ACE Inhibition Attenuates Sympathetic Coronary Vasoconstriction in Patients With Coronary Artery Disease

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Background. In humans, angiotensin converting enzyme (ACE) inhibition attenuates the vasoconstriction induced by sympathetic stimulation in a number of peripheral districts. Whether this is also the case in the coronary circulation is unknown, however.

Methods and Results. In nine normotensive patients with angiographically assessed coronary atherosclerosis, we measured the changes in mean arterial pressure (intra-arterial catheter), heart rate, rate-pressure product (RPP), coronary sinus blood flow (CBF, thermodilution method), and coronary vascular resistance (CVR, ratio between mean arterial pressure and CBF) induced by the cold pressor test (CPT, 2 minutes) and diving (30 seconds), i.e., two stimuli eliciting a sympathetic coronary vasoconstriction. The measurements were performed in the control condition and 30 minutes after captopril 25 mg p.o. In the control condition, CPT caused an increase in mean arterial pressure and heart rate. Despite the increase in RPP (+20.7±3.2%, p<0.01), CBF did not change and CVR increased (+12.2±4.0%, p<0.05); diving caused an increase in mean arterial pressure and a reduction in heart rate. RPP increased (+14.3±3.5%, p<0.01), but despite this increase, there was a reduction in CBF and a marked increase in CVR (+37.3±7.4%, p<0.01). Captopril did not modify the blood pressure and heart rate responses to both stimuli except for a slight accentuation of the bradycardia to diving. Despite the unchanged or only slightly reduced RPP response, the increase in CVR was markedly and significantly attenuated (p<0.01).


KEY WORDS • diving • angiotensin converting enzyme • heart disease, ischemic

A large body of evidence supports the concept that angiotensin II enhances sympathetic influences on the cardiovascular system.1 For example, in several animal species, the pressor effect of a sympathetic stimulation is augmented by angiotensin II infusion and reduced by ACE inhibition, with a reduction in the vasoconstriction occurring in various peripheral districts.2–6 Furthermore, in both normotensive and hypertensive animals, angiotensin II amplifies the pressor response to norepinephrine infusion7,8 and acts at various central and peripheral neural sites to increase sympathetic nerve firing and norepinephrine release.1,9,10 In essential hypertension, sympathetically mediated forearm vasoconstriction elicited by deactivation of volume cardiopulmonary receptors is reduced by administration of an ACE inhibitor11; thus, the sympathethic modulating effect of angiotensin II is also evident in humans.

In humans, angiotensin II exerts a direct coronary vasoconstrictor effect independent of sympathetic innervation12,13; however, its ability to modulate and amplify sympathetic coronary vascular control is unknown. Because of its pathophysiological and clinical importance, we have set out to investigate this problem and report our results.

Methods

Patients

We studied 19 patients who underwent coronary angiography for a history of chest pain and had evidence of a significant stenosis (≥50%) of two or three major coronary arteries with no coronary artery occlusion and no involvement of the left main trunk. The patients (mean age, 56.2±1.6 years; range, 42–68 years) were free from valvular heart disease. They had no history of congestive heart failure or recent myocardial infarction and no clinical evidence of noncardiovascular disease. Table 1 indicates the individual hemodynamic and angiographic data obtained during the catheterization. Values were (mean±SEM): mean arterial pressure, 102.1±2.1 mm Hg; heart rate, 72.3±2.6 beats per minute; CBF, 102.1±2.1 ml/min/m2; RPP, 2004±140.4 mm Hg·beats·min-1; CI, 3.4±0.2 l/min/m2; and systemic vascular resistance (SVR), 1345±115.5 dyne·sec·cm-5. Anesthesia was provided with fentanyl and diazepam. The patients were sedated but fully conscious. The heart rate and arterial pressure were monitored throughout the study. 

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Hemodynamic and Humoral Measurements

Arterial blood pressure was measured by a Judkins catheter (7F or 8F) positioned in the ascending aorta through the femoral artery and connected to a Statham Gould P231D transducer (Gould Medical BV Bilthoven, The Netherlands). Heart rate was measured by the reciprocal of the RR interval, which was derived from a standard ECG lead. The rate-pressure product (systolic blood pressure times heart rate, RPP) was calculated as an index of cardiac metabolic requirements. Coronary blood flow was measured by a thermodilution catheter inserted percutaneously into an antecubital vein and advanced under fluoroscopic control to lie deep within the coronary sinus. The position of the catheter in the coronary sinus was checked by a small bolus injection of contrast medium (Iopamidol 75.5 g·100 ml⁻¹) at the beginning of the study. The unchanged position of the catheter radiopaque tip with respect to surrounding reference points ensured that no displacement of the measuring catheter occurred throughout the study. Blood flow measurements were obtained by the continuous thermodilution method described by Ganz et al., i.e., by infusing a 5% glucose solution kept at room temperature at 1 ml·sec⁻¹ via the catheter tip and sampling the temperature of the venous blood by a thermistor closer to the right atrium. Coronary blood flow was obtained by the formula

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HR, heart rate; bpm, beats per minute; MAP, mean arterial pressure; LVEDP, left ventricular end-diastolic pressure; EF, ejection fraction; RCA, right coronary artery; DIA, diagonal branch; OM CX, obtuse marginal branch; LAD, left anterior descending artery; LCX, left circumflex artery; CAP, captopril; PHE, phentolamine; SAL, saline.
Table 2. Effects of Cold Pressor Test and Diving on Systemic and Coronary Hemodynamics in 19 Subjects

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<th>Cold pressor test</th>
<th>Diving</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Δ</td>
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<tr>
<td>MAP (mm Hg)</td>
<td>101.2±2.6</td>
<td>+14.7±2.1*</td>
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<tr>
<td>HR (bpm)</td>
<td>66.2±4.0</td>
<td>+7.0±1.2*</td>
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<tr>
<td>RPP (bpm · mm Hg)</td>
<td>9.625±663</td>
<td>+2.770±920*</td>
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<td>CBF (ml/min)</td>
<td>99.7±11.8</td>
<td>+3.4±2.8</td>
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<td>CVR (units)</td>
<td>1.11±0.16</td>
<td>+0.14±0.04*</td>
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Data are shown as mean±SEM. Δ, Change; MAP, mean arterial pressure; HR, heart rate; bpm, beats per minute; RPP, rate-pressure product; CBF, coronary blood flow; CVR, coronary vascular resistance.

*p<0.01, †p<0.05, statistical significance of changes from baseline values.

tp<0.01, §p<0.05, difference between changes induced by cold pressor test and diving.

\[ \text{Flow} = \text{Vi} \times 1.08 \times (\text{Tg} - \text{Tt}/\text{Tm}) \]

where Vi is the volume of the injectate (ml · min⁻¹); Tg, Ti, and Tm are the temperature of the blood, the injectate, and the mixture of blood and injectate; and 1.08 is a constant derived from the density and specific heat of the glucose solution and blood. Coronary vascular resistance was calculated by the ratio between mean aortic pressure (diastolic pressure plus one third of pulse pressure) and coronary blood flow. Aortic blood pressure, heart rate, and conductance at injection and sampling sites were recorded on a polygraph (Mingograph 7, Siemens).

Other measurements included 1) left ventricular end-diastolic pressure, which was obtained by a pigtail catheter (7F or 8F) immediately before the left ventricular angiogram; 2) left ventricular ejection fraction, which was obtained by computer analysis of the systolic and diastolic contour of the left ventricle as visualized by the left ventricular angiogram according to the method of Sandler and Dodge; and 3) plasma renin activity, which was measured radioimmunologically from 5 ml of blood taken from an antecubital vein immediately before the cold pressor test and diving.

Protocol

Five patients were untreated at the time of the study. In the remaining 14 patients, all drugs were withdrawn 6 days before cardiac catheterization, and only nitrate therapy was allowed. Cardiac catheterization was performed in the morning after an overnight fast, a premedication with 10 mg oral diazepam, and a local anesthesia with a 2% lidocaine solution at the site of insertion of the venous and arterial catheters.

The study began 30 minutes after coronary and left ventricle angiography to minimize the effects of the contrast medium injection. Initially, coronary blood flow was measured two to three times to check the existence of a steady-state condition. Blood flow was then measured over 10-second periods 1) immediately before the stimulus, 2) during the final period of a 30-second application of a bag filled with melting ice to the patient’s mouth and nose (diving reflex), 3) during the final part of a 120-second immersion of one hand into melting ice water (cold pressor test), and 4) 30 seconds after the bolus injection of 12 mg papaverine in the left coronary artery. Diving and the cold pressor test were performed for their ability to determine vasoconstrictor responses via activation of the sympathetic nervous system. Papaverine injection was performed to cause maximal coronary vasodilatation. The stimuli were applied in random order and separated by the time (usually 10 minutes) necessary for blood pressure and heart rate to regain prestimulus values.

In nine patients, the vasoconstrictor and vasodilator stimuli were repeated (using the same protocol described above) 30 minutes after the oral administration of 25 mg captopril. In five patients, the vasoconstrictor stimuli were repeated 30 minutes after the intravenous injection of phentolamine at the initial bolus dose of 10 mg followed by the infusion of 0.5 mg · min⁻¹. In the remaining five patients, the vasoconstrictor stimuli were repeated after an intravenous administration of saline at a volume similar to the one used for the phentolamine administration. Phentolamine was used to verify the adrenergic nature of the coronary vasoconstrictor responses, whereas saline was used to check the reproducibility of the responses with repetition of the stimuli.

Data Analysis

As mentioned above, coronary blood flow values were calculated over periods of 10 seconds. Arterial blood pressure and heart rate were also averaged over 10-second periods. The values obtained at the end of a vasoconstrictor or vasodilator stimulus were compared with those immediately before the stimulus. Data from individual subjects were averaged to obtain mean values for the group as a whole. The differences in mean values before and after the administration of captopril, phentolamine, or saline were assessed by the t test for paired observations. A value of \( p<0.05 \) was taken as the level of statistical significance.

Results

Effects of the Cold Pressor Test and Diving

The effects of the cold pressor test and diving before administration of captopril, phentolamine, or saline are shown in Table 2 for all 19 subjects of the study. The cold pressor test caused an increase in mean arterial pressure, heart rate and RPP, no significant change in coronary blood flow, and an increase in coronary vascular resistance. Diving caused an increase in mean arterial pressure, bradycardia, an increase in RPP, a
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COLD PRESSOR TEST

DIVING

Figure 1. Graphs show percent changes in mean arterial pressure (MAP), heart rate (HR; b/min, beats per minute), rate-pressure product (RPP), coronary blood flow (CBF), and coronary vascular resistance (CVR) induced by the cold pressor test (upper panel) and diving (lower panel) before and after saline infusion. Baseline values before and after saline infusion are shown at the bottom of each panel. Asterisks refer to statistical significance of changes induced by the cold pressor test and diving compared with baseline values. Differences between the responses before and during saline infusion were not statistically significant. Data are shown as mean ± SEM from five patients.

A reduction in coronary blood flow, and an increase in coronary vascular resistance. The increase in RPP was greater during the cold pressor test than during diving, whereas the increase in mean arterial pressure and coronary vascular resistance was greater during the latter than during the former stimulus.

Saline Infusion

As shown in Figure 1, the marked increase in mean arterial pressure induced by diving was not influenced by saline infusion. The blood pressure increase induced by the cold pressor test was somewhat less during than before infusion of saline, but the difference was not statistically significant. The changes in coronary blood flow, heart rate, and coronary vascular resistance induced by either the cold pressor test or diving were similar before and during saline infusion; thus, repetition of these stimuli was not accompanied by attenuation of their hemodynamic and coronary effects.
Phentolamine Infusion

Figure 2 shows the data obtained before and during phentolamine infusion. Phentolamine caused a small but significant reduction in baseline mean arterial pressure and a baseline tachycardia, whereas baseline coronary blood flow and vascular resistance did not show any significant alteration. The pressor response to the cold pressor test and diving were unchanged or only slightly diminished by phentolamine, which decreased cold pressor test--induced tachycardia and left the diving-induced bradycardia unaffected. After phentolamine, coronary blood flow increased in parallel with blood pressure during both stimuli; thus, the increase in coronary vascular resistance observed before the drug was abolished.

Administration of Captopril

As shown in Figure 3, bottom of each panel, baseline mean arterial pressure, heart rate, coronary blood flow, and coronary vascular resistance were not significantly altered by captopril compared with the control condition, although the large interindividual variability of coronary blood flow values may have obscured some tendency to
change (see the large standard errors of the baseline values). Baseline plasma renin activity was 0.4±0.1 ng/ml/hr in the control condition. This value did not increase significantly after captopril (0.4±0.1 ng/ml/hr).

Figure 3 also shows that the cold pressor test caused similar increases in mean arterial pressure, heart rate, and RPP before and after captopril but that although before the drug, coronary blood flow did not change significantly, after the drug, it increased significantly, the increase in coronary vascular resistance being thus significantly attenuated. Diving caused less increase in mean arterial pressure and RPP after captopril than in the control condition. The reduction in coronary blood flow induced by this stimulus was changed into an increase after administration of the drug, and thus, even in this instance, a significant attenuation of the coronary vasoconstrictor response was observed. The percent alterations of the hemodynamic responses to the cold pressor test and diving seen with saline, phentolamine, and captopril are summarized in Figure 4. Figure 5 shows that intracoronary papaverine caused no significant change in mean arterial pressure, a minor and
nonsignificant increase in heart rate, a more than twofold increase in coronary blood flow, and a marked reduction in coronary vascular resistance. All responses were not affected by captopril.

**Discussion**

Our study shows that in patients with coronary artery disease, the moderate increase in coronary vascular resistance induced by the cold pressor test and the more marked one induced by diving were greater before than after 25 mg of oral captopril. This suggests that ACE inhibition attenuates the coronary vasoconstriction induced by sympathetic stimulation, thus unmasking a potentiating role of angiotensin II on sympathetic influences on coronary circulation. Before accepting this conclusion, however, other possible explanations of our findings should be discussed.

First, because captopril administration always had to follow control measurements, it may be argued that the attenuation of the coronary vascular response was due to repetition of the stimuli. However, the increase in coronary vascular resistance induced by the cold pressor test and diving were unchanged when repeated after a saline infusion, ruling out this possibility.

Second, the cold pressor test and diving might have increased cardiac work to a greater degree after captopril administration, the resulting greater coronary vasodilatation counteracting the vasoconstrictor response. However, the cold pressor test increased an accepted index of cardiac work and metabolic requirement such as RPP to a similar degree before and after captopril. Furthermore, the increase in RPP induced by diving was accompanied by a reduction in coronary blood flow before captopril and an increase in coronary blood flow after captopril, indicating a striking qualitative change in the vasomotor response (Figure 6). The diving-induced increase in RPP was less after than before captopril, favoring rather than opposing a vasoconstrictor response; thus, this possibility can also be ruled out.

Third, captopril may have reduced the coronary vasoconstrictor response to the cold pressor test and diving by removing a direct vasoconstrictor effect of circulating angiotensin II. However, our subjects had low values of plasma renin activity, and a direct constrictor influence of angiotensin II on the coronary circulation has only been shown in subjects treated with thiazide diuretics or affected by renovascular hypertension, i.e., under stimulation of the renin-angiotensin system. Furthermore, in our subjects, the coronary vasoconstrictor responses were markedly attenuated by phentolamine, i.e., by a drug blocking $\alpha_1$- and $\alpha_2$-adrenergic receptors. Thus, although a direct effect of circulating angiotensin II on coronary circulation can-
not be excluded, the importance for these responses of sympathetic activation cannot be questioned.

The most likely explanation of our results is, therefore, that captopril attenuates the vasoconstrictor effect of sympathetic nerve activation on the coronary circulation. This is in line with data obtained in animals in which the reduction of coronary blood flow induced by stellate ganglion stimulation was less after than before ACE inhibition. It is also in line with data obtained in hypertensive humans in whom sympathetic forearm vasoconstriction was less after administration of captopril than in the pretreatment condition. An ACE inhibition-dependent modulation of sympathetic activity may thus take place and be quantitatively important in human coronary circulation as well. This conclusion applies to the type of patients involved in our study, i.e., patients with coronary atherosclerosis. Whether ACE inhibition also attenuates sympathetic vasoconstriction in normal coronary vessels remains to be seen.

The mechanisms responsible for the moderating effect of ACE inhibition on sympathetic coronary vasoconstriction are not clarified by our study. It can be argued that the drug that we used (captopril) exerts a direct sympathetic depressor influence, although no experimental evidence supports this possibility. It can also be argued that the coronary vasoconstrictor response is opposed by the reduced breakdown of bradykinins that follows ACE inhibition, and this is indeed in agreement with experimental data. However, there is no doubt that a large body of evidence from animal studies indicates that angiotensin II facilitates sympathetic function in the central nervous system, at the sympathetic ganglia, at the nerve terminals, and even at the adrenergic receptor level. Removal of this facilitation is thus likely to account for our results.

Few other observations deserve to be discussed. In our study, the sympathetic coronary vasoconstriction induced by diving and the cold pressor test was attenuated by captopril in patients in whom plasma renin levels were low. We can thus conclude that the circulating renin–angiotensin system does not need to be activated to facilitate the vascular effect of sympathetic stimulation. This may be due to the fact that the sympathetic circulatory drive is sensitive to levels of circulating angiotensin II lower than those that have a direct effect on the vasculature. We can also speculate, however, that this drive is modulated by the angiotensin II produced locally. This alternative explanation may find support in the results of Lindpaintner et al that the coronary vasoconstriction induced by stimulating cardiac sympathetic nerves is attenuated by ACE inhibition in isolated perfused hearts. It may also find further support in the present observation that plasma renin activity was unchanged by captopril, suggesting little interference with the generation of circulating angiotensin II. A dependence of coronary sympathetic vasoconstriction on the angiotensin II produced in the heart may explain why the pressor responses to diving and the cold pressor test were only slightly affected by ACE inhibition. This may be interpreted to mean that in districts of paramount importance for overall vascular resistance, facilitation of sympathetic influences depends on both local and circulating angiotensin II and thus is revealed only when the formation of both is blocked. Such interpretation is in line with our previous observations that in the forearm (i.e., a district reflecting the behavior of skeletal muscle circulation), reflex sympathetic vasoconstriction was attenuated by acute and chronic doses of captopril, which markedly increased plasma renin activity. It should be emphasized, however, that the pressor responses to diving and the cold pressor test were also slightly affected by phentolamine. It is thus possible that in the coronary circulation, any kind of vasoconstriction is more easily removed because vasoconstrictor influences are in a more critical balance, with metabolic vasodilator influences arising from myocardial contraction.

The maximal or near-maximal coronary vasodilatation induced by the intracoronary injection of a large dose of papaverine was superimposable before and after captopril. This is probably due to the fact that maximal coronary vasodilatation depends on the interplay be-
tween the release of cardiac metabolites and the structure of the coronary arteries (i.e., atherosclerotic lesions, intimal hyperplasia, medial hypertrophy, etc.) and that no humoral and other functional factors play any substantial role.39 Of course, this explanation may not apply to less marked degrees of coronary vasodilation, and Magrini et al40 have shown that in subjects with a high plasma renin activity, the coronary vasodilator response to a short-lasting submaximal exercise is indeed enhanced by ACE inhibition.

Although caution should be exercised in extrapolating data obtained in the laboratory to the clinical setting, our findings may have clinical implications. These implications are that interventions leading to ACE inhibition should not enhance the coronary vasodilation accompanying exercise, providing pathophysiological support to the prevailing evidence that this intervention is not beneficial against effort angina.41 They might, on the other hand, attenuate the coronary vasoconstriction resulting from the increases in sympathetic drive that occur over 24 hours42–44 and do this even in low-renin patients. At present, no clinical data support this implication. It might be worthwhile, however, to devote further clinical scrutiny to this issue in the future.

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