Modulation of Sympathetic Coronary Vasoconstriction by Cardiac Renin-Angiotensin System in Human Coronary Heart Disease

Antonio Saino, MD; Guido Pomidossi, MD; Rodolfo Peroni, MD; Alberto Morganti, MD; Lucia Turolo, PhD; Giuseppe Mancia, MD

Background—In humans, angiotensin II enhances the sympathetic coronary vasoconstriction elicited by the cold pressor test (CPT) and diving. Whether this enhancement depends on the circulating angiotensin II or on the locally produced angiotensin II is unknown, however.

Methods and Results—We addressed this issue in 14 patients with severe coronary artery disease by evaluating the effects of a 2-minute CPT (n=14) and a 30-second dive (n=8) on mean arterial pressure (MAP, arterial catheter), heart rate (ECG), coronary sinus blood flow (CBF, thermodilution technique), and coronary vascular resistance (MAP/CBF ratio). The 2 stimuli were applied at the end of left intracoronary infusion of either saline or benazeprilat diluted at the concentration of 25 mg/mL. The rate of benazeprilat infusion had been preliminarily demonstrated to reduce angiotensin II concentration in the coronary sinus without affecting its arterial concentration. The changes in MAP and heart rate induced by CPT and diving were superimposable during saline and benazeprilat infusions. The decrease in CBF induced by CPT and diving during saline infusion was changed into an increase during benazeprilat infusion with a significant attenuation of the coronary vasoconstrictor response.

Conclusions—In patients with coronary artery disease, an attenuation of sympathetic coronary vasoconstriction can be obtained by reducing cardiac angiotensin II formation without involving circulating angiotensin II. This suggests a role of the tissue renin-angiotensin system in modulating autonomic cardiac drive in humans. (Circulation. 2000;101:2277-2283.)

Key Words: circulation • nervous system, sympathetic • renin • angiotensin • coronary disease

In subjects with mild coronary atherosclerotic lesions, the intracoronary infusion of angiotensin II at doses devoid of systemic and local hemodynamic effects enhances coronary vasoconstriction induced through activation of the sympathetic nervous system by the cold pressor test or diving. Furthermore, in patients with severe coronary atherosclerosis, the sympathetic coronary vasoconstrictor responses to these stimuli are attenuated after an oral dose of an ACE inhibitor. Thus, the renin-angiotensin system exerts an important facilitating action on sympathetic vascular modulation of the human heart, which can be offset by reduction of angiotensin II production.

No information exists as to whether the renin-angiotensin system affects sympathetic influences on coronary vasomotor tone exclusively through circulating angiotensin II or through the local production of this substance. This is an important question because animal and human studies have provided evidence that angiotensin II can indeed be produced in the heart. Furthermore, data from isolated perfused rabbit hearts have shown that the cardiac effects of sympathetic stimulation are attenuated by ACE inhibition, which means that the cardiac production of angiotensin II might have a functional role. Finally, ACE inhibitors are known to differ in their ability to affect the tissue production of angiotensin II and thus presumably for their interference with any local angiotensin II modulation of sympathetic influences.

In the present study, we have examined the role of local angiotensin II on sympathetic cardiac influences by evaluating, in patients with severe coronary atherosclerosis, the effects of the intracoronary infusion of benazeprilat on the coronary vascular responses to the sympathetic activation induced by the cold pressor test and diving. The dose of benazeprilat infused was such as to reduce angiotensin II in the coronary sinus without affecting its arterial concentration.

Methods

Population
We studied 14 male patients (mean age [±SD] 59.5±9.6 years) who underwent cardiac catheterization because of anginal chest pain and myocardial ischemia detected at exercise stress test and/or thallium scintigraphy. No patient had history, clinical, or laboratory evidence of valvular heart disease, previous myocardial infarction, or conges-
tive heart failure, and none had hypertension, diabetes mellitus, or other major noncardiovascular diseases.

For all patients, the recruitment criterion was represented by the presence of a significant (≥75%) stenosis of the left anterior descending coronary artery, whereas occlusion of this artery and/or a stenosis of the left main trunk represented exclusion criteria. The hemodynamic and angiographic data obtained in each patient are reported in Table 1. All patients agreed to participate in the study after explanation of its nature and purpose. The protocol of the study was approved by the ethics committee of our institution.

**Measurements**

Arterial blood pressure was measured through the 8F arterial sheath used to perform coronary angiography through connection with an MX8004 Medex pressure transducer (Medex Medical Inc). Heart rate was calculated as the reciprocal of the R-R interval (ECG lead). Coronary blood flow was measured by a 7F Wilton-Webster thermodilution catheter inserted percutaneously into an antecubital vein and guided under fluoroscopy to lie deep within the coronary sinus. The position of the catheter was checked at the beginning of the study by injection of a small bolus of contrast medium (ipamidol 75.5 g/100 mL) and confirmed periodically thereafter to ensure that no displacement had occurred with respect to the surrounding reference points. Blood flow measurements were obtained by the continuous thermodilution method described by Ganz et al.,9 that is, by infusing a 5% glucose solution kept at room temperature at a rate of 1 mL/s through the catheter tip and sampling the temperature of the venous blood by a thermostor closer to the right atrium. Arterial blood pressure, heart rate, and the conductance at the injection and sampling sites of the thermodilution catheter were all recorded on a polygraph (Mingograph 7, Siemens Elema) at a paper speed of 10 mm/s.

Other direct or indirect measurements were (1) rate-pressure product (systolic blood pressure times heart rate), which was taken as an index of myocardial metabolic requirements,10 (2) coronary vascular resistance, which was calculated by the ratio between mean arterial pressure (diastolic blood pressure plus one third of pulse pressure) and coronary blood flow, and (3) left ventricular end-diastolic pressure, left ventricular ejection fraction, and cardiac output, which were obtained at the time of cardiac catheterization.

**Protocol**

In all patients, antianginal drugs were withdrawn 72 hours before the study, and only nitrate therapy was allowed when needed. Cardiac catheterization was performed in the morning after an overnight fast. The study proper began 45 minutes after completion of cardiac catheterization (to minimize the effect of contrast medium on reference points. Blood flow measurements were obtained by the continuous thermodilution method described by Ganz et al.,9 that is, by infusing a 5% glucose solution kept at room temperature at a rate of 1 mL/s through the catheter tip and sampling the temperature of the venous blood by a thermostor closer to the right atrium. Arterial blood pressure, heart rate, and the conductance at the injection and sampling sites of the thermodilution catheter were all recorded on a polygraph (Mingograph 7, Siemens Elema) at a paper speed of 10 mm/s.

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follows: Coronary blood flow \( \times ( \text{arterial O}_2 \text{ saturation} - \text{coronary sinus O}_2 \text{ saturation}) \times \text{hemoglobin concentration} \times 1.36 \). Measurements were obtained after 15 minutes of intracoronary infusion of saline or benazepril (25 \( \mu \text{g/mL at the rate of 60 mL/h} \). In either condition, data were collected before and at the end of the cold pressor test.

**Data Analysis**

Coronary blood flow was calculated over periods of 10 seconds. Arterial blood pressure and heart rate were also averaged over 10-second periods, which were thus also the time windows used for calculation of coronary vascular resistance. Data from individual subjects were averaged to obtain mean values for the group as a whole. The values obtained at the end of the cold pressor test and diving were compared with those immediately before the application of these stimuli. Comparisons were also made of data before and during saline and before and during benazepril infusion. The differences in the mean responses were assessed by ANOVA and the \( t \) test for paired observations. A value of \( P<0.05 \) was taken as the level of statistical significance. Unless otherwise indicated, the symbol \( \pm \) refers to SEM.

**Results**

**Effect of Benazepril on Arterial and Coronary Sinus Angiotensin II**

As shown in Figure 1, plasma concentration of angiotensin II in the control condition was slightly greater in the coronary sinus (12.4 \( \pm \) 2.6 pg/mL) than in the arterial blood (10.7 \( \pm \) 2.2 pg/mL). These values were not significantly modified during saline infusion and when benazepril was infused at the rate of 30 mL/h. When the infusion rate was increased to 60 mL/h, the venous angiotensin II concentration decreased in all subjects, with the arterial concentration showing no change in 4 subjects, an increase in 1 subject, and a decrease less than the decrease in the venous concentration in the remaining subject, with the average arterial concentration remaining unaffected. Both concentrations were on the other hand reduced when benazepril was infused at the rate of 120 mL/h. The reductions were not due to an increase in coronary blood flow because compared with baseline values, coronary blood flow was not altered by the infusions of benazepril, the value at the greater infusion rate versus baseline being 151.3 \( \pm \) 12.0 and 139.6 \( \pm \) 11.4 mL/min, respectively.

**Cardiac Oxygen Consumption During Saline and Benazepril Infusions**

As shown in Table 2, baseline blood pressure, heart rate, and rate-pressure product were similar during infusion of saline and benazepril. This was the case also for baseline coronary blood flow, coronary sinus \( \text{PO}_2 \), oxygen extraction across the coronary circulation, and \( \text{MV}_\text{O}_2 \). The cold pressor test caused a similar increase in blood pressure, heart rate, and rate-pressure product during saline or benazepril infusion. During benazepril infusion, however, coronary blood flow increased at variance with the decrease seen during saline infusion. Compared with saline infusion, in most individual patients and in the group as a whole, this was accompanied by a lesser reduction in oxygen saturation in the coronary sinus, by an

**TABLE 2. Effects of Cold Pressor Test on Systemic and Coronary Hemodynamics and Myocardial Oxygen Demand During Intracoronary Infusion of Saline or Benazepril**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Saline Baseline</th>
<th>Saline Cold Pressor Test</th>
<th>Benazepril Baseline</th>
<th>Benazepril Cold Pressor Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mm Hg</td>
<td>142.5 ( \pm ) 6.1</td>
<td>173.4 ( \pm ) 8.7</td>
<td>145.2 ( \pm ) 5.6</td>
<td>172.9 ( \pm ) 7.3</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>70.3 ( \pm ) 3.2</td>
<td>79.3 ( \pm ) 3.8</td>
<td>69.6 ( \pm ) 2.7</td>
<td>79.8 ( \pm ) 3.3</td>
</tr>
<tr>
<td>RPP, mm Hg bpm</td>
<td>10 015 ( \pm ) 832</td>
<td>13 820 ( \pm ) 1020</td>
<td>10 091 ( \pm ) 875</td>
<td>13 700 ( \pm ) 925</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>93 ( \pm ) 0.8</td>
<td>94 ( \pm ) 0.9</td>
<td>94 ( \pm ) 0.7</td>
<td>94 ( \pm ) 0.8</td>
</tr>
<tr>
<td>SVO₂, %</td>
<td>37 ( \pm ) 1.2</td>
<td>25 ( \pm ) 2.2</td>
<td>34 ( \pm ) 1.6</td>
<td>30 ( \pm ) 1.8</td>
</tr>
<tr>
<td>DSA-V_O₂, %</td>
<td>56 ( \pm ) 1.0</td>
<td>69 ( \pm ) 1.4</td>
<td>60 ( \pm ) 0.9</td>
<td>63 ( \pm ) 1.4</td>
</tr>
<tr>
<td>PV_O₂, mm Hg</td>
<td>24 ( \pm ) 0.6</td>
<td>23 ( \pm ) 0.6</td>
<td>23 ( \pm ) 0.7</td>
<td>26 ( \pm ) 0.8</td>
</tr>
<tr>
<td>CBF, mL/min</td>
<td>141.4 ( \pm ) 14</td>
<td>132.5 ( \pm ) 16</td>
<td>133.6 ( \pm ) 19</td>
<td>160.7 ( \pm ) 16</td>
</tr>
<tr>
<td>MV_O₂, mL O₂/min</td>
<td>156.15 ( \pm ) 9</td>
<td>180.29 ( \pm ) 10</td>
<td>158.08 ( \pm ) 6</td>
<td>205.99 ( \pm ) 12</td>
</tr>
</tbody>
</table>

Data are shown as mean \( \pm \) SE from 6 patients.

SBP indicates systolic blood pressure; HR, heart rate; RPP, rate-pressure product; SaO₂, arterial oxygen saturation; SVO₂, coronary sinus oxygen saturation; DSA-V_O₂, arteriovenous difference in oxygen saturation; PV_O₂, venous oxygen pressure; CBF, coronary blood flow; MV_O₂, calculated myocardial oxygen consumption.

Significance of response to cold pressor test: *\( P<0.05 \); † \( P<0.01 \).

Significance of differences in responses to cold pressor test during saline and benazepril: ‡ \( P<0.05 \); § \( P<0.01 \).
increase (rather than a decrease) of the Po2 value in the coronary sinus, and by a greater increase in calculated MVO2 (Figure 2).

**Saline Infusion: Cold Pressor Test and Diving**

Table 3 shows that blood pressure, heart rate, rate-pressure product, coronary blood flow, and coronary vascular resistance were similar before and after 15 minutes of saline infusion. During saline infusion, the cold pressor test caused in all patients a marked increase in mean arterial pressure, heart rate, and rate-pressure product (38 ± 8.2%), a small and variable change in coronary blood flow, and thus a marked increase in coronary vascular resistance (Figure 3). In all patients, diving caused a marked increase in mean arterial pressure, a reduction in heart rate, an increase in rate-pressure product that was less than that during the cold pressor test (+12 ± 3.2%), and a decrease in coronary blood flow that also led to an increase in coronary vascular resistance (Figure 4).

**Benazeprilat Infusion: Cold Pressor Test and Diving**

As shown in Table 3, systemic and coronary hemodynamics were similar before and after 15 minutes of the benazeprilat infusion, which led to a consistent decrease in the venous-arterial difference of angiotensin II (Figure 1), all values being

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**TABLE 3. Systemic and Coronary Hemodynamics Before and During Intracoronary Infusion of Saline and Benazeprilat**

<table>
<thead>
<tr>
<th>Variable, mm Hg</th>
<th>Saline</th>
<th>Benazeprilat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>15 min</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>142.6±6.2</td>
<td>145.7±6.0</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>78.1±3.8</td>
<td>79.6±3.9</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>101.0±3.5</td>
<td>102.7±4.5</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>69.1±3.1</td>
<td>70.6±3.3</td>
</tr>
<tr>
<td>RPP, mm Hg bpm</td>
<td>10 223±808</td>
<td>10 346±792</td>
</tr>
<tr>
<td>CBF, ml/min</td>
<td>136.2±14.1</td>
<td>135.0±15.2</td>
</tr>
<tr>
<td>CVR, U</td>
<td>0.74±0.08</td>
<td>0.76±0.09</td>
</tr>
</tbody>
</table>

Data are shown as mean±SE from 14 patients.

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; RPP, rate-pressure product; CBF, coronary blood flow; CVR, coronary vascular resistance.

Differences between values before and during infusions and between saline and benazeprilat infusions were never statistically significant.
superimposable to the values observed at corresponding times of saline infusion. As shown in Figures 3 and 4, the blood pressure, heart rate, and rate-pressure product responses to the cold pressor test and diving seen during the benazeprilat infusion were also superimposable to those seen during the saline infusion. In contrast, during the benazeprilat infusion, coronary blood flow increased significantly with the cold pressor test and did not change with diving, with a resulting marked attenuation of the coronary vasoconstrictor responses elicited by the 2 stimuli during saline infusion. The differences with the vasoconstrictor responses observed during saline infusion were visible in all patients and statistically significant.

**Discussion**

In our patients with angiographically documented severe stenosis of the left anterior descending coronary artery, the cold pressor test caused, as expected, a marked increase in coronary vascular resistance, namely, a coronary vasoconstriction that has been shown to be due to an increase in sympathetic drive. This response was markedly reduced by an intracoronary infusion of a dose of benazeprilat that (1) did not alter coronary or systemic hemodynamics, (2) did not modify baseline rate-pressure product, coronary sinus and arterial oxygen saturation, and cardiac oxygen consumption as compared with what was seen during saline infusion, thereby not altering cardiac metabolic needs, and (3) in a separate group of patients with similar angiographic alterations of the coronary arteries, caused a reduction of angiotensin II concentration in the coronary sinus but not in the arterial blood, thereby presumably reducing selectively the cardiac generation of this substance. This allows us to conclude that the vasoconstrictor influence exerted by the sympathetic nervous system on the human coronary circulation can be attenuated by intracoronary administration of a small dose of an ACE inhibitor and that this is mediated by a reduction in the production of angiotensin II in the human heart; namely, that the well-known sympathostimulating effect of angiotensin II can derive from its cardiac generation rather than from the amount secreted by a variety of organs and available in the systemic circulation. This clearly supports the hypothesis of a functional significance of the cardiac renin-angiotensin system in humans.

Several other results of our study deserve to be mentioned. (1) On the basis of the present findings, one cannot exclude that the effects of the intracoronary administration of benazeprilat are due also to an increase in concentration of bradykinin (caused by an ACE inhibitor-dependent reduction of bradykinin breakdown) because this substance has been shown to attenuate neurohumoral transmission at the sympathoafferent junctions. However, a sympathoattenuating effect of bradykinin thus far has been shown only in animal studies. Furthermore, in some animal studies, an opposite (ie, a sympathoactivating) effect of this substance has been reported, which implies that the increase in bradykinin levels during ACE
inhibition might have resulted in a facilitation of sympathetic coronary responses and should have led to a potentiation rather than to an attenuation of sympathetic vasoconstriction. Finally, even accepting that bradykinin might exert a sympathomoderating influence, this mechanism does not seem likely to play a major role in modulating sympathetic coronary responses because we have previously shown that sympathetic influences on coronary circulation are not only markedly attenuated by ACE inhibition but are markedly enhanced by intracoronary infusion of minute doses of angiotensin II, which is, they are exquisitely related to the final product of the renin-angiotensin cascade. (3) Animal studies have shown that in the normal heart, the amount of angiotensin II detectable in the coronary sinus is greater than the arterial one because the local release of angiotensin II exceeds the uptake of this substance by the myocardium. Our observation of consistently positive veno-arterial differences of angiotensin II indicates that this may be the case also in the human heart, in which a positive balance between angiotensin II generation and uptake exists also in the presence of coronary disease. (3) Our data cannot contribute to clarification of whether the delivery of angiotensin II from the heart into the coronary venous outflow depends on the conversion of locally synthesized or circulating angiotensin I. Our findings suggest, however, that with regard to the sympathoexcitatory influence, the angiotensin II produced by the action of ACE on angiotensin I is probably more important than that produced through alternative pathways such as those acting by chymase. On the basis of in vitro studies, this pathway has been reported to be responsible for 80% of the total angiotensin II formation of the human heart, the fraction produced through ACE accounting for only a small fraction. It would seem unlikely, however, that if so much local angiotensin II were still available after ACE inhibition, its enhancing effect on the sympathetic coronary vasomotor tone would not be largely preserved unless one speculates that a functional compartmentalization exists between the angiotensin II produced by ACE and that produced by chymase. This is a very unlikely speculation, however, because the chymase-dependent angiotensin II has been reported to be formed largely at the adventitial level, that is, at a site near the termination of sympathetic nerve fibers where, if anything, its influence should be even greater. (4) The reduction of the cardiac angiotensin II production that was obtained by the intracoronary infusion of benazepril markedly attenuated the sympathetic vasoconstrictor response to the cold pressor test and diving without significantly affecting baseline coronary blood flow and vascular resistance. This suggests that in the heart, the sympathomodulatory influence of local angiotensin II becomes manifest when this substance does not yet contribute to modulation of baseline coronary hemodynamics. We can speculate that this occurs because local angiotensin II modulates peripheral sympathetic functions (secretion of norepinephrine, responsiveness of adrenergic receptors, and so forth) at concentrations that are lower than those needed to directly affect vasomotor tone. It is possible, however, that any influence of local angiotensin

Figure 4. Systemic and coronary hemodynamic responses to diving (D) during saline and benazeprilat infusions. Data are shown as individual responses and mean ± SE from 8 patients. MAP indicates mean arterial pressure; HR, heart rate; CBF, coronary sinus blood flow; and CVR, coronary vascular resistance.
II on baseline coronary hemodynamics is compensated for by many other factors that control coronary vasomotor tone. During the intracoronary infusion of the dose of benazeprilat that reduced cardiac production of angiotensin II, the increase in blood pressure, heart rate, and rate-pressure product induced by the cold pressor test allowed coronary blood flow to increase rather than diminish, as during saline infusion. This was accompanied by lesser oxygen desaturation and reduction in PO$_2$ in the blood reffluent from the heart, indicating that the sympathoinhibitory effect of local ACE inhibition plays a favorable metabolic role insofar as it allows the increased oxygen demand to be more adequately met. It should be emphasized that this occurred together with an increase in the calculated MV$\dot{O}_2$ greater than that observed when the cold pressor test was performed under saline infusion. It is therefore possible that metabolic factors also participated in the attenuated sympathetic vasoconstrictor influences that were seen after ACE inhibition. Clearly, however, this participation did not originate from greater myocardial work after ACE inhibition, because in our patients the rate-pressure product during the cold pressor test (and diving) was superimposable during saline and benazeprilat infusion. Furthermore, in previous studies, myocardial contractility and left ventricular end-systolic wall stress/end-systolic volume ratio (ie, other determinants of myocardial oxygen consumption in addition to cardiac afterload and heart rate) were reduced by intracoronary enalaprilat. Finally, ACE inhibition is known not to increase but to reduce the secretion of substances with direct O$_2$-wasting properties such as norepinephrine.

In conclusion, our study provides evidence that in patients with coronary heart disease, the sympathetic coronary vasoconstrictor influences are markedly attenuated by selectively reducing the local production of angiotensin II through intracoronary ACE inhibition. Thus, at the cardiac level, the sympathomodulatory effect of angiotensin II can be explained by the tissue renin-angiotensin system. The demonstration that the cardiac renin-angiotensin system exerts a noticeable role in patients with coronary heart disease revives the issue of the possible importance of ACE inhibitors to oppose the tissue production of angiotensin II because of a greater diffusion, membrane permeability, and tissue affinity. The modification of the coronary vasoconstrictor responses to the cold pressor test and diving might be used for this purpose, although different ACE inhibitors would have to be tested as administered in the clinical setting.

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