Renin-Angiotensin System Inhibition in Acute Myocardial Infarction in Dogs

Effects on Systemic Hemodynamics, Myocardial Blood Flow, Segmental Myocardial Function and Infarct Size

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SUMMARY Acute left anterior descending coronary artery occlusion was produced in 21 conscious, chronically instrumented dogs. Forty minutes after coronary occlusion, nine dogs were given i.v. teprotide, 25 μg/kg/min, followed by oral doses of captopril, 10 mg/kg every 6 hours for 24 hours. The remaining 12 dogs served as saline-infused controls. In all dogs, acute coronary occlusion increased plasma renin activity and peripheral vascular resistance and reduced cardiac output, but did not change mean aortic blood pressure significantly. Teprotide significantly (p < 0.05) decreased peripheral vascular resistance (from 3804 ± 1158 to 2876 ± 816 dyn-sec-cm⁻²) (± SD) and mean aortic pressure (from 117 ± 12 to 107 ± 15 mm Hg), and increased cardiac output (from 2.63 ± 0.67 to 3.12 ± 0.74 l/min). Teprotide also produced a relative increase in flow to the renal and splanchnic circulations compared with the saline-treated controls. There were, however, no differences in segmental systolic shortening, blood flow in the normal or ischemic myocardium, or infarct size. These results indicate that the renin-angiotensin system may play an important role in dogs with acute coronary occlusion and that blockade of this system lowers systemic blood pressure and improves cardiac output. However, direct effects of renin-angiotensin system blockade on the myocardium are lacking; there were no changes in myocardial blood flow, myocardial mechanics or infarct size.

THE EXTENT to which the renin-angiotensin system participates in the hemodynamic response to acute myocardial ischemia is unknown. Acute systemic hypoxia elevates plasma renin activity and alters hemodynamic responses, and converting-enzyme inhibition attenuates the hemodynamic responses during severe hypoxia.¹ Recently, the major focus of interest in the effect of the renin-angiotensin system on hemodynamics has been during acute and chronic congestive heart failure.²⁻¹² Most reports conclude that after converting-enzyme inhibition, hemodynamic improvement occurs in both acute and chronic congestive heart failure.

During acute myocardial infarction, plasma catecholamines are elevated.¹³ Sympathetic stimulation of the renin-angiotensin system triggers the release of renin into the peripheral circulation. However, whether renin plays a role during acute coronary ischemia is unknown. Angiotensin increases coronary vascular resistance,¹⁴ but whether converting-enzyme inhibition alters coronary flow during acute ischemia is not known. Ertl et al.¹⁵ showed that infarct size was reduced by converting-enzyme inhibition in barbiturate-anesthetized dogs and attributed this effect to an increase in collateral flow and afterload reduction. However, anesthesia may by itself activate the renin-angiotensin system,¹⁶ suggesting interpretation of these results difficult.

The purpose of the present study was to evaluate the effects of converting-enzyme inhibition on global and regional cardiac performance, myocardial blood flow and peripheral tissue perfusion in a conscious canine model of myocardial infarction.

Methods

Adult healthy dogs were surgically prepared as follows. The heart was exposed by thoracotomy after anesthesia with i.v. pentobarbital, 25 mg/kg, and the dog was ventilated with room air by respiratory pump. After the pericardium was opened, a 3.5-mm balloon occluder (R.E. Jones) was placed along a dissected portion of the left anterior descending coronary artery distal to the first diagonal branch. Tygon catheters (1.02 mm i.d.) were inserted by direct puncture into the aorta, the main pulmonary artery and left atrium. Ultrasonic crystals (5 MHz) were implanted in the subendocardium through epicardial incisions in the zone of potential ischemia (ischemic zone), in the border zone and in a nonischemic control zone, as previously described.¹⁸ The chest was then closed and all wires and catheters were exteriorized. The dogs were allowed to convalesce for 2 weeks while receiving a normal diet supplemented by salt tablets (NaCl, 1 g/day) to prevent sodium depletion.

On the day of study, all dogs were mildly sedated with morphine sulfate (0.5 mg/kg, i.m.) and placed in a lateral decubitus position. Under local anesthesia with 0.5% lidocaine (Xylocaine, Astra Pharmaceutical Products), a micromanometer-tipped catheter (Millar Instruments, Inc.) was advanced through a femoral artery into the left ventricular cavity and a #7F catheter was fluoroscopically placed through a jugular vein into the coronary sinus. Catheters from the coronary sinus, left atrium and aorta were connected to Statham P23Db pressure transducers and a Brush multi-
channel recorder for measuring pressures. The Millar catheter also was connected to the Brush 480 recorder to measure left ventricular pressure and its rate of rise (dP/dt) by electronic differentiation. The ratio of left ventricular dP/dt to a developed left ventricular pressure of 50 mm Hg (left ventricular dP/dt/P) was calculated as described previously.19 Ultrasonic crystals were calibrated. Percent systolic shortening, defined as ([EDL - ESL]/EDL) x 100 (where EDL is end-diastolic segment length and ESL is end-systolic segment length), were determined as previously described.18 The ultrasonic instrument generates a voltage linearly proportional to the transit time of an acoustic impulse traveling at the sonic velocity of 1.5 x 10^6 mm/sec between the piezoelectric crystals. The location of the crystals was confirmed at autopsy.

Cardiac output was determined by injecting indocyanine green dye (Cardio-Green, Hynson, Westcott and Dunning, Inc.) into the pulmonary artery and sampling from the aorta using a Gilford model 140 dye-dilution cardiac output system (Gilford Instrument Laboratories, Inc.). Total peripheral vascular resistance was calculated by the conventional formula. Organ blood flows were determined using radioactive microspheres, 15 ± 3 μm in diameter, suspended in a 10% dextran solution containing 0.01% Tween-80 and labeled with cerium-141, tin-113 or scandium-46 at a specific activity of 10 mCi/g. After vigorous agitation and sonication, 0.6–1.0 million microspheres were injected before coronary occlusion and 1.2–1.6 million microspheres during occlusion into the left atrium, followed by a bolus injection of 10 ml of normal saline. Arterial blood sampling at a rate of 7.75 ml/min from the aorta was begun 10 seconds before microsphere injection and was continued for 80 seconds after injection for flow reference.

During the control period, three or four measurements were made 5 minutes apart to assure hemodynamic stability. At this time, baseline blood flows were measured by the radioactive microsphere method. Blood samples also were collected from the aorta and the coronary sinus to determine plasma renin activity by radioimmunoassay.20 The balloon occluder was then fully inflated with the same volume of saline that produced myocardial cyanosis at surgery. Hemodynamics and myocardial segmental function were measured serially 10, 20, 25, 30, 35 and 40 minutes after coronary occlusion. Regional blood flows and plasma renin activity of aortic and coronary sinus blood were again measured 35–40 minutes after occlusion. Beginning 40 minutes after occlusion, normal saline or the converting-enzyme inhibitor teprotide,21 25 μg/kg/min, was infused into a peripheral vein by a Harvard infusion pump at a rate of 0.19 ml/min while coronary occlusion was maintained. Thereafter, serial measurements were recorded every 5 minutes for 60 minutes. At 60 minutes of ischemia, a third set of radioactive microspheres was injected, and samples for plasma renin activity were collected from the coronary sinus and aorta. An oral dose of the converting-enzyme inhibitor captopril,22 10 mg/kg, was then administered.

With the balloon occluder still inflated, the monitoring equipment was disconnected and the dogs were returned to their cages. Two additional doses of captopril (10 mg/kg) were administered at 8-hour intervals after the hemodynamic study (total 30 mg/kg).

The effectiveness of teprotide and captopril in inhibiting converting enzyme was verified by measuring the mean aortic pressure response to (1-Asp, 5-Ile) angiotensin I (Schwartz/Mann Div., Becton, Dickinson and Company), 1 μg i.v., given before and 20 minutes after the beginning of teprotide infusion and again 24 hours after coronary artery occlusion. An ECG was taken to confirm the presence of ventricular tachycardia, which is a constant feature of experimental canine myocardial infarction in the first day after infarction.23 The dogs were then killed with a lethal dose of pentobarbital and the hearts were excised. The balloon occluder was confirmed to have remained inflated at this time. The region of myocardium at risk during ischemia was determined by injecting Monastral dye (E.I. du Pont de Nemours & Co., Inc.) directly into the coronary arteries.19 Monastral pigments were suspended in a mixture of dextran 70 and normal saline solution (Macrodex; Pharmacia Laboratories, Inc.) and agitated before use. Catheters were placed in the left anterior descending artery at the site of occlusion and at each coronary ostium. The catheter in the left anterior descending coronary artery was perfused under a pressure of 100 mm Hg with 1% Monastral red. A 0.5% Monastral blue solution was perfused simultaneously at 100 mm Hg into the ostial catheters. After 15 minutes, the left ventricle (including the interventricular septum) was isolated, weighed and then transected into 7–10-mm sections. Each was then weighed and photographed. The area stained red by the Monastral pigments was demarcated on each photograph. These areas represent regions of ischemic risk zone. Each section was subsequently immersed in a solution of nitroblue tetrazolium heated to 38°C until discrete areas of stained (viable) and unstained (infarcted) tissue were observed. The sections were rephotographed from the apical and basal views. The total area, region at ischemic risk and area of infarction were measured by planimetry. The areas from each tissue section were determined by an average of the basal and apical views. The total mass of infarction and the mass at ischemic risk were determined by summing the product of weight (Wt) of each section and the fractional area of each section representing infarction (I) or region of ischemic risk (R), using the following formulas: total infarct size = Σ (I x Wt); total risk zone = Σ(R x Wt).

Afterwards, a transmural block of tissue was removed from each zone in which segment length was measured. Each block was bisected into epicardial and endocardial units weighing 0.7–1.2 g each. The remainder of the left ventricle, brain, lungs, kidneys, liver, stomach, small intestine, large intestine, pancreas, spleen, adrenal glands, femoral muscle, skin and femur were cleaned, weighed and processed for radioactivity counting by a Packard gamma spectrometer.
and multichannel analyzer (Packard Instrument Co., Inc.). Regional blood flows were determined by the reference sample method with a PDP-11 minicomputer (Digital Equipment Corporation). Total left ventricular blood flow was determined as previously described. Myocardial blood flow was corrected for microsphere washout after ischemia in the border and ischemic zones.

Statistical Analysis

The results are reported as mean ± SD. Statistical differences were determined by two-way analysis of variance for two independent groups with repeated measures. Significant differences from control values were calculated by Dunnett’s test for each group. Statistical significance of differences between two means was determined by two-tailed t test. Values were considered significant if p < 0.05.

Results

Hemodynamic Responses to Acute Coronary Artery Occlusion and Teprotide Administration

Twenty-one dogs were studied; nine received converting-enzyme inhibitors and 12 served as controls. In the group that received teprotide, acute coronary artery occlusion decreased cardiac output but did not affect aortic blood pressure (fig. 1). Plasma renin activity increased in both aortic and coronary sinus blood after coronary artery occlusion. Infusion of teprotide 40 minutes after acute coronary artery occlusion increased cardiac output toward preocclusion values, decreased mean aortic blood pressure, and increased plasma renin activity further. Plasma renin activity, however, did not differ between arterial blood and coronary sinus blood. Teprotide significantly reduced the converting-enzyme activity, as evidenced by the finding that angiotensin I increased mean aortic pressure 21 ± 4 mm Hg before teprotide but only 1 ± 2 mm Hg after teprotide (p < 0.001). Arterial plasma renin activity also increased in the group receiving normal saline after coronary artery occlusion (4.1 ± 3.1 to 6.5 ± 2.9 ng/ml/hour; t = 3.27, p < 0.01), but, unlike that in the teprotide group, did not increase further after administration of normal saline (7.9 ± 3.3 ng/ml/hour). Normal saline did not affect the pressor response to angiotensin I (increase in mean aortic pressure before and after normal saline, 23 ± 8 vs 22 ± 5 mm Hg).

Other hemodynamic changes are listed in table 1. Because the values remained relatively steady between 10 and 40 minutes after coronary artery occlusion, the average values of the six measurements were taken for statistical analysis and are reported as “occlusion” data. Similarly, the four repetitive measurements taken during teprotide or saline infusion were averaged and given in table 1. As in the teprotide group, cardiac output fell after acute coronary artery occlusion in the normal saline group, but in contrast to the results with teprotide, remained significantly lower than control values after saline infusion. Acute coronary artery occlusion also increased heart rate and left atrial pressure and decreased left ventricular dP/dt and dP/dt/P. These changes were similar in the two groups and were not affected by teprotide or saline infusion. Total peripheral vascular resistance increased after coronary artery occlusion. This increase was abolished by teprotide infusion, but not by normal saline.

Myocardial Wall Systolic Shortening

The effects of coronary artery occlusion and teprotide infusion on myocardial segmental systolic shortening are listed in table 2. In the control zone, there were no significant changes in systolic shortening after coronary occlusion in either group or after teprotide or saline infusion. Both the border and ischemic zones showed a significant decrease in systolic shortening after coronary occlusion. The infusion of teprotide after occlusion did not alter the depressed systolic performance in either segment. The saline controls showed changes similar to those in the teprotide-treated group during this same time after occlusion. The loss of systolic shortening was much greater in the
TABLE 1. Systemic Hemodynamic Effects of Coronary Artery Occlusion and Teprotide in Conscious Dogs

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats/min)</th>
<th>Mean aortic blood pressure (mm Hg)</th>
<th>Cardiac output (l/min)</th>
<th>Left atrial pressure (mm Hg)</th>
<th>Left ventricular dP/dt (mm Hg/sec × 10^-3)</th>
<th>Total peripheral vascular resistance dyn/sec/cm^-5 × 10^-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n = 9; 18 ± 4 kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>97 ± 15</td>
<td>112 ± 12</td>
<td>3.10 ± 0.86</td>
<td>5 ± 3</td>
<td>3.38 ± 0.68</td>
<td>54 ± 8</td>
</tr>
<tr>
<td>Occlusion</td>
<td>102 ± 21</td>
<td>117 ± 12</td>
<td>2.63 ± 0.67*</td>
<td>9 ± 5*</td>
<td>2.94 ± 0.49</td>
<td>47 ± 6*</td>
</tr>
<tr>
<td>Occlusion + teprotide</td>
<td>107 ± 21*</td>
<td>107 ± 15</td>
<td>3.12 ± 0.74*</td>
<td>9 ± 5*</td>
<td>2.96 ± 0.54</td>
<td>49 ± 5*</td>
</tr>
<tr>
<td>Group 2 (n = 12; 17 ± 5 kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>99 ± 24</td>
<td>118 ± 17</td>
<td>3.22 ± 0.76</td>
<td>5 ± 7</td>
<td>3.15 ± 0.69</td>
<td>51 ± 12</td>
</tr>
<tr>
<td>Occlusion</td>
<td>114 ± 26*</td>
<td>126 ± 14</td>
<td>2.77 ± 0.79*</td>
<td>8 ± 5*</td>
<td>2.82 ± 0.55</td>
<td>47 ± 10*</td>
</tr>
<tr>
<td>Occlusion + saline</td>
<td>117 ± 35*</td>
<td>124 ± 14</td>
<td>2.64 ± 1.04*</td>
<td>9 ± 7*</td>
<td>2.76 ± 0.37</td>
<td>45 ± 11*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
* p < 0.05 vs preocclusion control.
† p < 0.05 vs occlusion values.

ischemic zone than in the border zone in both groups. These differences reflect the greater reduction of blood flow into the ischemic region (table 3).

Myocardial Blood Flow

Myocardial blood flow in the control zone was normal during coronary occlusion in both teprotide and saline groups and was unaffected by teprotide or saline infusion (table 3). Border zone blood flow fell significantly after coronary artery occlusion in both groups, and the normal endocardial-to-epicardial blood flow ratio was reversed. During the teprotide infusion, blood flow to the border zone was not altered further. The saline control group continued to show similar reductions. Myocardial blood flow decreased markedly in the ischemic zone of both groups after coronary artery occlusion. As in the border zone, teprotide infusion had no effect, and serial measurements of flow in saline controls also remained constant.

Regional Blood Flows

Forty minutes after acute coronary artery occlusion, blood flow was reduced (p < 0.05) to the kidneys (from 541 ± 117 to 450 ± 123 ml/100 g/min) and splanchnic beds (from 71 ± 30 to 59 ± 24 ml/100 g/min), but did not significantly change in other regional vascular beds. Subsequent infusion of teprotide for 20 minutes was associated with a small increase in renal and splanchnic flow, whereas dogs given saline showed a further small decrease in renal and splanchnic flow. The differences in these responses between the two groups, analyzed as percent change before and after the infusion, were significant (fig. 2). Such differences were not noted for the total ventricle or brain flow (fig. 2) or for any other regional circulations.

Infarct Size

On the second day of the experiments, ECG recordings showed that all dogs had ventricular tachycardia. Administration of 1 μg of angiotensin I caused no pressor response (0 ± 4 mm Hg) in the dogs that received teprotide and captopril. In contrast, angiotensin I increased mean aortic blood pressure by 20 ± 6 mm Hg in the dogs that received normal saline.

At autopsy, left ventricular weight did not differ

TABLE 2. Effects of Coronary Artery Occlusion and Teprotide on Myocardial Segmental Systolic Shortening

<table>
<thead>
<tr>
<th></th>
<th>Control zone (%)</th>
<th>Border zone (%)</th>
<th>Ischemic zone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>12 ± 6</td>
<td>11 ± 6</td>
<td>13 ± 7</td>
</tr>
<tr>
<td>Occlusion</td>
<td>12 ± 5</td>
<td>7 ± 4*</td>
<td>2 ± 6*</td>
</tr>
<tr>
<td>Occlusion + teprotide</td>
<td>12 ± 5</td>
<td>8 ± 3*</td>
<td>2 ± 7*</td>
</tr>
<tr>
<td>Group 2 (n = 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>11 ± 4</td>
<td>12 ± 6</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>Occlusion</td>
<td>11 ± 7</td>
<td>7 ± 6*</td>
<td>2 ± 5*</td>
</tr>
<tr>
<td>Occlusion + saline</td>
<td>10 ± 4</td>
<td>7 ± 7*</td>
<td>2 ± 4*</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
* p < 0.05 vs preocclusion control.
between the group treated with teprotide and captopril (86 ± 17 g) and the control group (79 ± 10 g). Infarct size was 16 ± 9 and 15 ± 9 g in the two groups, respectively. Infarct size constituted 18 ± 8% of the left ventricular weight and 59 ± 8% of the risk zone in the treatment group, and 17 ± 9% of the left ventricular weight and 58 ± 18% of the risk zone in the control group. None of the differences between groups were statistically significant.

**Discussion**

The renin-angiotensin system is activated in a variety of circulatory stress states and clinical syndromes, including sodium deprivation, hypoxia, and congestive heart failure. These states influence the secretion of renin by the renal juxtaglomerular apparatus by acting upon the renal arteriolar receptors or by renal sympathetic stimulation. The present study shows that acute coronary artery occlusion also activates the renin-angiotensin system, as indicated by elevation of plasma renin activity. The renin-angiotensin system also appears to play a role in maintaining peripheral vascular resistance and systemic arterial pressure after acute coronary occlusion, as both decreased after blockade of the converting enzyme using teprotide. Activation of the renin-angiotensin system, however, probably does not cause significant positive inotropic and chronotropic effects on the heart, because neither left ventricular function, as assessed by left ventricular dP/dt, dP/dt/P and segmental systolic shortening, nor heart rate changed significantly after converting-enzyme inhibition.

The renin-angiotensin system may be activated by hemodynamic and neurohumoral changes brought about by acute coronary occlusion. The hemodynamic effects of left anterior descending coronary artery occlusion in the conscious dog include reduction in cardiac output and an increase in left ventricular filling pressure. Systemic arterial blood pressure is usually well maintained because peripheral vascular resistance increases. The decline in cardiac output and the increase in left ventricular filling pressure due to myocardial ischemia, and further evidence for this decline is shown by the fall in left ventricular dP/dt and dP/dt/P. The rise in systemic vascular resistance has been ascribed to activation of the sympathoadrenal system. The further observation that acute coronary occlusion in conscious dogs is accompanied by reduction in regional blood flow to the kidneys and splanchnic circulation, a finding confirmed in the present study, is also consistent with sympathetic vasoconstriction. In addition, occlusion of the left anterior descending coronary artery in anesthetized dogs increases renal sympathetic nerve activity. Both the renal sympathetic stimulation and decrease in renal blood flow could have been responsible for the renin-angiotensin system activation. The exact cause of this sympathoadrenal discharge, however, is uncertain. It may be due to activation of the arterial baroreceptors or to direct release of catecholamines by the ischemic myocardium.

In addition to the generalized heightened sympathetic activity and reduction in renal blood flow, changes in low-pressure receptors in the right or left atrium or in left ventricular stretch receptors may influence renin release from the kidneys. Left ventricular receptors activated during coronary ischemia are selectively influenced by the coronary artery occluded: occlusion of the left anterior descending coronary artery increases renal sympathetic nerve activity, whereas circumflex artery occlusion does not. However, the increase in left atrial mean pressure or activation of stretch receptors by dyssynergic bulging of the ischemic ventricular myocardium would suppress renin release rather than facilitate it.

Our measurements of plasma renin activity in the arterial and coronary sinus blood did not show local renin release from the heart before or after coronary occlusion. Nevertheless, the finding that peripheral plasma renin activity increased after coronary artery occlusion provides another possible mechanism for the sympathoadrenal stimulation, because angiotensin II may act on the central vasomotor neurons to cause adrenergic discharge and on postsynaptic sympathetic neurons to facilitate norepinephrine release and inhibit norepinephrine reuptake.

The possibility that the reductions in renal and splanchnic flow observed in the present study are not caused by sympathetic vasoconstriction but, instead, are mediated wholly or in part by activation of the renin-angiotensin system and an increase in circulating levels of angiotensin II, must also be considered. Angiotensin II is a potent vasoconstrictor; our previous studies have shown that converting-enzyme blockade

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**Table 3. Effects of Teprotide on Myocardial Blood Flow after Acute Myocardial Infarction**

<table>
<thead>
<tr>
<th>Group 1 (n = 9)</th>
<th>Control zone</th>
<th>Border zone</th>
<th>Ischemic zone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Epicardium</td>
<td>Endocardium</td>
<td>Epicardium</td>
</tr>
<tr>
<td>Occlusion</td>
<td>97 ± 30</td>
<td>130 ± 42</td>
<td>67 ± 42*</td>
</tr>
<tr>
<td>Occlusion + t</td>
<td>97 ± 33</td>
<td>130 ± 39</td>
<td>66 ± 33*</td>
</tr>
<tr>
<td>Group 2 (n = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion</td>
<td>102 ± 24</td>
<td>140 ± 33</td>
<td>61 ± 39*</td>
</tr>
<tr>
<td>Occlusion + s</td>
<td>112 ± 28</td>
<td>150 ± 30</td>
<td>70 ± 36*</td>
</tr>
</tbody>
</table>

Values are mean ± SD. Myocardial blood flows are ml/100 g/min.

*p < 0.05 vs control zone blood flow.
with teprotide during activation of the renin-angiotensin system by either salt-deprivation or hypoxia reduced vascular resistance and increased blood flow to the renal and splanchnic circulations. These changes occurred independent of sympathoadrenal stimulation. In the present experiments, converting-enzyme blockade produced a relative increase in flow to the renal and splanchnic circulations, compared with the controls (fig. 2). The results suggest that the initial reduction in regional flow after coronary occlusion could have been caused, at least in part, by increases in circulating levels of angiotensin II.

Angiotensin II also constricts the coronary vasculature, yet no increase in coronary blood flow to either nonischemic or ischemic myocardium was noted in our present experiments after converting-enzyme inhibition. In normal myocardium, however, the predominant factor that controls myocardial blood flow is the level of myocardial oxygen demand, which is in turn controlled by myocardial work load. Neurohormonal effects upon coronary blood flow are likely to be dominated by changes in hemodynamic state. Our inability to demonstrate effects of converting-enzyme inhibition on coronary blood flow may also have been conditioned by the degree of activation of the renin-angiotensin system. We previously showed that teprotide infusion increased coronary blood flow in salt-depleted dogs. The level of plasma renin activity attained was 19.4 ng/ml/hour, roughly three times the values observed in the present study. These findings may also explain the difference between our study and that of Ertl et al., who noted an increase in ischemic zone blood flow after administration of a smaller i.v. dose of captopril in barbiturate-anesthetized dogs with coronary occlusion. The basal levels of plasma renin activity before coronary artery occlusion were high in these dogs. Barbiturate anesthesia is a potent stimulator of renin release, and the vasodilator effects of converting-enzyme inhibitors are potentiated by anesthesia. In conscious, sodium-replete dogs, however, converting-enzyme inhibition has no effect on renin release or systemic hemodynamics.

We also noted no effect of converting-enzyme inhibition on the size of the ischemic risk region or infarct size 24 hours after coronary occlusion. This finding apparently contrasts with the results of Ertl et al., who noted an increase in ischemic zone flow after occlusion with captopril, and attributed this to an improvement in collateral flow and afterload reduction resulting from converting-enzyme inhibition. Again, the discrepancy may relate to the use of barbiturate anesthesia in the latter study. In addition, the salt supplements in our present experiments may have suppressed renin release. Coronary artery occlusion could produce a greater increase in plasma renin activity in salt-depleted dogs, and inhibition of the renin-angiotensin system might result in significantly greater hemodynamic changes and increased myocardial blood flow. Whether converting-enzyme inhibitors reduce infarct size in salt-depleted dogs is not known.

There is much evidence that the acute hemodynamic effects produced by inhibition of converting enzyme in states of renin-angiotensin system activation are due in large measure to reduction in circulating levels of angiotensin II. However, converting enzyme also participates in the degradation of bradykinin, a circulating polypeptide with marked vasodilator properties. Efforts to document a physiologic role for bradykinin in contributing to the vasodilatory effects of converting-enzyme inhibition have been hampered by the rapid degradation of circulating bradykinin. It has also been suggested that prostaglandins function as mediators of vasodilator prostaglandins. The ultimate role of bradykinin and prostaglandins in these experiments remains to be determined.

In summary, converting-enzyme inhibitors reduced arterial pressure and increased cardiac output in the present experiments, as in clinical congestive heart failure. These changes occurred even though the degree of cardiac decompensation was modest, due to relatively small size of the experimental infarcts. The results suggest that converting-enzyme inhibitors may have a role in treating heart failure associated with myocardial infarction. However, the effects appear to be exerted primarily upon the peripheral circulation, and there is no evidence of a direct effect upon myocardial performance, perfusion or infarct size in the intact, conscious dog with coronary artery occlusion. Thus, converting-enzyme inhibitors may have no advantage over other vasodilators, which would equally decrease peripheral vascular resistance and increase cardiac output, and could at the same time increase blood flow to ischemic myocardium.

Acknowledgment

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