Effect of Selective Angiotensin II Receptor Antagonism and Angiotensin Converting Enzyme Inhibition on the Coronary Vasculature In Vivo

Intravascular Two-dimensional and Doppler Ultrasound Studies

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Background. Although angiotensin converting enzyme (ACE) inhibitors have been reported to increase coronary blood flow, the effect of selective angiotensin II (AT1)-receptor antagonism on the coronary circulation has not been defined.

Methods and Results. We examined the effects of the AT1-receptor antagonist Losartan (DuP 753, 0.2–3.2 mg/kg) on coronary arteries in vivo in 11 dogs, using a combination of intravascular two-dimensional and Doppler ultrasound. In six dogs, a 30-MHz, 4.3F ultrasound imaging catheter was placed in the midsegment of the circumflex coronary artery to measure cross-sectional area (CSA), and a 0.018-in. Doppler wire was placed alongside to measure coronary flow velocity. At peak effect (1.6 mg/kg), Losartan increased mean coronary CSA from 7.9±0.5 to 9.5±0.8 mm² and average peak velocity (APV) from 32±10 to 55±18 cm/sec, resulting in an increase in coronary blood flow from 74±19 to 151±36 ml/min. The maximal effect of the ACE inhibitor enalaprilat (5 mg) was an increase in CSA from 7.7±0.7 to 8.4±0.8 mm² and an increase in APV from 36±10 to 53±20 cm/sec, with an increase in coronary blood flow from 82±25 to 122±41 ml/min. Relative to maximal hyperemia with adenosine (6 mg i.c.), the magnitude of flow increase from baseline was 0.37 with the AT1-receptor antagonist and 0.19 with the ACE inhibitor (p<0.05). These effects were seen without changes in heart rate or systemic arterial pressure. In an additional five dogs, the ultrasound imaging catheter was introduced directly over a 0.014-in. Doppler wire, and the effects of indomethacin, propranolol, and N’-nitro-L-arginine methylester (L-NAME) on the vasodilator effect of Losartan (1.6 mg/kg) were examined. Indomethacin and propranolol had no effect on Losartan-induced vasodilation, suggesting that it was not mediated via prostaglandins or β-adrenoceptors. However, Losartan-induced epicardial vasodilation was partially inhibited by L-NAME, suggesting an action partly dependent on endothelial release of nitric oxide.

Conclusions. Thus, these acute studies in anesthetized dogs suggest that inhibition of AT1-receptors in the coronary circulation results in vasodilator responses greater in magnitude than ACE inhibition and partly endothelium dependent. The exact role for AT1-receptors in human coronary physiology and pathology remains to be defined. (Circulation 1993;87:931–938)

KEY WORDS • Losartan • enalaprilat • N’-nitro-L-arginine • methylester • adenosine • angiotensin converting enzyme inhibitors

Angiotensin II has been shown to exert a direct vasoconstrictor effect on the coronary arteries.1-3 In experimental animals, angiotensin converting enzyme (ACE) inhibition increases epicardial coronary artery diameter,4 whereas in humans, the ACE inhibitor enalaprilat has been shown to increase coronary blood flow in dilated cardiomyopathy when administered directly into the coronary circulation.5 However, after intravenous administration of enalaprilat in humans, absolute coronary blood flow does not increase, yet flow remains in excess of metabolic demand, despite a fall in perfusion pressure, suggesting primary coronary vasodilation mediated by ACE inhibition.6 Although increased local kinin activity may in part mediate the vasodilator properties of ACE inhibitors,7 their predominant action is said to be via inhibition of circulating or local vascular ACE and, thus,

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decreased production of angiotensin II. We therefore hypothesized that a selective angiotensin II (AT₁) receptor antagonist would cause coronary vasodilation, similar to that resulting from ACE inhibition, and allow a more direct, detailed study of the role of AT₁ receptors in the control of coronary blood flow and vascular tone. Losartan (DuPont Pharmaceuticals, Wilmington, Del.) is a new selective AT₁ antagonist with antihypertensive properties. It increases total peripheral conductance and dilates the renal vasculature in experimental animals, but its effect on the coronary arteries is not known. Unlike the peptide angiotensin II antagonist saralasin, Losartan does not have partial agonistic effects, rendering it ideally suited to the study of the properties of AT₁ receptors.

Intravascular two-dimensional ultrasound imaging is a recent technique that permits real-time visualization of cross-sectional slices of the coronary arteries, allowing accurate determination of cross-sectional area. Catheter-based intravascular Doppler ultrasound has been used to measure coronary flow velocity, particularly in studies of coronary flow reserve, and in the assessment of regional flow. We have shown that a combined approach using both intravascular imaging and Doppler ultrasound in the coronary arteries permits simultaneous measurements of both luminal area and coronary blood flow velocity. Such an approach permits analysis of the differential effects of pharmacological agents on the epicardial coronary arteries and on the microcirculation and therefore is useful in studies of coronary vascular reactivity.

In the present study, in which we used intravascular two-dimensional and Doppler ultrasound to measure epicardial coronary dimensions and coronary flow velocity, respectively, we examined the effect of selective AT₁ receptor blockade and ACE inhibition on the coronary circulation in vivo. To limit changes in loading conditions of the left ventricle, which greatly influence coronary blood flow, pharmacological agents were administered directly into the coronary circulation. We compared the vasodilator properties of AT₁ receptor blockade by Losartan and ACE inhibition by enalaprilat with the coronary hyperemic response induced by adenosine. We then sought to investigate the interaction of Losartan-induced AT₁ receptor antagonism with other potential coronary vasodilator mechanisms, i.e., release of endothelium-derived nitric oxide, release of vasodilator prostaglandin(s), and β-adrenoceptor stimulation.

Methods

Eleven mongrel dogs of either sex (eight males and three females; mean weight, 26.5 ± 0.8 kg) were anesthetized with Innovar (0.04 mg/kg s.c.) and sodium pentobarbital (15 mg/kg i.v.), with additional doses of sodium pentobarbital as needed to maintain the level of anesthesia. They were mechanically ventilated with room air. Heart rate was monitored from the ECG, and blood pressure was monitored from a cannula placed in the right internal carotid artery. All studies conformed to the "Position of the American Heart Association on Research Animal Use" adopted November 11, 1984.

Catheterization Procedures

Under fluoroscopic guidance, the left main coronary artery was cannulated via the transfemoral approach using an 8F canine guiding catheter (Advanced Cardiovascular Systems, Calif.). As previously described, one of the following approaches was then used to introduce both a two-dimensional ultrasound catheter (Cardiovascular Imaging Systems, Sunnyvale, Calif.) and a Doppler guide wire (Cardiometrics Inc., Mountain View, Calif.) into a coronary artery.

First, in the first six dogs (protocol 1), an 0.018-in. Doppler wire was introduced through the 8F guiding catheter into the circumflex coronary artery. The guiding catheter was then withdrawn into the ascending aorta, and a second guiding catheter was introduced through the opposite femoral artery into the ostium of the left main coronary artery. The two-dimensional catheter was then introduced over a 0.014-in. guide wire into the coronary circulation alongside the Doppler guide wire already within the coronary artery.

Second, in the next five dogs (protocol 2), an 0.014-in. Doppler wire was first introduced through the 8F guiding catheter, after which the two-dimensional imaging catheter was introduced directly over the Doppler wire into the circumflex coronary artery. With both approaches, the Doppler transducer was positioned 2 cm distal to the tip of the imaging catheter.

Experimental Protocols

Unless otherwise indicated, drugs were given as 2-mL bolus injections directly into the coronary circulation through the guiding catheter in the ostium of the left main coronary artery. Measurements of coronary artery cross-sectional areas and flow velocity were made at 1 and 2 minutes after each administration to minimize errors caused by the effect of a bolus injection on blood flow (see "Results").

Protocol 1. In six dogs, adenosine (Fujisawa Pharmaceuticals, Deerfield, Ill.) (6 mg) was administered into the coronary artery to produce maximal hyperemia. After return to baseline flow, Losartan (0.2, 0.4, 0.8, 1.6, and 3.2 mg/kg body wt) and enalaprilat (Merck Sharp & Dohme, West Point, Pa.) (2.5 and 5 mg) were administered. The two drugs were given in random sequence, and a sufficient time interval of 30 minutes was allowed for complete restoration of baseline conditions between drugs.

Protocol 2. In the next five dogs, the effect of Losartan (1.6 mg/kg body wt) was examined at baseline and after the following pharmacological interventions: 1) inhibition of nitric oxide synthesis by intracoronary administration of N'-nitro-L-arginine methyl ester (L-NAME) (Sigma Chemical Co., St. Louis, Mo.) over 1 minute to obtain a final concentration of 10⁻³ M in the coronary artery, assuming a flow rate of 80 ml/min; 2) inhibition of prostaglandin synthesis by intravenous infusion of indomethacin (DuPont-Merck Pharmaceuticals, West Point, Pa.) (5 mg/kg i.v. over 5 minutes)—previous studies have suggested that this dose is sufficient to block prostaglandin synthesis; and 3) β-adrenoceptor blockade by intravenous infusion of propranolol (SoloPak Laboratories, Franklin Park, Ill.) (0.75 mg/kg body wt over 5 minutes). This dose of propranolol has been shown to fully antagonize the β-adrenoceptor-mediated effects of isoproterenol.

Two-dimensional ultrasound system description and image analysis. The ultrasound catheter (4.3F) has a fixed 30-MHz transducer and a rotating mirror assem-
ly. Images are displayed on a video monitor; axial resolution was approximately 150 µm, and lateral resolution was approximately 250 µm. Gain, contrast, and reject settings were adjusted by the operator to yield a well-balanced gray-scale appearance on the video display. Real-time images were stored on high-quality super VHS videotape for subsequent off-line analysis. As previously described, selected portions of the videotape were digitized (8 bits, Rasterops 324, Santa Clara, Calif.) in real-time (30 frames per second) and stored on a computer disk for off-line determination of luminal area.

**Doppler ultrasound system description.** Doppler-derived blood flow velocities were measured using a steerable Doppler guide wire (FloWire® Cardiometrics Inc., Mountain View, Calif.). This guide wire system has a miniature Doppler ultrasound crystal that transmits signals at a carrier frequency of 12 or 15 MHz (depending on the guide wire size) and receives pulsed wave ultrasound signals, sampled at a distance of 5 mm from the guide wire tip. The Doppler signals are analyzed by a FloMap instrument (Cardiometrics Inc.) where dedicated digital signal-processing chips perform the fast Fourier transformation required for the spectral display. The signals are transformed into a gray scale, and the resultant spectrum is displayed on a monitor. In our study, the ECG and arterial pressure waveform were simultaneously displayed on the monitor. Also displayed were quantitative measurements of average peak velocity throughout the cardiac cycle. The monitor display was continuously recorded on a VHS videotape for further off-line analysis and comparison to corresponding cross-sectional ultrasound images.

**Calculations and statistical analysis.** Luminal cross-sectional areas at baseline and after administration of drugs were determined by computer-assisted planimetry. Cross-sectional area measurements were gated to the time points in the cardiac cycle when cross-sectional area was maximal and minimal, representing end-diastolic and end-systolic dimensions, respectively. A mean cross-sectional area value was obtained by correcting for the fractional diastolic time interval (IDTI, the duration of diastole as a fraction of the cardiac cycle length) and the fractional systolic time interval (ISTI, the duration of systole as a fraction of the cardiac cycle length) as follows: mean CSA = (IDTI × end-diastolic CSA) + (ISTI × end-systolic CSA); where CSA is cross-sectional area. Off-line analysis of Doppler spectra was performed on a commercially available computer (Freeland Systems, Prism Imaging Inc., Louisville, Colo.) to determine systolic and diastolic time intervals.

Absolute coronary blood flow was determined from the relation CBF = CSA × APV × 0.5²⁶; where CBF is coronary blood flow and APV is average peak velocity. The factor of 0.5 has been validated in canine studies and corresponds to the ratio of spectral peak velocity as measured by the Doppler system and the spatial average velocity required for calculation of volumetric flow.²⁶

Dose–response relations with Losartan and enalaprilat were analyzed using repeated-measures ANOVA, followed by a post-hoc Student-Newman-Keuls test. The effects of Losartan (1.6 and 3.2 mg/kg body wt) and enalaprilat (2.5 and 5 mg) on coronary blood flow were compared using a two-way repeated-measures ANOVA. The effects of indomethacin, propranolol, and L-NAME were analyzed using a Student's t test for paired observations. Values are expressed as mean±SEM.

**Results**

Interpretable two-dimensional images and Doppler flow spectra were obtained in all animals. There were no instances of arrhythmias, thrombosis, spasm, or perforation during catheter/Doppler wire placement.

**Resting Coronary Dimensions and Flow**

Mean resting heart rate was 144±10 beats per minute, and mean arterial pressure was 95±5 mm Hg. Mean resting coronary cross-sectional area was 7.9±0.5 mm², and mean average peak velocity was 32±10 cm/sec. Average volumetric coronary blood flow was 74±19 mL/min, and the ratio of systolic to diastolic time intervals was 0.67±0.33 at rest. Saline (vehicle) infusions of 2-mL volumes caused small “bolus effects,” with a transient 15–20% increase in average peak velocity, that returned to baseline in 20 seconds and had no effects on coronary cross-sectional area.

**Effect of Losartan on Coronary Artery Dimensions and Flow**

Losartan caused dose-dependent increases in coronary cross-sectional area (to 9.5±0.8 mm² at 1.6 mg/kg) and absolute coronary blood flow (to 151±36 mL/min at 1.6 mg/kg, p<0.01), as shown in Figures 1 and 2. Average peak velocity rose significantly at the two highest doses, i.e., 1.6 (to 56±18 cm/sec, p<0.01) and 3.2 mg/kg. The peak effect was seen between 90 and 120 seconds, and the mean duration of the vasodilator response was 5.2±0.8 minutes. The ratio of systolic to diastolic time intervals remained unchanged with Losartan. No significant changes in systemic arterial pressure (93±6 mm Hg at 1.6 mg/kg) or heart rate (146±8 beats per minute at 1.6 mg/kg) were observed with any dose.

**Effect of Enalaprilat on Coronary Artery Dimensions and Flow**

Intracoronary enalaprilat (2.5 mg) did not influence mean arterial pressure (96±6 mm Hg) or heart rate (142±10 beats per minute) but caused a significant increase in coronary cross-sectional area and average peak velocity, resulting in an increase in coronary blood flow (Figure 3). The higher dose (5 mg) caused a small additional vasodilation (cross-sectional area, 7.7±0.7 to 8.4±0.8 mm²; average peak velocity, 36±10 to 53±20 cm/sec; coronary blood flow, 82±25 to 122±41 mL/min; p<0.05) but no change in heart rate or blood pressure. The magnitude of the increase in coronary blood flow with enalaprilat was significantly less than that with Losartan (F=4.767, p=0.04, from two-way ANOVA). The peak effect of enalaprilat was observed at 2.5–3 minutes after administration, and the mean duration of the vasodilator response was 5.9±1.1 minutes.

**Effect of Adenosine on Coronary Artery Dimensions and Flow**

Intracoronary adenosine (6 mg) caused no change in coronary cross-sectional area, but resulted in a 3.7-fold increase in average peak velocity, so coronary blood flow increased from 78±16 mL/min to 285±64 mL/min.
Losartan-Induced Effect of Intracoronary Losartan (DuP 753, 1.6 mg/kg). The ultrasound transducer is seen as a black circle within the vessel, and the calibration marks are 0.5 mm apart. Bottom panels: Simultaneous Doppler velocimetry recordings from the same artery at baseline and after intracoronary Losartan (DuP 753, 1.6 mg/kg). Vel, velocity.

(p=0.014). The maximal effect of adenosine was seen at 40±5 seconds after administration. Mean arterial pressure (92±6 mm Hg) and heart rate (146±10 beats per minute) remained unchanged. Relative to adenosine, the maximal effect of Losartan (1.6 mg/kg) was 0.37, whereas the maximal effect of enalaprilat (5 mg) was 0.19 (Figure 4).

**Effect of Indomethacin on Losartan-Induced Vasodilation**

Indomethacin did not cause any change in blood pressure, heart rate, coronary artery cross-sectional area, average peak velocity, or volumetric blood flow. The vasodilator response to Losartan (1.6 mg/kg) was not altered by indomethacin, with regard to cross-sectional area as well as average peak velocity.

**Effect of Propranolol on Losartan-Induced Vasodilation**

Propranolol reduced mean arterial pressure from 98±3 to 85±5 mm Hg (p=0.056) and heart rate from 150±10 to 119±4 beats per minute (p=0.02). Coronary artery cross-sectional area was unchanged, but average peak velocity decreased slightly from 34±11 to 27±2 cm/sec (p=0.08). The vasodilator response to Losartan (1.6 mg/kg) was not altered in any way by β-adrenoceptor blockade.

**Effect of L-NAME on Losartan-Induced Vasodilation**

Intracoronary L-NAME (10^-4 M) caused a decrease in coronary artery cross-sectional area from 8.01±0.97 to 7.02±0.61 mm² (p=0.016) but no significant change in average peak velocity, blood pressure, or heart rate. The vasodilator response to Losartan (1.6 mg/kg) in the epicardial coronary vessels was significantly reduced by L-NAME, but the increase in average peak velocity was not significantly affected. As a result of the attenuated effect of Losartan on the epicardial arteries, the increase in volumetric coronary blood flow tended to be reduced by L-NAME (p=0.08) (Figure 5).

**Discussion**

The present study suggests that selective AT₁-receptor blockade causes vasodilator effects on both epicardial and resistance vessels in the coronary circulation. Although the maximal effect on flow induced by Losartan was 37% of the hyperemic response caused by adenosine, it was about twice that caused by ACE inhibition. Losartan-induced coronary vasodilation does not appear to be mediated by either prostacyclin production or β-adrenoceptor stimulation, but its effect on epicardial vessels may depend in part on endothelial release of nitric oxide.

The role of AT₁-receptors, if any, in the regulation of coronary vascular tone and blood flow is unclear. Inves-
tigation has been hampered by the unavailability of a suitable selective antagonist since saralasin has partial agonist activity. Losartan is a selective, competitive, nonpeptide AT₁-receptor antagonist with no agonistic activity. Losartan caused an increase in epicardial coronary dimensions as well as a rise in Doppler-derived flow velocity. Since normal epicardial coronary vessels do not contribute more than approximately 10% to total coronary vascular resistance, it follows that the increase in flow velocity must result primarily from dilatation occurring in resistance arteries. Thus, by demonstrating a vasodilator effect of Losartan, the present study suggests a role for AT₁-receptors in both the epicardial coronary circulation and the resistance vasculature. However, the maximal effect on coronary blood flow was only 37% of that resulting from intracoronary adenosine (6 mg), suggesting that AT₁-receptor antagonists do not induce maximal hyperemia.

A coronary vasodilator effect of ACE inhibitors has been shown in isolated perfused hearts. In humans, direct intracoronary administration of enalaprilat in patients with dilated cardiomyopathy caused a significant elevation of coronary sinus blood flow with a reduction of coronary vascular resistance. Intravenous administration of enalaprilat, on the other hand, did not change coronary blood flow; however, the lack of a fall in coronary flow in the presence of a decrease in diastolic blood pressure and, thus, in coronary perfusion pressure suggested that coronary vasodilation did occur. The present study confirms a coronary vasodilator effect of enalaprilat but suggests that the magnitude of its effect is significantly less than the effect obtained with AT₁-receptor blockade. This discrepancy was mainly due to a lesser degree of epicardial coronary vasodilation induced by enalaprilat compared with Losartan with effects on resistance vessels that are similar in magnitude.

There are at least three possible reasons for our finding of a difference between the effects of Losartan and enalaprilat. First, there may be other non-ACE biochemical pathways for conversion of angiotensin I to angiotensin II, so local angiotensin II generation might still occur despite administration of ACE inhibitors. In contrast, direct receptor antagonism would block the effect of angiotensin II irrespective of the pathway by which it is generated. This would account for greater vasodilation with Losartan. Second, circulating ACE may not have been completely inhibited at the dose of enalaprilat used in the present study. However, the occurrence of substantial dilation of resistance vessels at this dose argues against this explanation. Furthermore, at the 5-mg dose, the effective concentration of enalaprilat in the coronary arteries during the first minute after injection is approximately $10^{-4} \text{M}$ (at an assumed flow rate of 100 mL/min). This concentration has been previously shown to completely inhibit cardiac ACE activity in isolated rat hearts. Third, there may be a
lower concentration of ACE in the conductance vessels than in resistance vessels, resulting in a greater effect of ACE inhibition further downstream. Precedents exist for variability in vascular renin-angiotensin system activity depending on blood vessel size. For example, in spontaneously hypertensive rats, topical application of saralasin to the microvasculature resulted in selective dilation of third- and fourth-order arterioles. Local vascular renin-angiotensin system activity has also been observed in conduit vessels: In humans, ACE inhibitors increase the compliance and diameter of large peripheral arteries, even at doses that are without a systemic hypotensive response. ACE is known to occur in coronary arteries, but its physiological significance is unclear. The present study suggests that, at least acutely, inhibition of vascular ACE in the coronary arteries is less effective than direct AT1-receptor antagonism in producing vasodilation in normal canine epicardial coronary vessels. It remains to be seen if chronically administered ACE inhibitors, as in clinical hypertension and heart failure, differ in their effect on the coronary vasculature from AT1-antagonists.

Recent in vitro studies have suggested that Losartan increases release of prostacyclin and prostaglandin

**Figure 3.** Left panels: Dose-dependent increase in epicardial cross-sectional area (CSA) and Doppler-derived average peak velocity (APV) after administration of intracoronary enalaprilat. Right panel: Dose-dependent increase in coronary blood flow after intracoronary administration of enalaprilat. *Significant difference from baseline at p<0.05.

**Figure 4.** Maximal effects of intracoronary Losartan (1.6 mg/kg), enalaprilat (5 mg), and adenosine (6 mg) on coronary blood flow.

**Figure 5.** Effect of Nω-nitro-L-arginine methylester (L-NAME, 10⁻⁴ M) on Losartan-induced (1.6 mg/kg) vasodilation showing a significant attenuation of Losartan-induced increase in epicardial cross-sectional area (CSA) but no significant attenuation of increases in average peak velocity (APV) or coronary blood flow (CBF). *Significant difference from pre-L-NAME value at p<0.05.
(PG) E₂ in porcine vascular smooth muscle cells. It has been proposed that such a shift in the pathway of endoperoxide metabolism could result in removal of the vasoconstrictor thromboxane A₂ and the formation of the vasodilator PGH₂. Whether such effects actually contribute to the vasodilator properties of Losartan is unclear; they may represent unrelated intrinsic effects of the compound. In the present study, the vasodilator effect of Losartan was unaffected by indomethacin administered in a dose reported to block cyclooxygenase. Therefore, coronary vasodilation caused by Losartan is unlikely to be mediated by the release of vasodilator prostaglandins. β-Adrenoceptors in the coronary arteries are known to mediate vasodilation. To rule out the theoretical possibility that Losartan may act via stimulation of these receptors, its vasodilator effect was examined after β-blockade, and no difference was observed. Thus, it is unlikely that the vasodilator effect of Losartan is via β-adrenoceptor stimulation. Interestingly, β-blockers themselves caused a small decrease in coronary flow velocity, possibly related to a reduction in heart rate and blood pressure, associated with a decrease in metabolic demand. Recent evidence has shown that ACE inhibition attenuates the vasoconstrictor effect of sympathetic nerve activation on the coronary circulation. Although we found no change in the Losartan-induced vasodilation after β-blockade, we did not test the effect of Losartan on stimuli known to cause sympathetic activation. Furthermore, angiotensin II stimulates endothelin secretion, which may contribute to its vasoconstrictor effect. In the present study, however, we did not test the hypothesis that part of the effect of AT₁-receptor blockade may be via reduced endothelin release.

L-NAME, an arginine analogue that is a potent inhibitor of nitric oxide synthetase, decreased the vasodilator effect of Losartan on epicardial coronary arteries. This suggests that its vasodilator effect in coronary conductance arteries may in part be mediated by the release of nitric oxide from the endothelium. The mechanism of such an effect is unclear. However, AT₁-receptors occur on the endothelium, and their stimulation may be inhibitory to endothelium-derived relaxing factor release; it is conceivable that blockade of such receptors enhances nitric oxide production. Nitric oxide has been reported to mediate the vasodpressor effect of ACE inhibitors in an animal model of hypertension; it is possible that this beneficial effect of ACE inhibition may be related to mechanisms similar to Losartan-induced release of endothelium-derived relaxing factor. In fact, a preliminary report suggests that nitric oxide contributes to the renal vasodilator effect of both the ACE inhibitor lisinopril and the AT₁ antagonist Losartan. Consistent with the participation of endothelium-derived relaxing factors other than nitric oxide in coronary resistance arteries, L-NAME had less of an effect on Losartan-induced increase in coronary flow velocity. As a potential therapeutic agent in myocardial ischemia, the efficacy of Losartan as an epicardial coronary vasodilator may be reduced by disruption of the endothelium, a hallmark of atherosclerotic disease; however, Losartan may be useful in syndromes of resistance vessel dysfunction such as microvascular angina.

In the present study, changes in coronary flow induced by AT₁-receptor antagonism and ACE inhibition occurred independent of changes in heart rate and blood pressure since drugs were administered by direct intracoronary injections. Rate-pressure product is a significant determinant of coronary blood flow; hence, it was important to minimize systemic effects to study the direct effects of Losartan and enalaprilat on the coronary arteries. This study also demonstrates the potential advantage of a combined two-dimensional and Doppler ultrasound system to simultaneously monitor changes in arterial dimensions and flow and thus dissect out effects on conductance versus resistance vessels. However, there are certain potential limitations to this approach. There may be local flow disturbances caused by the imaging catheter; these can be minimized, as in the present study, by placing the sample volume of the Doppler transducer at a distance at least 10 catheter diameters (about 14 mm) downstream. As a corollary, therefore, cross-sectional area measurements could not be made at exactly the same site as Doppler velocimetry; however, in the context of normal canine coronary vessels, this was not a major source of inaccuracy in measurement since cross-sectional areas were measured in a 25-mm segment where dimensions remained constant. Furthermore, in the present study, all measurements were made in comparison to baseline data, so any errors of estimation were unlikely to have interfered with the interpretation of drug effects. For similar reasons, it is unlikely that the general anesthesia used in our study interfered with our results; any vascular effects of the anesthetic agents would likely have influenced baseline data and data obtained after drug infusions to a similar degree.

From these acute studies in anesthetized dogs, we conclude that selective AT₁-receptor antagonism results in coronary vasodilation in both conductance and resistance arteries, an effect that does not depend on vasodilator prostaglandin release or β-adrenoceptor stimulation. The vasodilator effect of Losartan in the epicardial coronary circulation may be mediated, in part, by nitric oxide production. ACE inhibition also causes coronary vasodilation, but its magnitude is less than that of AT₁-receptor antagonism, especially in epicardial coronary arteries. Further studies in conscious human subjects are needed to define the role of AT₁-receptors in the coronary circulation in physiological and pathological states and the therapeutic role of their antagonists in coronary vascular disease.

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