovascular pathology, the surgical instrumentation, and general anesthesia required for the reservoir studies could potentially affect the results. The studies in humans that have reported changes in venous tone have extrapolated alterations in ventricular filling pressures or limb pressure-volume relations to the systemic venous bed. Since ventricular filling pressure, right atrial pressure, or pulmonary artery wedge pressure are affected by heart rate, afterload, chamber stiffness, and inotropic state, as well as by venous tone, such extrapolations may not be valid. Likewise, measurement of the pressure-volume relation in an isolated limb may not reflect changes in the systemic venous circulation as a whole.

While the purpose of this study was to study the effects of captopril on the peripheral circulation and determine the mechanism(s) whereby captopril decreases LVEDP and end-diastolic volume in heart failure, the experimental design has allowed us to confirm and extend the observations of other investigators on the effects of captopril in noninfarcted rats. Captopril decreased mean arterial pressure; this was probably responsible for the decrease in LV weight and LV weight-to-body weight ratio in noninfarcted rats. Captopril treatment decreased right ventricular weight in animals with heart failure and had no effect on noninfarcted animals. Captopril also had no effect on LV volume or the pressure-volume relation in noninfarcted animals. We conclude that the effects of angiotensin converting enzyme inhibition on the venous circulation and blood volume is dependent on the unique pathophysiological milieu of heart failure.
Acknowledgments

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Key Words • converting enzyme inhibitor • heart failure • venous compliance • venuodilation • myocardial infarction
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