Central and Peripheral Hemodynamic Effects of Angiotensin Inhibition in Patients with Refractory Congestive Heart Failure

DAVID P. FAXON, M.D., MARK A. CREAGER, M.D., JONATHAN L. HALPERIN, M.D., HARALAMBOS GAVRAS, M.D., JAY D. COFFMAN, M.D., AND THOMAS J. RYAN, M.D.

SUMMARY The central and peripheral hemodynamic responses to the angiotensin-converting enzyme inhibitor teprotide (SQ20881) were simultaneously determined in 10 patients with severe, refractory congestive heart failure using Swan-Ganz catheterization and venous-occlusion calf plethysmography. Significant declines in mean arterial pressure (82.5 ± 4.9 to 67.1 ± 5.0 mm Hg [± SEM], p < 0.001), systemic vascular resistance (1787 ± 130 to 1272 ± 115 dyn-sec-cm−4, p < 0.001) and mean pulmonary capillary wedge pressure (26.8 ± 2.5 to 17.1 ± 2.5 mm Hg, p < 0.001) accompanied improvement in cardiac index (2.04 ± 0.17 to 2.47 ± 0.20 l/min/m2, p < 0.001). Reduction in mean right atrial pressure (9.8 ± 2.0 to 5.2 ± 1.8 mm Hg, p < 0.005) was not a result of limb venodilation, as calf venous capacitance did not change. The decrease in limb vascular resistance (76.6 ± 11.0 to 62.9 ± 10.7 units, p < 0.05) did not parallel the fall in systemic vascular resistance in either magnitude or duration (p < 0.05). Pulmonary arteriolar resistance was not appreciably changed.

Teprotide therefore reduces ventricular afterload and significantly improves cardiac function in patients with congestive heart failure. The greater change in systemic than in limb vascular resistance implies preferential redistribution of flow to other regions. These findings shed light upon the role of the renin-angiotensin system in the regulation of regional vasconstriction in congestive heart failure and suggest that teprotide may act as a unique "vasoreleaser" of pathophysiologic arteriolar constriction.

ELEVATION of systemic vascular resistance is associated with low-output cardiac failure and contributes to systolic ventricular wall tension (afterload). The rise in afterload may further increase myocardial oxygen consumption in the face of impaired cardiac function. Excessive diastolic ventricular distention (preload) may result, in part, from the status of the capacitance vasculature and further detract from cardiac performance. Vasodilator drugs have become promising adjuncts to the therapy of congestive heart failure, because reductions in ventricular preload and afterload accompanying their use can significantly improve cardiac function.

Although enhanced sympathetic nervous activity has been shown to limit vascular distensibility in congestive heart failure1, the renin-angiotensin-aldosterone system has also been implicated in the augmentation of vascular resistance in congestive heart failure. Because levels of plasma-renin activity vary in heart failure,2,3 efforts to define the roles of renin and angiotensin have awaited the development of a competitive antagonist of angiotensin II (saralasin)4 and inhibitors of angiotensin-converting enzyme (teprotide, captopril)5. Watkins et al.6 demonstrated in a low-cardiac-output canine model that arterial pressure was renin-dependent during the development of right-heart failure. We reported a patient with congestive heart failure attributed to renovascular hypertension and ischemic heart disease in whom saralasin increased cardiac output and reduced arterial pressure and left ventricular end-diastolic pressure.7 We and others8,9 have also shown in acute studies in patients with chronic refractory left ventricular failure that the converting-enzyme inhibitor teprotide reduces systemic vascular resistance, arterial pressure and left ventricular end-diastolic pressure, with significantly improved cardiac output.

While these studies clearly indicate that converting-enzyme inhibition reduces afterload, effects on the capacitance vessels were not examined and no clear understanding of a reduction in preload has been reported with the use of these agents. The present study was undertaken to examine the influence of converting-enzyme inhibition on the capacitance vessels of the lower extremity and to correlate these findings with the central hemodynamic effects known to occur in patients with refractory congestive heart failure. We also studied regional flow to the limb in light of the finding by Gavras and Liang10 of redistribution of regional blood flow after teprotide administration in normotensive, sodium-depleted dogs with enhanced flow to the cerebral, coronary and renal vascular circuits. As Mason11 pointed out, vasoconstriction in cardiac failure occurs differentially in the various regional circulatory beds. Accordingly, the reordering of territorial blood flow is pertinent to the therapy of congestive heart failure.

Methods

Ten patients with chronic congestive heart failure (New York Heart Association functional class III–IV) were admitted at least 48 hours before investigation. Clinical characteristics of the subject pop-
ulation are presented in table 1. The protocol was approved by the Institutional Review Board for Human Research, and informed consent was obtained from each subject. Vasodilator drugs and medications other than digitalis and clinically indicated antiarrhythmic agents were discontinued at least 24 hours before study. Dietary sodium was restricted to 2 g/day. Eight of the subjects underwent diagnostic cardiac catheterization and coronary and left ventricular cineangiography. In each such instance, converting-enzyme inhibition studies were deferred at least 24 hours, by which time resting hemodynamic measurements were similar to those obtained at catheterization before angiography.

Studies were conducted in the cardiac care unit where subjects underwent right-heart catheterization. Instrumentation Laboratories #7F Swan-Ganz thermodilution catheters were inserted by venous cutdown, and radial arterial cannulae were placed. Diuretics were withheld 24 hours before study. Pressures were recorded on a Hewlett-Packard multigraph recorder using Bentley model 508 strain-gauge pressure transducers. Mean pressures were obtained by electronic integration and the heart rate was determined from the simultaneously recorded ECG signal. The midaxillary line was defined as the zero-pressure reference level. Cardiac output was measured by the thermodilution technique using an Instrumentation Laboratories model 601 cardiac-output computer, taking the average of at least three separate determinations differing by less than 0.50 l/min.

The oxygen content of arterial blood was determined with a Lexington Instruments Company Lex-O₂-Con-TL analyzer. Plasma-renin activity was quantitated in peripheral venous blood by radioimmunoassay of angiotensin I generation13 and norepinephrine by a modified radioenzymatic assay.18

Venous-occlusion calf plethysmography was done by means of a circumferential Whitney mercury/Silastic strain gauge placed around the calf, connected to a modified Parks Electronics Laboratories model 270 plethysmograph in conjunction with a Hewlett-Packard multichannel recorder. Each subject was positioned with the leg bearing the plethysmographic apparatus elevated above the level of the heart. A sphygmomanometric cuff placed around the ankle was inflated to at least 50 mm Hg above systolic blood pressure during measurement of limb hemodynamics to exclude the foot vasculature. Venous occlusion was produced by sudden inflation of a 20-cm sphygmomanometric cuff placed at the thigh. The lowest venous occlusion pressure sufficient to elicit a maximum rate of circumferential calf enlargement was determined at the outset for each subject and

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### Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Ejection fraction*</th>
<th>Total teprotide dose (mg/kg)</th>
<th>Plasma renin activity Before (ng/mL/hr)</th>
<th>Plasma renin activity After (ng/mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>M</td>
<td>Ischemic cardiomyopathy with 3+ mitral regurgitation; CHF class IV; normotensive</td>
<td>0.36</td>
<td>0.25</td>
<td>13.0</td>
<td>58.0</td>
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<td>2</td>
<td>51</td>
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<td>Ischemic cardiomyopathy; CHF class III; normotensive</td>
<td>0.25</td>
<td>0.25</td>
<td>5.6</td>
<td>21.0</td>
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<td>3</td>
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<td>M</td>
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<td>0.38</td>
<td>0.75</td>
<td>—</td>
<td>—</td>
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<tr>
<td>4</td>
<td>59</td>
<td>M</td>
<td>Ischemic cardiomyopathy; CHF class IV; normotensive</td>
<td>—</td>
<td>0.88</td>
<td>42.0</td>
<td>118.0</td>
</tr>
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<td>5</td>
<td>57</td>
<td>M</td>
<td>Nonrheumatic mitral regurgitation with left ventricular dysfunction; CHF class IV; normotensive</td>
<td>0.41</td>
<td>1.00</td>
<td>1.1</td>
<td>2.3</td>
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<tr>
<td>6</td>
<td>43</td>
<td>M</td>
<td>Ischemic cardiomyopathy; CHF class III; hypertensive</td>
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<td>0.75</td>
<td>3.3</td>
<td>4.3</td>
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<td>7</td>
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<td>Hypertensive cardiomyopathy; CHF class III; normotensive</td>
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<td>0.75</td>
<td>27.0</td>
<td>74.0</td>
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<td>8</td>
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<td>0.50</td>
<td>14.0</td>
<td>90.0</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>M</td>
<td>Ischemic cardiomyopathy with 2+ mitral regurgitation; CHF class IV; normotensive</td>
<td>0.34</td>
<td>0.75</td>
<td>16.0</td>
<td>44.0</td>
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<tr>
<td>10</td>
<td>65</td>
<td>F</td>
<td>Ischemic cardiomyopathy with 2+ mitral regurgitation; CHF class IV; normotensive</td>
<td>0.31</td>
<td>1.00</td>
<td>11.2</td>
<td>102.0</td>
</tr>
</tbody>
</table>

* Determined in patients 2 and 7 by gated radionuclide technique, in patient 3 by echocardiography and in the remainder by contrast ventriculography.

Abbreviations: CHF = congestive heart failure.
averaged 42 mm Hg for the 10 patients. Limb arterial blood flow was derived from the rate of increase in calf circumference during venous occlusion and was expressed in ml/100 ml of limb tissue/min. Limb vascular resistance was calculated as the ratio of mean arterial pressure to blood flow and expressed in resistance units (mm Hg/ml per 100 ml of limb tissue/min). Limb venous volume was measured during inflation of the thigh cuff to 30 mm Hg above effective venous filling pressure; pressure was maintained at this level until graphic evidence of equilibration was achieved. Resultant venous capacitance was expressed in ml/100 ml of limb tissue.

Systemic, central and peripheral hemodynamic measurements were repeated until a basal state was demonstrated over at least three determinations 15 minutes apart. Plasma was sampled before treatment for measurement of plasma-renin activity and norepinephrine concentration. Teprotide (SQ20881), 0.25 mg/kg i.v., was then injected over a 1-minute period and central and peripheral hemodynamic measurements were serially obtained at 1/4, 1/2, 1, 1 1/2, 2, 3, 4 and 5 hours after the initial injection. To maximize hemodynamic effect, a second dose of teprotide, 0.25-0.75 mg/kg depending upon the initial blood pressure response, was given 30-45 minutes after the first. The total dose given each subject is indicated in table 1. Plasma-renin activity and norepinephrine concentration were again determined 1 hour after the initial administration of teprotide.

Hemodynamic indexes were derived from pressure and output data according to standard formulae. Systemic vascular resistance was calculated as SVR = (AP - RA)/cardiac output; total pulmonary resistance was derived as TPR = (PA)/cardiac output; pulmonary arteriolar resistance was derived as PAR = (PA - PCW)/cardiac output. All were expressed in dyn-sec-cm⁻⁵.

Data were pooled and analyzed by the paired t test, as well as through multiple analysis of variance, and expressed as mean ± SEM for 10 subjects. The F ratios for linear, quadratic and higher residual functions were comparatively evaluated. The Pearson product-moment correlation coefficient was computed for the peak effect along selected parameters. Statistical significance was accepted at the probability level of p < 0.05.

Results

The clinical characteristics of the patients studied are presented in table 1. Plasma-renin activity increased in all patients after teprotide administration. This rise is consistent with the known negative-feedback action of angiotension II on renal renin release. A direct correlation was identified between pretreatment plasma-renin activity and the magnitude of the decline in systemic vascular resistance (r = 0.63; p < 0.05) (fig. 1). Plasma-renin activity did not cor-

*AP denotes mean arterial pressure, RA mean right atrial pressure, PA mean pulmonary arterial pressure and PCW mean pulmonary capillary wedge pressure.

relate with other hemodynamic data. Plasma norepinephrine levels did not change significantly after teprotide from the mean pretreatment value of 0.290 ± 0.075 ng/ml. Control norepinephrine concentration did not correlate with alterations in systemic vascular resistance.

Systemic Hemodynamic Response (fig. 2)

Arterial blood pressure was reduced by teprotide in all 10 patients, nine of whom were initially normoten-

![Figure 1](https://example.com/figure1.png)  
**Figure 1.** Relationship between the pretreatment plasma renin activity and percent decrease in systemic vascular resistance after teprotide in nine patients with refractory heart failure. Plasma renin activity was not obtained in one patient.

![Figure 2](https://example.com/figure2.png)  
**Figure 2.** Systemic hemodynamic response to teprotide over a 5-hour period. Doses of teprotide are indicated by the arrows at 0 and 30 minutes. Results are mean ± SEM.
sive. Mean pressure decreased from the average pretreatment value of 82.5 ± 4.9 mm Hg to a nadir of 67.1 ± 5.0 mm Hg 1 hour after teprotide administration (p < 0.001) and returned toward baseline 5 hours after the initial dose. Declines in both systolic (15%) and diastolic (22%) pressures were statistically significant (p < 0.001).

Systemic vascular resistance fell substantially, from the elevated resting level of 1787 ± 130 to 1272 ± 115 dyn-sec-cm⁻² 15 minutes after administration of teprotide and remained significantly depressed throughout the monitoring period (p < 0.001).

Heart rate slowed from 83 ± 5 to 79 ± 6 beats/min (p < 0.005) and persisted for 5 hours after the first injection of teprotide. Cardiac index improved 21%, from a mean resting value of 2.04 ± 0.17 1/min/m² to a maximum of 2.47 ± 0.20 1/min/m² 15 minutes after teprotide injection, while stroke volume index increased 24% from 25.9 ± 3.1 to 32.2 ± 3.3 ml/beat/m²; increments in both indexes were significant (p < 0.001) and lasted for 5 hours.

Pulmonary and Right-heart Hemodynamic Responses

Figure 3 shows comparative data derived from right-heart catheterization. Mean pulmonary arterial pressure was reduced 19%, from 37.1 ± 2.8 mm Hg to a minimum of 29.9 ± 3.1 mm Hg 1 hour after the initial teprotide injection; this effect persisted throughout the period of observation (p < 0.005). Pulmonary capillary wedge pressure fell 36%, from an average pretreatment value of 26.8 ± 2.5 to 17.1 ± 2.5 mm Hg 1 hour after teprotide was given and did not return to initial levels by 5 hours (p < 0.001). Mean right atrial pressure decreased from an average of 9.8 ± 2.0 to 5.2 ± 1.8 mm Hg 1 hour after intervention (p < 0.005) but returned to baseline by 2 hours. Although the total pulmonary resistance decreased significantly by 1 hour after teprotide injection, from 909 ± 122 to 624 ± 95 dyn-sec-cm⁻³, and remained reduced (p < 0.025), direct pulmonary vasodilatation did not occur, as no change in pulmonary arteriolar resistance was recorded (p > 0.05). The oxygen content of arterial blood not change significantly after teprotide administration.

Limb Hemodynamic Response

Variations in peripheral hemodynamics, as assessed by calf plethysmography, are shown in figure 4. Before treatment, calf blood flow ranged from 0.87–4.33 ml/100 ml of limb tissue/min. The average value, 1.39 ml/100 ml/minute, was below values obtained in normal subjects in this laboratory (2–4 ml/100 ml/min). Calf blood flow was not significantly changed by teprotide despite improved cardiac output. Calculated limb vascular resistance diminished from an average initial value of 76.6 ± 11.0 units to a minimum of 62.9 ± 10.7 units 2 hours after drug injection, but returned to pretreatment levels by 5 hours (p < 0.05). Resting venous volumes averaged 1.07 ± 0.12 ml/100 ml of limb tissue, lower than the normal values in this laboratory (2–4 ml/100 ml of limb tissue). No significant variation in venous capacitance occurred with converting-enzyme inhibition.

Comparative Regional Hemodynamic Responses

Figure 5 compares the changes in systemic, pulmonary and limb vascular resistances 1, 2 and 4 hours after teprotide administration. The reduction in systemic vascular resistance was significant at each interval but greatest (29% below pretreatment levels) 1 hour after drug injection (p < 0.05). Pulmonary arteriolar resistance, in contrast, did not change significantly at any time. Limb vascular resistance was significantly reduced from baseline only at 2 hours (−19%, p < 0.05), with inconsistent and insignificant fluctuations 1 and 4 hours after teprotide administration.

**Figure 3.** Pulmonary and right-heart hemodynamic response to teprotide over a 5-hour period.

**Figure 4.** Limb hemodynamic response to teprotide over a 5-hour period.
While improved cardiac function might reduce sympathetic tone in congestive heart failure, the lack of change in plasma norepinephrine concentration suggests direct or indirect sympathetic agonistic effect. The recorded decrease in right atrial pressure in these patients may have resulted either from improved myocardial performance or from venodilatation in other regional capacitance beds.

Resting limb arterial blood flow averaged lower than normal in these patients, a phenomenon regularly described in patients with heart failure, and did not change appreciably after teprotide injection. A modest but statistically significant reduction in limb vascular resistance was transient and did not parallel the reduction in total systemic resistance in either magnitude or duration of effect. These findings suggest that the increased limb vascular stiffness in patients with congestive heart failure is not influenced by activity of the renin-angiotensin system. Zelis and Mason have shown that these changes may be due in part to augmented sympathetic tone and to increased sodium and water content of the arterial wall.

The effect of teprotide on limb vascular resistance contrasts with the actions of other vasodilator drugs. Miller et al. compared the influence of nitroprusside, phentolamine and nitroglycerin in patients with congestive heart failure and demonstrated reductions in both limb vascular resistance and venous tone. Comparison of proportionate decreases in limb vascular resistance and venous tone indicated a balanced effect on the resistance and capacitance vessels with nitroprusside. Phentolamine acted principally upon the resistance vasculature, while nitroglycerin expanded predominantly the capacitance circuit. Prazosin has recently been shown to reduce both forearm vascular resistance and venous tone in patients with congestive heart failure, but the latter effect apparently predominates. Hydralazine is known to affect only the resistance vasculature. Teprotide seems to differ from other vasodilator agents in that no limb venodilatation and limited reduction of limb vascular resistance occurred in these patients. Considering the potent vasoconstrictor effect of angiotensin, this finding appears paradoxical. Because total systemic vascular resistance decreased substantially after teprotide, arteriolar dilatation must have developed in other regional vascular beds.

Because pulmonary arteriolar resistance did not vary after therapy with teprotide, diminished pulmonary arterial pressure and total pulmonary resistance reflect improved left-heart diastolic pressures rather than direct pulmonary vasodilatation. This corroborates investigation with animal preparations in which infusion of angiotensin had little effect upon the isolated pulmonary vasculature despite the relatively high local concentration of converting enzyme in the microvessels in this region. The stability of arterial oxygen content after administration of teprotide argues against the development of significant pulmonary arteriovenous shunting, which has been shown with other vasodilator drugs.

These data indicate that converting-enzyme inhibi-

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**Discussion**

All patients studied had both clinical and hemodynamic evidence of severe congestive heart failure. After the administration of teprotide, there was a prompt (within 15 minutes) and sustained (up to 5 hours) reduction of systemic vascular resistance, pulmonary capillary wedge pressure and arterial blood pressure, with a consequent increase in cardiac index. These results and the demonstrated relationship between the decrease in systemic vascular resistance and the resting plasma-renin activity confirm reported observations. Right atrial mean pressure was significantly reduced in all patients, reflecting either improved left ventricular systolic emptying from reduction in aortic impedance or increased venous capacitance. Limb venous volume was unchanged after the administration of teprotide, even though these subjects had venoconstriction at rest.

Research has provided no consensus regarding the effect of angiotensin upon the veins of the extremities. Direct application of angiotensin to isolated vein segments has resulted in constriction, yet forearm venoconstriction persists only briefly after local intrarterial injection of angiotensin. Moreover, while angiotensin has been reported to reduce limb venous volume in normal subjects, other studies have found no change. In patients with congestive heart failure, improvement in cardiac output alone might be expected to result in reflex sympathetic withdrawal and consequent venodilatation, as shown by Mason and Braunwald in their studies using ouabain. Blockade of angiotensin-converting enzyme in the present investigation was not accompanied by such a response. This suggests that limb venoconstriction in congestive heart failure either is not mediated by reversible activity of the renin-angiotensin system or that teprotide itself may have some direct venoconstricting effect.
tion does not significantly increase regional flow to the limb or pulmonary circuit in patients with congestive heart failure. Regional redistribution of blood flow, however, has been verified in sodium-depleted dogs given tetroside, and flow to the renal, cerebral, myocardial and adrenal vasculature increased at the expense of cutaneous, skeletal muscular and hepatomesenteric flow. Renal blood flow has been shown to increase after angiotensin inhibition in sodium-depleted normal and hypertensive patients. Faxon et al. showed that coronary blood flow increases in relation to the resting plasma renin activity in normal subjects given tetroside. Possible mechanisms for this phenomenon of regional redistribution of flow after converting-enzyme inhibition include differences in tissue concentrations of converting enzyme or in local affinity of angiotensin II receptors. Central or autonomic neural control may also influence regional blood flow. Converting-enzyme inhibition may influence the tissue concentrations of bradykinin and prostaglandins.

Tetroside thus promotes ventricular afterload reduction and significantly improves myocardial function in patients with chronic, severe heart failure. Prolonged hemodynamic benefit followed intravenous administration of tetroside, without adverse effects. The data support a role for the renin-angiotensin system in the maintenance of systemic vasoconstriction and arterial pressure in congestive heart failure. The pronounced vasodilatation induced by tetroside involves no change in the status of limb capacitance vessels, indicating either little direct effect on preload or regionally distinct effects on capacitance vessels. The smaller decline in limb vascular resistance than in systemic vascular resistance and the lack of pulmonary arteriolar dilatation imply preferential redistribution of flow to other regions.

Converting-enzyme inhibitors are a unique class of vasodilator agents whose effects appear to differ from those of other known vasodilators in mode and site of action and, hence, might be better regarded as "vasoreleasers" of pathophysiologic arteriolar vasoconstriction. Further investigation with angiotensin inhibitors may enhance understanding of the pathophysiology of congestive heart failure and provide an innovative approach to the therapy of patients with refractory congestive heart failure.

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