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Angiotensin Type 1 Receptor Antagonism Reverses Abnormal Coronary Vasomotion in Atherosclerosis

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OBJECTIVES This study was performed to determine whether angiotensin type 1 (AT1) receptor inhibition improves abnormal coronary vasomotion and endothelial dysfunction in patients with atherosclerosis or its risk factors.

BACKGROUND Endothelial dysfunction, an early feature of atherosclerosis, contributes to abnormal vasomotion during stress. Angiotensin II may contribute to endothelial dysfunction in atherosclerosis.

METHODS In 25 patients, mean age 59 ± 2 years, with atherosclerosis or its risk factors, we measured coronary vasomotion during flow-mediated dilation (FMD) in response to adenosine, cold pressor test (CPT) and exercise before and after AT1 receptor blockade with intracoronary losartan (5 mg).

RESULTS Losartan did not alter resting coronary vascular tone, but epicardial FMD improved from 5.6 ± 1.5% to 8.9 ± 1.8% ($p = 0.02$). Abnormal epicardial vasomotion during CPT and exercise also improved with losartan from −1.7 ± 0.8% to 1.5 ± 0.1% ($p = 0.02$) and −0.6 ± 0.9% to 3.4 ± 1.2% ($p = 0.009$), respectively. Improvement in epicardial vasomotion was most prominent in segments with baseline endothelial dysfunction evidenced as constriction during stress. Microvascular dilation during adenosine, an endothelium-independent response, was unchanged with losartan.

CONCLUSIONS Inhibition of the coronary vascular AT1 receptors in patients with atherosclerosis improves epicardial vasomotion during stress, probably by improving endothelial dysfunction. Whether AT1 receptor blockade will provide long-term therapeutic benefits in atherosclerosis needs further investigation. (J Am Coll Cardiol 2001;38:1089–95) © 2001 by the American College of Cardiology

Physical and mental stress dilate human coronary epicardial arteries and microvessels in normal individuals, and the resulting augmentation in blood flow serves to meet the increased myocardial oxygen requirements (1–4). The vascular endothelium is pivotal in regulating this vasomotion by the release of a variety of relaxing and constricting factors (5–7). One important endothelium-derived relaxing factor is nitric oxide (NO) or an adduct of NO that contributes almost entirely to epicardial, and to a lesser extent, microvascular dilation during metabolic stress (8,9). Atherosclerosis and its risk factors are associated with depressed microvascular dilator responses and paradoxical constriction of epicardial arteries with exercise, which may contribute to the pathogenesis of myocardial ischemia in these patients (1,2,4,10). Endothelial cell dysfunction associated with reduced NO activity is believed to be the major underlying cause for this abnormal vasomotion, and, thus, interventions that ameliorate endothelial dysfunction and increase NO bioavailability are likely to improve coronary vasomotion and reduce myocardial ischemia in patients with coronary atherosclerosis.

While the precise cellular and molecular mechanisms for endothelial injury are still not clear, a large body of evidence suggests that alterations in the cytoplasmic redox state is a major contributory factor. In disease states, increased generation of reactive oxygen species, such as the superoxide anion and a relative deficiency of cellular antioxidant defense mechanisms, lead to an increase in oxidant stress. High concentration of superoxide anion contributes to atherogenesis by inactivating NO and increasing the activity of the transcription factor nuclear factor kappa B (11). Recent experimental studies have confirmed that angiotensin II (AII), the effector peptide of the renin-angiotensin system, can promote endothelial dysfunction by increasing superoxide anion generation (12,13), an effect that is mediated through angiotensin type 1 (AT1) receptors (14). It is also known that hypercholesterolemia and atherosclerosis lead to marked upregulation of angiotensin-converting enzyme activity (ACE) in epicardial vessels that results in increased local generation of AII (15). We recently demonstrated that AT1 receptor blockade selectively improved peripheral vascular endothelial dysfunction, measured as the response to the pharmacologic probe acetylcholine in patients with atherosclerosis.

In this study, we hypothesized that AII also contributes to coronary endothelial injury in human atherosclerosis and that inhibition of the AT1 receptor, by reversing endothelial dysfunction, will lead to improved coronary vasomotor function during physiologic stress.

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme activity
AT1	= angiotensin type 1
AII	= angiotensin II
CPT	= cold pressor test
FMD	= flow-mediated dilation
NADH/NADPH	= nicotinamide adenine dehydrogenase/nicotinamide adenine phosphate dehydrogenase
NO	= nitric oxide

METHODS

Patients. We studied 25 consecutive patients with either coronary atherosclerosis or those with angiographically normal coronary arteries and risk factors for atherosclerosis undergoing diagnostic cardiac catheterization for investigation of chest pain or abnormal noninvasive tests. Risk factors were defined as the presence of hypertension (blood pressure >140/90 mm Hg), hypercholesterolemia (low-density lipoprotein >160 mg/dl), diabetes, current smoking or smoking in the previous year (Table 1). Patients with a myocardial infarction in the previous month, valvular heart disease or those treated with an ACE inhibitor or AT1 receptor antagonist in the previous two weeks were excluded. Cardiac medications were withdrawn for at least 48 h and aspirin a week before the study. The study was approved by the Institutional Review Board of the National Heart, Lung and Blood Institute, and informed written consent was obtained from all patients.

Protocol. After completion of diagnostic coronary arteriography, a 6F guide catheter was introduced into the coronary artery, and blood flow velocity was measured using a 0.014 in. wire equipped with a Doppler crystal at its tip (Cardiometrics Flowire, Cardiometrics, Inc., Mountain View, California) (16). Adenosine was infused directly into the midsegment of the study vessel using an infusion catheter that was advanced over the Doppler wire. Losartan was given via the same infusion catheter after it was withdrawn proximal to the coronary segment being evaluated for flow-mediated dilation (FMD). Infusion rates ranged between 1 ml/min to 2 ml/min.

Table 1. Patient Characteristics

Variables	Study		
	FMD	CPT	Exercise
Number	18	14	8
Men	9	6	4
Age, yr	58 ± 2	60 ± 3	57 ± 1
LDL, mg/dL	146 ± 12	148 ± 12	129 ± 11
HDL, mg/dL	45 ± 3	48 ± 4	45 ± 6
Hypertension, n (%)	13 (72)	10 (71)	4 (50)
Diabetes, n (%)	4 (22)	0 (0)	5 (63)
Atherosclerosis, n (%)	10 (56)	6 (43)	7 (88)
Plasma ACE, U/l	11.0 ± 1	10.9 ± 1.6	9.7 ± 1.7

ACE = angiotensin-converting enzyme level; CPT = cold pressor test; FMD = flow-mediated dilation; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

After a 5-min infusion of dextrose 5% at 1 ml/min, baseline coronary blood flow velocity was measured and coronary angiography performed. This was repeated after each intervention. In 18 patients, adenosine was infused into the midvessel at 2.2 mg/min for 2 min to stimulate maximal increase in coronary blood flow in order to assess FMD in the proximal segment of the vessel (17). Fourteen patients were subjected to the cold pressor test (CPT) by immersing one hand in ice water for 90 s to 120 s. Eight patients performed arm exercise in the supine position using an ergometer (KHL Inc., 8450A ergometer, Kirkland, California). The workload was set at 10 W and increased every 2 min by 10 W to a symptom-limited maximum level. Thus, 15 of the 25 patients studied had two interventions.

After a 15-min recovery period, losartan (Merck, Westpoint, Pennsylvania), an AT1 receptor antagonist, was infused at 250 μg/min for 20 min. This dose was chosen to produce AT1 receptor blockade similar to that achieved by 50 mg of orally administered losartan and was shown to inhibit peripheral vasoconstriction with AII (18,19). Subsequently, adenosine infusion, CPT and exercise were repeated in each respective group as previously described.

Measurement of coronary blood flow and diameter. Coronary blood flow was derived from the coronary blood flow velocity and diameter measurements using the formula ($\Pi \times$ average peak velocity $\times$ 0.125 $\times$ diameter^2) (1). Coronary vascular resistance was calculated as mean arterial pressure ÷ coronary blood flow. For calculating flow, coronary artery diameter was measured in a 0.25-cm to 0.5-cm segment of vessel beginning 0.25 cm beyond the tip of the flow wire. Coronary angiograms were recorded using a cineangiographic system (Toshiba, Inc., Japan), and quantitative angiography was performed with the ARTREK software (Quantim 2001, Statview, ImageComm Systems, Inc., Mountain View, California) by an investigator blinded to the sequence of the interventions.

In addition to the measurement of the diameter at the level of the Doppler flow wire, 0.25 cm to 0.5 cm segments of midregions and distal regions of the epicardial coronary arteries were also measured by quantitative coronary angiography in patients who performed the CPT and exercise.

Reproducibility. The reproducibility of the coronary vascular responses to adenosine and CPT were evaluated in six patients over a period of 1 h. Percent change in coronary vascular resistance ($-75 \pm 4\%$ and $-76 \pm 3\%$, $p = 0.9$) and FMD ($6.2 \pm 1\%$ and $6.3 \pm 1\%$, $p = 0.7$) were similar during the two infusions of adenosine. Also, the percent change in coronary vascular resistance ($-6.3 \pm 6.9\%$ and $-12.7 \pm 5.8\%$, $p = 0.6$) and diameter ($-1.5 \pm 0.9\%$ and $-2.0 \pm 0.7\%$, $p = 0.7$) in response to CPT were reproducible.

Statistical analysis. Data are expressed as mean ± SEM. Differences between means were compared by paired or unpaired Student *t* test, as appropriate. All p values are

two-tailed, and a p value <0.05 was considered to be statistically significant. Multiple comparison adjustment was performed using Holm's method to keep the experimental α at 0.05. Univariate correlations were performed using the Pearson's correlation coefficient. Two-way repeated measures analysis of variance was performed that included patients, study medication (group: baseline vs. losartan) and stress modality (stage: baseline vs. stress [CPT or exercise and FMD]) as main effects and incorporated the two-factor interactions between them.

RESULTS

Coronary vascular response to losartan. After 10 min of intracoronary losartan infusion, there was no change in coronary epicardial diameter (1.73 mm ± 0.06 mm vs. 1.71 mm ± 0.07 mm, p = 0.2), blood flow (36.7 ± 4.8 ml/min vs. 37.4 ± 5.2 ml/min, p = 0.9) or vascular resistance (4.7 ± 0.5 mm Hg × cm^{-1} × s vs. 4.6 ± 0.5 mm Hg × cm^{-1} × s, p = 0.2). Heart rate (77 ± 2 beats/min to 76 ± 2 beats/min, p = 0.2) and mean arterial pressure (115 ± 3 mm Hg to 113 ± 3 mm Hg, p = 0.3) also remained unchanged.

Effect of losartan on FMD. Flow-mediated dilation was determined in the proximal segment of the study vessel that was exposed to increased blood flow and shear forces but not to the adenosine that was infused distally. During the control infusion of adenosine, mean epicardial FMD was 5.6 ± 1.5% (p < 0.001). After losartan, this was significantly enhanced to 8.9 ± 1.8%, p < 0.001 (p = 0.02 compared with before losartan, Fig. 1). There was no difference in the increase in coronary blood flow in response to adenosine (310 ± 25% to 310 ± 28%, p = 0.4 before vs. after losartan).

Effect of losartan on coronary vasomotor responses to CPT. Cold pressor test significantly increased heart rate and blood pressure, but there was no difference in the systemic hemodynamic response to CPT with losartan (Table 2), nor was there a difference in the change in microvascular tone with CPT after losartan. Coronary blood flow increased by 17 ± 6% before compared with 18 ± 5% after losartan, p = 0.5 (Table 2). Epicardial coronary artery diameter tended to decrease with CPT before losartan (by −1.7 ± 0.8%). After losartan, CPT resulted in epicardial coronary dilation (by 1.5 ± 1.1%, p = 0.02 compared with before losartan, Fig. 2).

Effect of losartan on coronary vasomotor responses to exercise. Exercise significantly increased heart rate, blood pressure and coronary blood flow. These changes were similar after losartan (Table 2). Peak workload during arm exercise was 39 ± 7 W and mean duration was 5.6 ± 0.4 min during the control study, and each patient exercised to the same workload and duration after treatment with losartan. Coronary microvascular vasodilation was similar before and after losartan; blood flow increased by 102 ± 37% and 87 ± 15% (p = 0.6) before compared with after losartan. Before losartan, exercise did not alter mean epicardial coronary artery diameter (−0.6 ± 0.9%, p = 0.2, compared with rest). However, after losartan there was significant epicardial coronary artery dilation with exercise (3.4 ± 1.2%, p = 0.02 compared with rest, p = 0.016 compared with before losartan, Fig. 3).

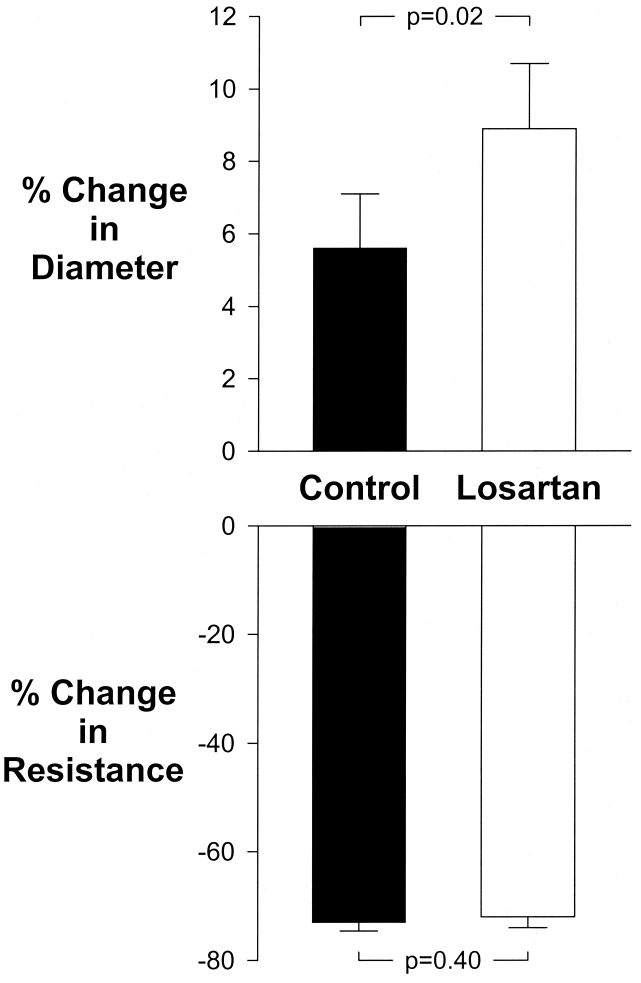

Figure 1. Percent change in epicardial diameter (flow-mediated dilation) **(top)** and coronary vascular resistance **(bottom)** during adenosine, before (control) and after losartan.

There was a negative correlation between the diameter changes in response to either exercise or CPT and the magnitude of improvement with losartan (r = −0.38, p = 0.013). Thus, improvement with losartan was only observed in segments that constricted (endothelial dysfunction) with either exercise or CPT (from −3.8 ± 1% constriction to +1.1% dilation, p < 0.001, n = 30). In contrast, segments that initially dilated with stress (normal endothelial function), dilated to the same degree after losartan (3.1 ± 0.4% before to 4.1 ± 2% after losartan, p = 0.9, n = 14). Two-way repeated measures analysis of variance suggested that the interactions between group × stage were significant for both stress modalities (CPT/exercise and FMD, p = 0.003 and p = 0.008, respectively), indicating that the p values for the main event (group or stage) are not interpretable. Therefore, separate pairwise *t* test comparisons were

Table 2. Response to CPT and Exercise

Variables	Before Losartan		After Losartan		p Value Before vs. After Losartan During Stress
	Baseline	Stress	Baseline	Stress	
CPT					
Heart rate (beats/min)	77 ± 4	87 ± 4†	76 ± 3	83 ± 4†	0.2
Mean arterial pressure (mm Hg)	113 ± 4	140 ± 4†	112 ± 5	138 ± 4†	0.4
Coronary blood flow (ml)	39 ± 7	46 ± 10	37 ± 8	44 ± 10*	0.5
Coronary vascular resistance (mm Hg·ml^{-1}·min)	4.0 ± 0.6	4.2 ± 0.6	4.4 ± 0.6	4.7 ± 0.7	0.2
Exercise					
Heart rate (beats/min)	80 ± 4	112 ± 5†	77 ± 5	113 ± 4†	0.8
Mean arterial pressure (mm Hg)	112 ± 4	145 ± 5†	112 ± 5	146 ± 4†	0.5
Coronary blood flow (ml)	31 ± 5	63 ± 14*	32 ± 4	58 ± 8†	0.4
Coronary vascular resistance (mm Hg·ml^{-1}·min)	4.3 ± 0.8	3.3 ± 0.9*	4.2 ± 0.8	3.1 ± 0.6†	0.4

*$p < 0.05$; †$p < 0.01$ compared with baseline.
CPT = cold pressor test.

made for each intervention, and each comparison was significant after adjusting for multiple comparisons (n = 3) using Holm's method.

DISCUSSION

Increasing evidence suggests that the renin-angiotensin system is implicated in the pathogenesis of atherosclerosis, although the precise mechanisms remain controversial. The major findings of this study are that acute AT1 receptor blockade with losartan can improve endothelium-dependent and physiologic epicardial coronary vasomotion in patients with atherosclerosis or its risk factors, as indicated by augmentation of FMD and the reversal of abnormal epicardial vasomotion during CPT and exercise.

AT1 receptor blockade and basal coronary vascular tone. The dose of losartan used in our study appears to be sufficient to block AT1 receptors in humans, and the blockade persists for at least 60 min, the period during which we investigated the effects of losartan on various maneuvers (18–20). Acute AT1 receptor blockade with intracoronary losartan did not alter conductance or resistance vessel tone, suggesting that endogenous AII is not a determinant of resting tone in atherosclerotic coronary vessels in vivo. This observation is consistent with previous studies in young healthy volunteers in whom acute AT1 receptor blockade did not alter basal tone in the forearm microcirculation (18,20). Alternatively, the reduced AII-mediated constriction during AT1 receptor blockade may be offset by simultaneous alteration in activity of other endogenous vasoactive substances that autoregulate resting coronary vasomotor tone.

AT1 receptor blockade and endothelial dysfunction. Flow-mediated dilation is an important endothelium-dependent mechanism that modulates coronary epicardial tone in response to increased shear stress (21). Conductance vessel FMD is abolished by damaging the endothelium or by inhibiting NO synthesis (1,22). Flow-mediated dilation is impaired in the atherosclerotic human coronary arteries in vivo (17), and its magnitude reflects NO release in response to increased shear stress. In this study, losartan improved epicardial coronary FMD, suggesting that it augmented the endothelium-dependent release of NO. The maximal blood flow increase in response to adenosine was similar, indicating that the stimulus for FMD was comparable before and after losartan and that endothelium-independent microvascular dilation was unchanged with losartan. This result illustrates that the improvement in brachial artery FMD after oral losartan therapy observed in our recent study, which was also accompanied by an increase in serum nitrogen oxide levels, also occurs in the coronary circulation (19).

AT1 receptor blockade and physiologic epicardial coronary vasomotion. Microvascular and epicardial coronary vasodilation during stress, which, under maximal stimulation is able to increase coronary blood flow by up to fivefold, is designed to meet myocardial oxygen demands. In atherosclerosis, stresses such as pacing, exercise, mental stress or CPT result in paradoxical coronary constriction or impaired vasodilation, as observed in this study (1–4). We have shown that this is secondary to endothelial cell injury and occurs because sympathetically mediated alpha-adrenergic receptor activation and myogenic constriction cannot be opposed by increased release of endothelium-derived relaxing factors (1).

We now demonstrate that epicardial coronary vasomotion during exercise or CPT in patients with atherosclerosis or its risk factors can be improved by acutely inhibiting AT1 receptors. Improvement in epicardial reactivity occurred without alteration in coronary blood flow and, hence, shear stress between the two tests before and after losartan. Furthermore, improvement with losartan was most marked in segments with the greatest constriction in response to physical stress, suggesting that improvement preferentially occurred in patients with the worst endothelial dysfunction (23,24). Although the latter observation raises the possibility of regression to the mean as an explanation, several potential mechanisms may contribute to this finding.

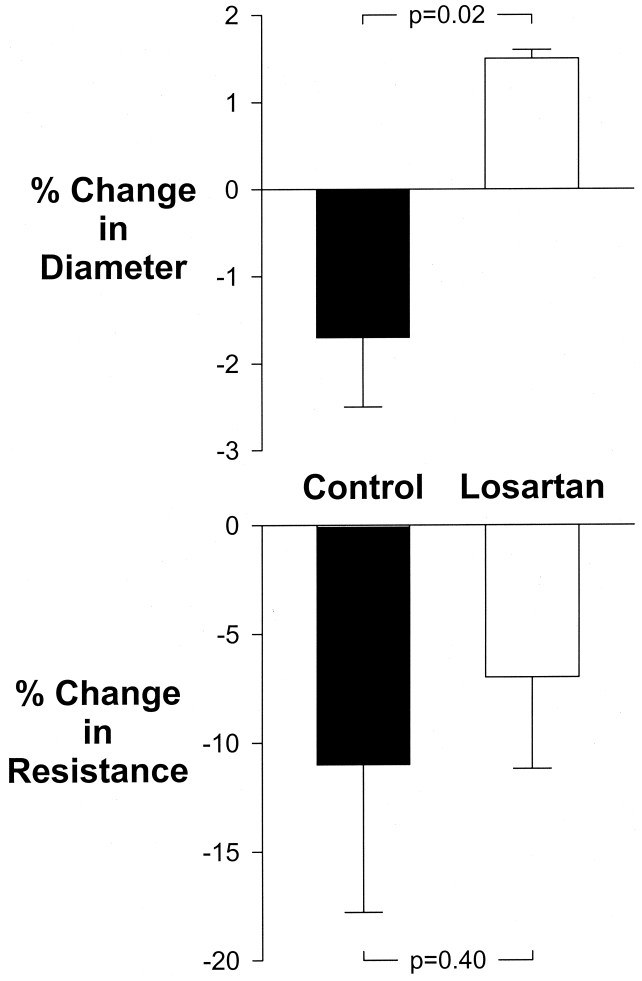

Figure 2. Percent change in epicardial diameter **(top)** and coronary vascular resistance **(bottom)** during cold pressor testing, before (control) and after losartan.

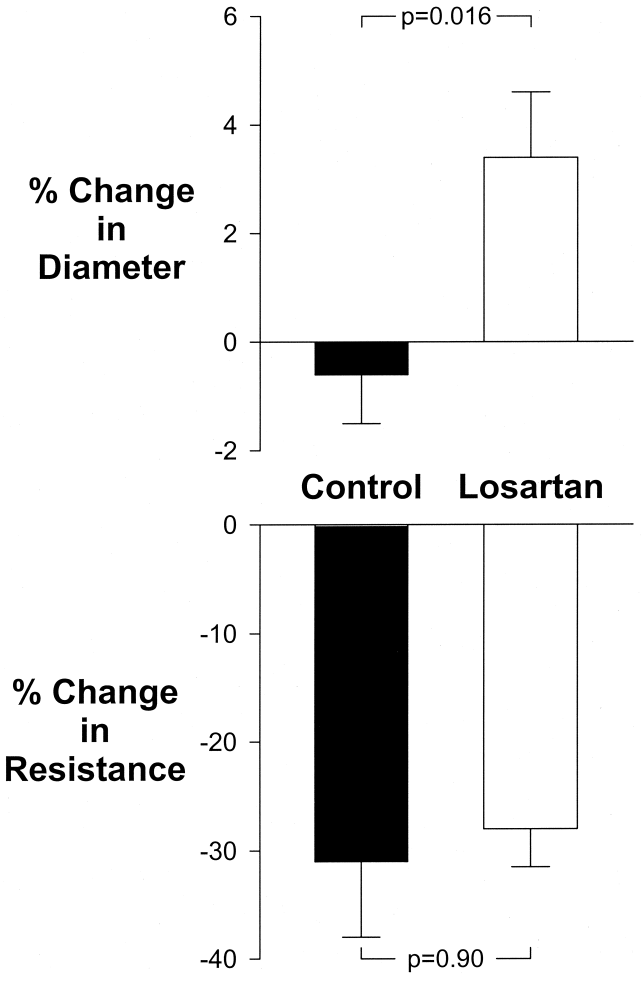

Figure 3. Percent change in epicardial diameter **(top)** and coronary vascular resistance **(bottom)** during exercise, before (control) and after losartan.

Potential mechanisms underlying the improvement in endothelial function by AT1 receptor antagonism. Experimental evidence supports the presence of increased ACE and AII levels in atherosclerotic lesions (25). Angiotensin II is a powerful stimulus for nicotinamide adenine dehydrogenase/nicotinamide adenine phosphate dehydrogenase (NADH/NADPH) oxidase-dependent vascular superoxide anion generation that inactivates endothelial NO (12,13,15), a mechanism that also appears to be instrumental in precipitating endothelial dysfunction in hypercholesterolemia, atherosclerosis, hypertension and diabetes. Infusion of AII in rats increases vascular superoxide anion production and NADH/NADPH oxidase activity, and the consequent impairment of endothelium-dependent relaxation is restored to normal by treatment with losartan. Indeed, losartan lowers the production of superoxide to below normal levels, suggesting that endogenous AII may modulate basal superoxide anion production (13). Thus, AT1 receptor antagonism may reverse endothelial dysfunction by improving NO bioavailability.

An alternate proposed mechanism of action of AT1 receptor antagonists is via the release of NO by angiotensins I, II, III, IV and angiotensin peptide (1–7). The effect of angiotensin fragments can be inhibited by NO synthase inhibition, bradykinin B2 receptor blockade and protease inhibitors (26,27). Thus, angiotensin peptides promote NO activity by activating local kinin production, an effect that is mediated, at least partly, through AT2 receptor stimulation (28,29). Therefore, during acute AT1 receptor blockade, greater local AII may be available to stimulate AT2 receptors, an effect that may be mediated via the bradykinin B2 receptor and involves enhancement of both prostaglandins and NO (28,29).

Angiotensin II, via stimulation of the AT1 receptor, also releases potent vasoconstrictors including endothelin and the prostanoid PGH_2 and augments sympathetic constrictor tone, and inhibition of these effects by losartan may also be responsible for the improved vasodilator function observed (30).

Thus, AT1 receptor antagonism may improve coronary vasomotion by several mechanisms including improvement of NO bioavailability. This study supports this concept by demonstrating losartan-mediated improvement in FMD, considered to be primarily dependent on NO release (1,22).

The study was not specifically designed to evaluate whether an increase in NO activity is responsible for the beneficial effect of losartan on epicardial vasomotion with CPT and exercise. However, we have previously observed that losartan improves endothelium-dependent acetylcholine responses in the femoral microcirculation, and oral therapy increases NO activity in humans (19). Other mechanisms that may contribute to the observed improvement are inhibition of sympathetic nervous system activation during stress with AT1 receptor blockade, an effect that has also been observed with ACE inhibitors and is consistent with the synergy between AII and the sympathetic nervous system (31,32).

It is unlikely that the observed improvement in coronary vasomotion with losartan was due to endothelium-independent effects of losartan. First, there was no baseline alteration of tone with losartan, and, secondly, microvascular dilation with adenosine, which is almost entirely due to endothelium-independent actions, was unaltered by losartan in this study, and, finally, we had previously noted a lack of effect in femoral microvascular dilation with sodium nitroprusside or of brachial dilation with nitroglycerin after losartan (19).

Comparison with ACE inhibitors. Previous studies have demonstrated that ACE inhibition reverses endothelial dysfunction in atherosclerosis (33,34) and improve FMD (32). As observed in this study, improvement in epicardial coronary vasomotion during stress with ACE inhibition was only evident in segments with endothelial dysfunction measured as the constrictor response to stress (31,32). This effect is, at least partly, due to increased bioavailability of bradykinin and can be inhibited by NO synthase blockade (35). This study offers circumstantial evidence that prevention of AII synthesis by ACE inhibitors may also contribute to their beneficial vascular effects. Further experiments evaluating whether ACE inhibition reverses endothelial dysfunction during concomitant AT1 and AT2 receptor inhibition will provide definitive data. Whether ACE inhibition, particularly with tissue-avid compounds, will be superior to AII receptor antagonists in the coronary circulation needs further study (31,34).

AT1 receptor blockade and microvascular coronary dilation during stress. Exercise and CPT reduced coronary vascular resistance, but this was not altered by losartan. Thus, unlike epicardial vasomotion, microvascular dilation is not potentiated by AT1 receptor inhibition in patients with atherosclerosis or its risk factors. That coronary microvascular dilation during stress is, at least partly, dependent on endothelium-derived NO activity has been demonstrated by us previously. L-N^G monomethyl arginine, an inhibitor of NO synthesis, partly inhibited pacing-induced increase in coronary blood flow in patients with normal endothelial function, but this contribution was reduced in those with endothelial dysfunction (1). In contrast with its relatively modest effects on the microvessels, NO synthase inhibition completely inhibited pacing-mediated epicardial coronary dilation, indicating that conductance vessel dilation is almost entirely, and microvascular dilation is only to a small extent, dependent on endothelial NO (1,36). Coronary microvascular dilation during exercise, in addition to NO, is also mediated by release of local metabolites including adenosine, prostaglandins, carbon dioxide, hypoxia, circulating catecholamines and withdrawal of sympathetic tone (36). Additionally, these multiple mechanisms may compensate for any deficiency in NO activity in patients with endothelial dysfunction because of the known autoregulatory capacity of the coronary microcirculation (36–38). Deficiency in the contribution of NO to microvascular dilation may, therefore, only become evident during peak stress. In our study, neither exercise nor CPT produced maximal stress on the coronary microcirculation. Although this observed discrepancy between the epicardial and microvascular circulations may explain why AT1 antagonists do not appear to be effective antianginal agents, in the majority of cases myocardial ischemia is a consequence of one or more flow-limiting stenoses in the epicardial circulation. However, clinical studies specifically addressing this issue have not been performed.

Study limitations. We did not study vessels with >50% stenosis and, thus, cannot conclude whether AT1 receptor blockade would also improve function in vessels with more severe atherosclerosis. Due to the limited number and heterogeneous nature of patients studied, we are unable to investigate whether the beneficial effects of AT1 receptor antagonists is more likely to occur in patients with one or another of the specific risk factors for atherosclerosis. Additionally, since our study examines the effect of acute AT1 receptor blockade, we cannot comment on whether similar results would be achieved with chronic losartan therapy. However, we have recently demonstrated improvement in physiologic vasomotion in the brachial artery with long-term losartan therapy, suggesting that vascular endothelial dysfunction can be improved by both acute and chronic AT1 receptor antagonism (19). These issues need to be clarified by further appropriately designed studies.

Conclusion and implications. Angiotensin type 1 receptor antagonism improves physiologic coronary vasomotion and endothelial dysfunction in patients with atherosclerosis and its risk factors. In experimental models of atherosclerosis, AT1 receptor blockade appears to have a protective effect (39). Potential mechanisms for these vasculoprotective effects include the prevention of endothelial injury (40–42), augmentation of NO activity (40), inhibition of lipid peroxidation (39) and an antiproliferative effect (43). These findings, together with our observations that losartan improves coronary and peripheral endothelial function, provides impetus for studying the antiatherogenic potential of AT1 receptor antagonism in patients with atherosclerosis (19).

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