Role of the Renin-Angiotensin System in the Systemic Vasoconstriction of Chronic Congestive Heart Failure

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SUMMARY  In 15 patients with severe chronic left ventricular failure, plasma renin activity (PRA) ranged widely, from 0.2–39 ng/ml/hr. The level of PRA was unrelated to cardiac output (CO) or pulmonary artery wedge pressure (PWP), but was slightly negatively correlated with mean arterial pressure (MAP) ($r = -0.45$) and systemic vascular resistance (SVR) ($r = -0.40$). After infusion of the angiotensin converting enzyme inhibitor teprotide (SQ 20,881) PWP fell from $26.3 \pm 1.3$ (SEM) to $20.3 \pm 1.4$ mm Hg ($P < 0.001$), CO rose from $3.94 \pm 0.23$ to $4.75 \pm 0.31$ l/min ($P < 0.001$), MAP fell from $87.5 \pm 3.8$ to $77.9 \pm 4.1$ mm Hg ($P < 0.001$) and SVR from $1619 \pm 148$ to $1252 \pm 137$ dyne-sec-cm$^2$ ($P < 0.001$). The fall in MAP and in SVR was significantly correlated with control PRA ($r = 0.68$ and $r = 0.58$, respectively). When subjects were divided on the basis of control PRA the hemodynamic response to teprotide was greatest in the high renin group. PRA rose after teprotide $(8.7 \pm 3.4$ to $7.9 \pm 7.7$ ng/ml/hr, $P < 0.05$) but plasma norepinephrine fell $(619.1 \pm 103.6$ to $449.7 \pm 75.7$, $P < 0.05$). The renin-angiotensin system thus appears to have an important role in the elevated SVR in some patients with heart failure. Chronic inhibition of converting enzyme should be explored as a possible therapeutic approach.

IN PATIENTS WITH LOW cardiac output (CO) due to heart failure, arterial pressure usually is supported by a rise in systemic vascular resistance. Several mechanisms could contribute to this systemic vasoconstriction, including neural, hormonal and structural factors. An understanding of the mechanism of the vasoconstriction of heart failure has taken on particular importance because of the recent interest in using vasodilator drugs in the treatment of left ventricular failure.$^1$

Increased activity of the renin-angiotensin (R-A) system has been demonstrated in clinical and experimental heart failure.$^{2,3}$ Since angiotensin is a potent vasoconstrictor substance,$^4$ enhanced renin activity in patients with heart failure could be an important factor in the systemic vasoconstriction.

The introduction of a competitive inhibitor of angiotensin II (saralasen)$^5$ and of a converting enzyme inhibitor (teprotide) which blocks the conversion of angiotensin I to angiotensin II$^6$ has provided fairly specific means of studying the activity of the R-A system. Johnson and Davis$^7$ found that normal dogs had no significant change in blood pressure after infusion of saralasen, whereas sodium-depleted dogs and those with low CO secondary to thoracic caval obstruction had significant lowering of blood pressure. Watkins et al.$^8$ used teprotide in a dog model of right-sided heart failure and found that the R-A system was important in maintaining arterial pressure early in the course of heart failure but not later, after plasma volume had re-equilibrated. Gavras et al.$^9$ described a patient with hypertensive heart failure in whom saralasen exerted a marked vasodilator effect.

Since saralasen has angiotensin-like agonist properties,$^{10}$ the hemodynamic response to this drug does not provide a precise assessment of the circulatory effects of inhibiting the R-A system. In contrast, the converting enzyme inhibitor teprotide (SQ 20,881) blocks much of the endogenous generation of angiotensin II without producing any direct vasoconstrictor effect of its own. In the present study we have evaluated the hemodynamic effects of teprotide in 15 non-hypertensive patients with severe left ventricular failure in an attempt to quantitate the role of the R-A system in the
maintenance of systemic vasoconstriction in this syndrome.

**Methods**

Studies were performed on 15 hospitalized patients with chronic congestive heart failure (table 1). Seven had the diagnosis of ischemic heart disease based on a previous documented myocardial infarction or coronary angiography. The other eight had cardiomyopathy without apparent ischemia. One (patient 10) had previously had an aortic valve prosthesis inserted for aortic insufficiency. The other seven had no known etiology for their myocardial disease. All patients had been symptomatic for at least six months and were on chronic treatment with digitalis and diuretics. Several had been previously treated with oral vasodilator drugs. Diuretics and vasodilators were withheld for at least 24 hours before study. Ten of the patients were assessed to be in class IV (New York Heart Association) heart failure and five in class III. The study protocol was approved by the Committee on the Use of Human Subjects in Research.

All patients were studied in the fasting state and in the supine position. After informed consent was obtained, right heart catheterization was performed using a #7 thermodilution Swan-Ganz flow-directed balloon-tipped catheter (Edwards Laboratories, Santa Ana, California) inserted percutaneously or by cut-down via an antecubital or femoral vein. The brachial artery was cannulated with a short Teflon catheter advanced over an 18-gauge thin-walled needle. Pressures were monitored with P23D Statham pressure transducers positioned at the midaxillary line and a Hewlett-Packard multichannel direct writing recorder. An ECG lead was monitored continuously during the study.

After the catheters were positioned the patients were allowed to rest for 1 hour before baseline data and blood samples were collected. Right atrial pressure (RAP), pulmonary arterial pressure (PAP) and pulmonary capillary wedge pressure (PWP) were then recorded. CO was determined in triplicate by the thermodilution technique using an Edwards 9510 thermodilution CO computer. Blood specimens were obtained for measurement of plasma renin activity (PRA) by the method of Sealey et al. and catecholamines by radioenzymatic assay (CAT-A-KIT, Upjohn Company, Kalamazoo, Michigan).

After baseline values were recorded and blood samples were drawn, 0.25 mg/kg teprotide (SQ 20,881, The Squibb Institute, Princeton, NJ) was diluted with sterile water and injected intravenously in about 1 minute. If after 20 minutes the PWP was reduced less than 40% from control pressure and systolic AP remained above 90 mm Hg, a second dose of 0.50 mg/kg teprotide was administered. This sequence was repeated at 30-minute intervals using 1 mg/kg and finally 2 mg/kg teprotide. Twenty minutes after the last dose of the drug, PAP, RAP, PWP, AP, and CO were recorded. Blood samples were drawn for determination of renin activity and catecholamines.

Intravascular pressures and CO were then monitored for an additional hour. Additional plasma for renin activity was withdrawn 4 and 24 hours after the peak teprotide dose.

Mean intravascular pressures were obtained by electronic integration and the following resistances in dyne-sec-cm\(^{-5}\) were calculated: systemic vascular resistance (SVR) = \(\frac{\text{CO}}{\text{AP} - \text{RAP}}\); pulmonary vascular resistance (PVR) = \(\frac{\text{CO}}{\text{AP} - \text{PWP}}\); and arteriolar resistance (PAR) = \(\frac{\text{PWP}}{\text{CO}}\) (fig. 1).

Statistical analysis was carried out using the paired \(t\) test.

**Results**

**Control Hemodynamics and Renin activity**

Resting arterial pressure varied widely. One patient had a slightly elevated arterial pressure at the time of study (172/102 mm Hg), while in four others the systolic arterial pressure was 100 mm Hg or less. The PWP was elevated in all patients, averaging 26.3 mm Hg (table 2). CO varied from 2.6–5.9 l/min (average 3.9 l/min) and cardiac index varied from 1.5–2.8 l/min/m\(^2\) (average 2.06 l/min/m\(^2\)). SVR averaged 1619 dyne-sec-cm\(^{-5}\); PVR averaged 851 dyne-sec-cm\(^{-5}\) and PAR 568 dyne-sec-cm\(^{-5}\).

PRA ranged from 0.2–39 ng/ml/hr, and averaged 8.7 ng/ml/hr. A slight negative correlation was apparent between PRA and mean arterial pressure \((r = -0.45)\) and between PRA and SVR \((r = -0.40)\) (fig. 1). CO was not related to control PRA \((r = 0.19)\).

**Response to Teprotide**

At peak effect of teprotide there were significant decreases in RAP, PAP, PWP, and AP (table 2). Heart rate fell slightly, but the change was not statistically significant. The CO rose by an average of 21% \((P < 0.001)\), while SVR was reduced by an average of 23% \((P < 0.001)\). PVR fell 31% \((P < 0.001)\) and PAR fell by 11% (NS).

The fall in arterial pressure and in SVR in response to teprotide were significantly correlated with control PRA \((r = 0.68\) and \(r = 0.58\), respectively) (figs. 1 and 2). The rise in CO was weakly related to PRA \((r = 0.38)\). When subjects were divided arbitrarily into three groups on the basis of control PRA, the hemodynamic response was greatest in the highest renin group (fig. 3).

PRA increased after teprotide from an average of 8.7 to 37.9 ng/ml/hr \((P < 0.05)\). The rise appeared to be greatest in subjects with high control PRA (fig. 4). The effect of the teprotide gradually waned, but at 1 hour after the final injection MAP and PWP were still significantly lower than in the control period (fig. 5). PRA, however, remained markedly elevated 4 hours after teprotide administration (average 51.0 ± 12.6.
ng/ml/hr) and was still higher than control levels 24 hours after injection (average 23.9 ± 8.3 ng/ml/hr, P < 0.02).

No side effects were detected after administration of teprotide. Even in patients exhibiting a prominent fall in arterial pressure, there were no untoward symptoms.

Catecholamines

Plasma norepinephrine concentration in the control period averaged 620 pg/ml. This control level was not correlated with control PRA (r = 0.01). After teprotide, plasma norepinephrine fell significantly to an average of 450 pg/ml (P < 0.05) (table 3).

Discussion

In the present study most normotensive or modestly hypotensive patients with chronic left ventricular failure exhibited vasodilation in response to the administration of converting enzyme inhibitor. Although teprotide inhibits the degradation of bradykinin as well as blocking the generation of angiotensin II, previous studies have suggested that its acute hemodynamic effects are due predominantly to a fall in circulating levels of angiotensin II. The fall in SVR in these patients with heart failure was significantly correlated with the control PRA, but a role for kinin-induced vasodilation cannot be excluded.

These data therefore suggest that the R-A system plays a role in supporting the SVR in heart failure. The mechanism of the stimulation of renin in heart failure is not entirely known. A reduction in renal perfusion, stimulation of renal sympathetic nerves, increased circulating catecholamines, or alteration in the sodium load presented to the macula densa, all could be involved.

The sympathetic nervous system could enhance renin release either through a hemodynamic effect on the renal vasculature or by direct neural or humorally mediated stimulation. It is notable, therefore, that circulating norepinephrine levels were not closely correlated with PRA in these patients with heart failure. Consequently, it must be assumed either that sympathetic nervous system stimulation is not the major factor stimulating renin release in the setting of clinical heart failure or that the circulating level of catecholamines provides an unreliable guide to activity of the sympathetic nervous system.

The wide range of values for PRA in this group of

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Table 1. Clinical Findings in 15 Patients with Congestive Heart Failure

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>BSA (m²)</th>
<th>Diagnosis</th>
<th>Previous drug therapy</th>
<th>NYHA Class</th>
<th>AP (mm Hg)</th>
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<tr>
<td>1</td>
<td>60/M</td>
<td>1.88</td>
<td>IHD</td>
<td>Digoxin, furosemide</td>
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<td>108/60</td>
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<td>99/63</td>
</tr>
<tr>
<td>3</td>
<td>49/M</td>
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<td>Digoxin, furosemide</td>
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<td>38/M</td>
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<td>CM</td>
<td>Digoxin, hydralazine</td>
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<td>6</td>
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<tr>
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<td>Digoxin, furosemide</td>
<td>3</td>
<td>130/73</td>
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Abbreviations: BSA = body surface area; IHD = ischemic heart disease; CM = nonischemic cardiomyopathy; AP = arterial pressure at the time of study; ISDN = isosorbide dinitrate; NGO = nitroglycerin ointment.
patients with heart failure is unexplained. The level of PRA appeared to be unrelated to the severity of the heart failure as assessed by CO, PWP or SVR. Since diet was not controlled in these patients and diuretics had been administered to some up to 24 hours before study, varying states of sodium balance must be considered as a factor in the variation in PRA. However, in contrast to sodium-restricted or diuretic-treated normal subjects in whom renin rises because of volume depletion, these patients with congestive heart failure were not hypovolemic. PWP was markedly elevated in all of them, RAP was elevated in all but one, and pulmonary congestion and peripheral edema were present in most. Therefore, it is unlikely that previous diet or diuretic therapy had a dominant effect on the level of PRA in these subjects or on their response to teprotide. Nonetheless, further studies of the effect of salt intake and treatment on the PRA in congestive heart failure are needed.

The fall in SVR in response to teprotide is consistent with a reduction in circulating angiotensin II levels. The rise in CO is typical of the response to non-specific vasodilator drugs in patients with heart failure.26 The fall in RAP, though modest, is greater than is seen when comparable patients are given hydralazine, a drug that is devoid of a systemic venodilator effect.26 Therefore, the response suggests a modest venodilator effect of teprotide. Since angiotensin appears to lack a significant venoconstrictor action,27,28 the apparent venodilator effect could be attributed to the concomitant fall in circulating norepinephrine levels noted in these patients. Indeed,
Figure 1. Relationship between control plasma renin activity (PRA) and mean arterial pressure (MAP) before and after administration of teprotide in 15 patients with heart failure. Control arterial pressure is slightly negatively correlated with MAP \( r = -0.45 \). The fall in MAP is generally greater in subjects with high PRA.

Figure 2. Relationship between control plasma renin activity (PRA) and the percent change in systemic vascular resistance (SVR) after administration of teprotide.
FIGURE 3. Hemodynamic response to teprotide in three patient subgroups based on control plasma renin activity (PRA) (1, PRA < 3 ng/ml/hr; 2, PRA 3–16 ng/ml/hr; 3, PRA > 16 ng/ml/hr). Hemodynamic response is greatest in group 3. MAP = mean arterial pressure; CO = cardiac output; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance.

FIGURE 4. Plasma renin activity before (C) and 20 minutes after peak dose of teprotide (T). Mean and SEM shown by brackets.

This fall in circulating catecholamines could also contribute to the arteriolar dilating effect of the teprotide infusion and the tendency for cardiac slowing.

The mechanism of the fall in norepinephrine levels after teprotide is unknown. The R-A system has been shown in animal models to activate the sympathetic nervous system both centrally29, 30 and peripherally.31

**Table 3. Effect of Teprotide on Plasma Norepinephrine (pg/ml)**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Control</th>
<th>Teprotide</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>281</td>
<td>278</td>
</tr>
<tr>
<td>4</td>
<td>475</td>
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<td>644</td>
<td>153</td>
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<td>11</td>
<td>1623</td>
<td>1078</td>
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<tr>
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<td>737</td>
<td>711</td>
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<td>14</td>
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<td>394</td>
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<tr>
<td>15</td>
<td>760</td>
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<td>Mean</td>
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<td>449.7</td>
</tr>
<tr>
<td>SEM</td>
<td>103.6</td>
<td>75.7</td>
</tr>
</tbody>
</table>

$p < 0.05$
It is therefore possible that reduced circulating levels of angiotensin II resulted in a reduced release of norepinephrine. The baroreceptors also regulate sympathetic nervous system activity. In normal subjects a vasodilator-induced fall in arterial pressure would be expected to result in reflex sympathetic stimulation. This expected reflex response does not occur after vasodilator administration in heart failure, possibly because augmented stroke volume stimulates the baroreceptor with an altered pulsatile pressure wave. Indeed, heart rate often falls during vasodilator treatment of heart failure, thus suggesting that sympathetic outflow may be paradoxically inhibited.

The present data therefore suggest that a converting enzyme inhibitor may be an effective vasodilator in at least some patients with heart failure. The recent synthesis of an orally effective inhibitor of converting enzyme makes it likely that chronic blockade of angiotensin II generation will be possible. On the basis of the present preliminary observations, further exploration of the therapeutic potential of inhibiting angiotensin effect in selected patients with heart failure is justified.

Acknowledgment

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References

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Angiotensin Converting Enzyme Inhibition in Patients with Congestive Heart Failure

HARALAMBOS GAVRAS, M.D., DAVID P. FAXON, M.D., JOHN BERKOBEN, M.D., HANS R. BRUNNER, M.D., AND THOMAS J. RYAN, M.D.

SUMMARY The etiology of afterload elevation in congestive cardiac failure is unclear, but experimental evidence suggests a role for the renin-angiotensin system in maintaining elevated peripheral vascular resistance. The angiotensin converting enzyme inhibitor SQ20,881 was administered to eight patients with congestive cardiac failure (four hypertensives, four normotensives) during or one day after diagnostic cardiac catheterization. Various hemodynamic measurements performed before and during blockade indicate that this agent caused improvement in cardiac function in all patients by decreasing afterload. This improvement correlated with the decrease in total vascular resistance but was independent of the baseline blood pressure and plasma renin activity. These results suggest that inhibition of angiotensin converting enzyme is a worthwhile approach to the treatment of congestive heart failure, although its exact mechanism of action remains unclear.

THE ROLE OF THE renin-angiotensin system in congestive cardiac failure is not fully understood. This condition is usually characterized by decreased cardiac output and increased left ventricular end-diastolic pressure accompanied by raised peripheral resistance. Measurements of plasma renin activity and angiotensin in experimental or clinical heart failure have yielded conflicting results, with reports of either high, normal or low levels.1-4 A recent experimental study5 seemed to reconcile these contradictory findings by using angiotensin blockade in different stages of congestive cardiac failure. The data have suggested that the renin-angiotensin system remained activated only when circulatory impairment was severe or compensation was inadequate. Thus, uncompensated cardiac failure, like other low cardiac output states, may exhibit elevated plasma renin activity leading to raised peripheral vascular resistance in order to maintain effective arterial pressure. However, the resulting increased impedance to left ventricular outflow could, conceivably, further depress cardiac performance.6 Elimination of angiotensin in this case might induce a fall in peripheral vascular resistance resulting in left ventricular unloading and thus constitute a rational form of therapy.

In this study, we studied the effects of angiotensin blockade by the converting enzyme inhibitor SQ20,881 (teprotide) on cardiovascular hemodynamics in eight patients — four hypertensive and four normotensive — undergoing conventional medical therapy for congestive cardiac failure and varying degrees of coronary insufficiency.

Methods

Patients with recent severe congestive heart failure were studied either at the time of diagnostic cardiac catheterization (six patients) or the day after catheterization in the coronary care unit (two patients). All patients received conventional doses of digitalis and diuretics. Vasodilating agents were withheld for 48 hours. They were maintained on a 2,000 mg NaCl diet. At the time of the study their functional class ranged from II–IV. Indications for catheterization included evaluation of valvular heart disease, left ven-
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