Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 33, No. 3, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(98)00611-1

Vascular Biology

Abnormal Flow-Mediated Epicardial Vasomotion in Human Coronary Arteries Is Improved by Angiotensin-Converting Enzyme Inhibition

A Potential Role of Bradykinin

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OBJECTIVES This study was performed to determine whether angiotensin converting enzyme (ACE) inhibition improves endothelium-dependent flow-mediated vasodilation in patients with atherosclerosis or its risk factors and whether this is mediated by enhanced bradykinin activity.

BACKGROUND Abnormal coronary vasomotion due to endothelial dysfunction contributes to myocardial ischemia in patients with atherosclerosis, and its reversal may have an antiischemic action. Previous studies have shown that ACE inhibition improves coronary endothelial responses to acetylcholine, but whether this is accompanied by improved responses to shear stress remains unknown.

METHODS In 19 patients with mild atherosclerosis, metabolic vasodilation was assessed during cardiac pacing. Pacing was repeated during separate intracoronary infusions of low-dose bradykinin (BK) and enalaprilat. Endothelium-dependent and -independent vasodilation was estimated with intracoronary BK and sodium nitroprusside respectively.

RESULTS Enalaprilat did not alter either resting coronary vascular tone or dilation with sodium nitroprusside, but potentiated BK-mediated dilation. Epicardial segments that constricted abnormally with pacing ($-5 \pm 1\%$) dilated ($3 \pm 2\%$) with pacing in the presence of enalaprilat ($p = 0.002$). Similarly, BK at a concentration (62.5 ng/min) that did not alter resting diameter in the constricting segments also improved the abnormal response to a $6 \pm 1\%$ dilation ($p < 0.001$). Cardiac pacing-induced reduction in coronary vascular resistance of $27 \pm 4\%$ ($p < 0.001$) remained unchanged after enalaprilat.

CONCLUSIONS Thus ACE inhibition: A) selectively improved endothelium-dependent but not -independent dilation, and B) abolished abnormal flow-mediated epicardial vasomotion in patients with endothelial dysfunction, in part, by increasing endogenous BK activity. (J Am Coll Cardiol 1999;33:796–804) © 1999 by the American College of Cardiology

Exercise and cardiac pacing 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 (1–5). The vascular endothelium is pivotal in regulating this vasomotion by the release of a variety of relaxing and constricting factors (6–8). One important endothelium-derived relaxing factor is nitric oxide (NO) or an adduct of NO (9,10) that contributes almost entirely to epicardial and, to a lesser extent, microvascular dilation during metabolic stress. Atherosclerosis and its risk factors are associated with depressed microvascular dilator responses and paradoxical constriction of epicardial arteries with exercise and cardiac pacing which may contribute to the pathogenesis of myocardial ischemia in these patients (1–3,5,11). Endothelial cell dysfunction associated with reduced NO activity is believed to be the major underlying cause for this abnormal vasomotion, and, thus, interventions which ameliorate endothelial dysfunction and increase NO bioavailability are likely to improve coronary vasomotion and reduce myocardial ischemia in patients with coronary atherosclerosis.

A potential therapeutic target for improving endothelial dysfunction appears to be the inhibition of the angiotensin converting enzyme (ACE/kininase II). This enzyme, present in large quantities on the surface of endothelial cells, is a key component of the circulating and vascular kallikrein-kinin and the renin-angiotensin systems. One of

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Manuscript received January 14, 1998; revised manuscript received October 9, 1998, accepted November 16, 1998.

Abbreviations and Acronyms
ACE = angiotensin-converting enzyme
BK = bradykinin
NO = nitric oxide

its functions is to degrade bradykinin (BK), a locally synthesized polypeptide that is known to regulate resting tone and flow-mediated vasodilation in the normal human coronary circulation (12), possibly through the release of NO (13,14), prostacyclin (15) and endothelium-derived hyperpolarizing factor (16). Thus, inhibition of ACE would increase BK activity and potentially improve endothelial function, especially if BK activity is depressed in atherosclerosis. In addition to its effects on BK metabolism, ACE also promotes the synthesis of angiotensin II from angiotensin I, which among several actions, also stimulates vascular superoxide generation (17,18). Thus, ACE inhibition may rectify endothelial dysfunction by reducing angiotensin II synthesis and thus attenuating vascular oxidant stress. In this study, we investigated whether: A) ACE inhibition improves shear stress-induced (physiological) vasodilation in patients with mild coronary atherosclerosis or its risk factors, and B) any observed improvement in vasomotion is mediated by increased BK activity.

METHODS

Patients. We studied 19 patients with angiographically normal, or near normal (<30% narrowing) coronary arteries, undergoing diagnostic cardiac catheterization for investigation of chest pain or abnormal noninvasive tests. Patients with myocardial infarction in the previous month, valvular heart disease or those treated with ACE inhibitors in the previous two weeks were excluded. The mean age was 50 ± 10 years; there were 15 (79%) men. Eight patients were hypertensive (blood pressure >140/90 mm Hg), hypercholesterolemia (total cholesterol >200 mg/dl) was present in 14 patients and 2 had diabetes (both on pharmacologic antidiabetic therapy). Seven patients were either current smokers or had smoked in the previous 2 years; 13 patients were exposed to 1, and 6 patients to >1 risk factors. Angiographic atherosclerosis was present in 11 patients. Cardiac medications were withdrawn for at least 48 h, and aspirin a week before the study. The study was approved by the National Heart, Lung, and Blood Investigational Review Board and informed written consent was obtained from all patients.

Protocol. After completion of diagnostic coronary arteriography, a six-French guide catheter was introduced into the coronary artery and blood flow velocity was measured using a 0.018 inch wire equipped with a Doppler crystal at its tip (Cardiometrics Flowire, Cardiometrics, Inc., Mountain View, California) (19,20). Quantitative angiography was performed with the ARTREK software (ImageComm Systems, Inc.). A total of 50 segments were analyzed; 3 segments of epicardial coronary arteries could be measured in 13 patients, 2 segments in 5 patients, 1 segment in 1 patient. Coronary blood flow and resistance were calculated as described previously (1,21). All drugs were infused directly into the left main coronary artery via the guide catheter at infusion rates ranging between 1 to 2 ml/min. Infusion rates were halved for studies performed in the right coronary artery.

After a five-minute infusion of dextrose 5% at 1 ml/min, baseline coronary blood flow velocity was measured and coronary angiography performed. Rapid atrial pacing was performed in 17 patients at heart rates ranging between 130 to 150 bpm. Pacing from the right ventricle was performed at 150 bpm in the remaining two patients who developed atrioventricular Wenckebach at rates below 115 bpm. Thus the mean cardiac pacing rate was 144 ± 7 bpm.

Endothelium-dependent vasodilation was estimated in all patients by performing a dose-response curve with incremental infusions of intracoronary BK starting at 62.5 ng/min (n = 19) for 3 min, followed by 2-min infusions of 1 μg/min (n = 17) and 4 μg/min (n = 19).

Five minutes after performing the dose-response curve with BK, endothelium-independent function was estimated with sodium nitroprusside and flow reserve with adenosine. Intracoronary sodium nitroprusside was given at 40 μg/min for 3 min, and intracoronary adenosine at 2.2 mg/min for 2 min.

After a 15-min interval, an infusion of BK (62.5 ng/min) was given and pacing was repeated during the infusion. Following a 10-min recovery period, baseline measurements were made. Intracoronary enalaprilat, a potent ACE inhibitor, was then infused at 20 μg/min for 10 min. In a previous study, this intravascular concentration of enalaprilat adequately blocked the constrictor response to angiotensin I (22). While continuing the infusion, pacing was repeated at the control rate in all the patients, BK (62.5 ng/min, n = 17) was co-infused for 2 min, and 40 μg/min sodium nitroprusside was given for 3 min (n = 11). Blood flow velocity was measured and coronary angiography was performed after each intervention.

Statistical analysis. Data are expressed as mean ± SEM. Differences between means were compared by paired or unpaired Student *t* test, as appropriate. The effect of multiple doses of BK were analyzed using the two-way analysis of variance (ANOVA). Appropriate interaction (dose X drug) tests were employed. All P values are two-tailed, and a value <0.05 was considered of statistical significance. Correlation analysis was performed using Pearson's correlation coefficient.

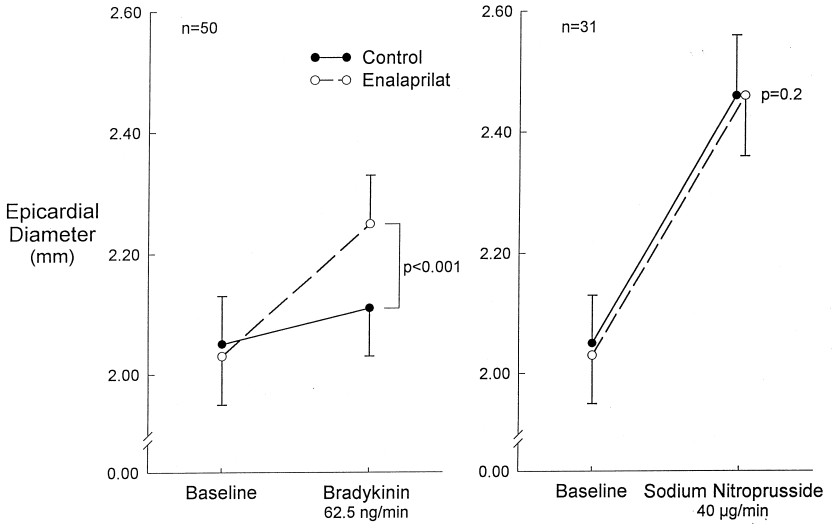

Figure 1. Effects of bradykinin **(left)** and sodium nitroprusside **(right)** before **(control, ●)** and after enalaprilat (○) on epicardial diameter. (Data represent mean ± SEM).

RESULTS

Effect of enalaprilat on endothelium-dependent and -independent epicardial coronary artery responses. Resting mean coronary epicardial diameter remained unchanged 10 minutes after infusion of enalaprilat; 2.1 ± 0.1 versus 2.0 ± 0.1 mm (p = ns), suggesting that ACE did not regulate resting epicardial vessel tone. There was also no alteration in mean arterial blood pressure (105 ± 2 to 106 ± 2 mm Hg) and heart rate (79 ± 2 to 81 ± 3 bpm).

Epicardial diameter increased progressively with the 62.5 ng/min, 1 μg/min, and 4 μg/min doses of BK by 1.5 ± 1%, 8.3 ± 1% and 11.4 ± 1%, respectively ($p < 0.001$, ANOVA). When the 62.5 ng/min dose of BK was coinfused with enalaprilat, the response was enhanced to a 5.6 ± 1% ($p < 0.001$) increase in epicardial diameter (Fig. 1). In contrast, dilation of epicardial coronary arteries with sodium nitroprusside was similar before and after enalaprilat (p = 0.2) (Fig. 1). Thus, enalaprilat significantly potentiated BK- but not sodium nitroprusside-mediated epicardial vasodilation.

Effect of enalaprilat on pacing-induced coronary epicardial changes. During control pacing, epicardial coronary artery diameter increased by a mean 3.7 ± 1% (p = 0.06) in the 50 segments analyzed in 19 patients. After enalaprilat, there was no significant further increase in pacing-mediated epicardial vasodilation (5.8 ± 2%, p = 0.4, compared with control). Further analysis was performed in the 20 segments from 12 patients that constricted (abnormal response) and the 30 segments from 16 patients that dilated (normal response) with pacing (Fig. 2). A mean 5.1 ± 1% constriction observed during control pacing improved to a 6.1 ± 2% dilation when pacing was repeated in the presence of enalaprilat (p = 0.002, Fig. 2). In contrast, enalaprilat did not further potentiate the 9.6 ± 1% dilation observed in the dilating segments (Fig. 2). Thus, ACE inhibition selectively improved epicardial dilation in segments with abnormal pacing-mediated vasomotion.

Effect of BK and sodium nitroprusside on epicardial segments with abnormal vasomotion during pacing. Bradykinin (62.5 ng/min) produced no vasodilation (0 ± 2%) in the segments that constricted abnormally with pacing, compared with a 4.9 ± 2% (p = 0.003) dilation in segments that dilated normally during pacing (Fig. 3). In contrast, vasodilation with sodium nitroprusside was similar in the constricting and dilating segments; 19 ± 3% and 20 ± 3%, respectively, p = 0.9. Enalaprilat enhanced BK-mediated epicardial vasodilation in both constricting and dilating segments (11.6 ± 3%, $p < 0.001$ and 10.7 ± 3%, respectively, p = 0.04, Fig. 3). Thus, segments of epicardial coronary arteries with abnormal pacing-mediated vasomotion demonstrated abnormal reactivity to endothelium-dependent, but not endothelium-independent vasodilators, and ACE inhibition improved BK-mediated dilation in both groups.

Effects of low-dose BK on pacing-induced epicardial vasomotion. To investigate whether the improvement of epicardial constriction during pacing by enalaprilat was secondary to increased local BK levels, we studied the effects on pacing-induced epicardial vasomotion of low-dose BK at a concentration that did not alter resting diameter in the constricting segments. Segments that initially constricted by 5.1 ± 1% during pacing, dilated by 5.9 ± 1% ($p < 0.001$) during pacing with BK (62.5 ng/ml, Fig. 4). Segments of epicardial coronary arteries that initially dilated with pacing also dilated with BK and there was no further change during pacing with BK (Fig. 4). Thus, BK selectively improved

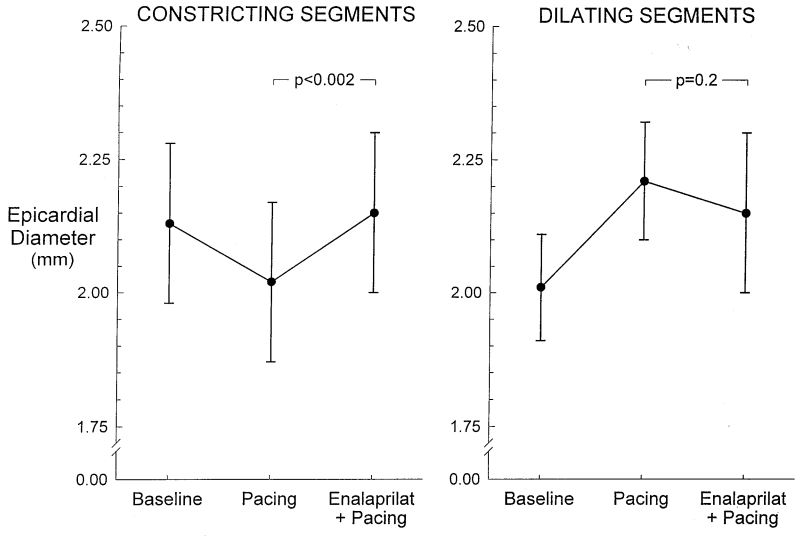

Figure 2. The effects of cardiac pacing before and after enalaprilat on coronary epicardial segments that initially constricted (**left,** n = 20) or dilated (**right,** n = 30) with cardiac pacing. There was no significant difference (p = 0.5) between the mean baseline diameters of constricting segments (2.1 ± 0.1 mm) compared to dilating segments (2.0 ± 0.1 mm). Data represent mean ± SEM.

abnormal pacing-induced vasomotion in segments with endothelial dysfunction, mimicking the action of enalaprilat.

Effect of enalaprilat on coronary microvascular function. Resting mean coronary blood flow and vascular resistance remained unchanged 10 min after infusion of enalaprilat; 39 ± 4 ml/min and 3.3 ± 0.4 mm Hg·ml^{-1}·min before, versus 39 ± 4 ml/min and 3.2 ± 0.3 mm Hg·ml^{-1}·min after, respectively (p = ns for all), suggesting that ACE did not regulate resting coronary microvascular tone. Bradykinin produced graded increases in coronary blood flow and reduction in vascular resistance; at the 62.5 ng/min, 1 μg/min and 4 μg/min doses; mean blood flow increased by 14 ± 3%, 79 ± 9% and 162 ± 18%, respectively, and vascular resistance decreased by 10 ± 2%, 41 ± 4% and 58 ± 4%, respectively, (p < 0.001, ANOVA, both). Enalaprilat enhanced the response of BK (62.5 ng/min) to a 40 ± 13% (p = 0.08) increase in flow and a 25 ± 5% (p = 0.02) reduction in vascular resistance, indicating inhibition of coronary ACE with enalaprilat. In contrast, the 137 ± 19% increase in coronary blood flow and 62 ± 2% reduction in vascular resistance with sodium nitroprusside remained unaltered after enalaprilat (146 ± 19% [p = 0.5] and 61 ± 3% [p = 0.6]) change, respectively.

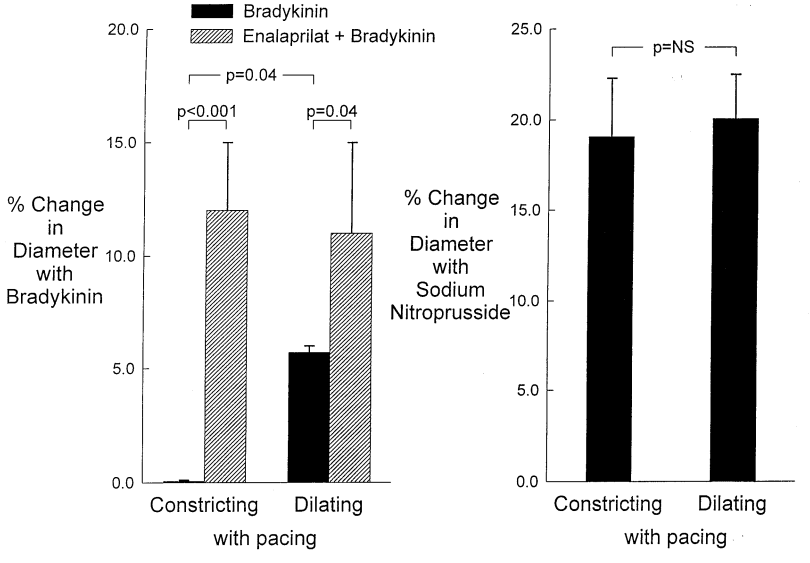

Figure 3. The effects of bradykinin **(left)** and sodium nitroprusside **(right)** on coronary epicardial segments that constricted or dilated with cardiac pacing. The potentiation of bradykinin by enalaprilat is demonstrated in hatched bars. Data represent mean ± SEM.

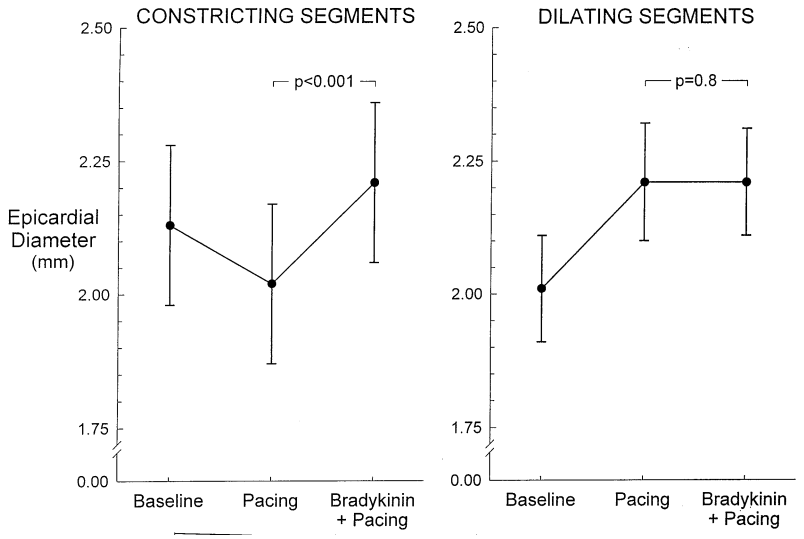

Figure 4. The effects of cardiac pacing before and after 62.5 ng/min of intracoronary bradykinin on coronary epicardial segments which constricted **(left)** or dilated **(right)** with control pacing. Data represent mean ± SEM.

During initial cardiac pacing, coronary blood flow increased by 54 ± 10% and vascular resistance decreased by 27 ± 4%. In the presence of enalaprilat, these indices were not significantly different at 47 ± 9% ($p = 0.5$) and 27 ± 5% ($p = 0.9$), respectively. There was also no correlation between the magnitude of reduction in vascular resistance with control pacing and the change observed when pacing was repeated in the presence of enalaprilat ($r = 0.2$, p = NS). Thus, ACE inhibition did not influence pacing-mediated metabolic coronary microvascular dilation in patients with depressed responses. Furthermore, pacing-induced microvascular vasodilation was similar in patients with epicardial vessel constriction and those with dilation during pacing (52 ± 10% vs. 55 ± 11% [p = ns] increase in flow with pacing). Finally, flow reserve with adenosine was similar in both groups (345 ± 44% vs 324 ± 24% increase in flow in patients with epicardial dilation and constriction, respectively).

DISCUSSION

Coronary epicardial and microvascular dilation accompanies increases in myocardial oxygen demand. Whereas epicardial dilation is primarily believed to be due to endothelium-dependent release of NO (1,21,23,24), the causes for microvascular dilation are multifactorial in origin (25,26). Endothelial dysfunction associated with diminished NO activity in patients with atherosclerosis, or those with normal coronary arteries and risk factors for atherosclerosis, results in absence of flow-mediated dilation (1). In epicardial coronary arteries of these patients, increased shear precipitated by exercise, pacing or mental stress causes paradoxical coronary constriction, probably as a result of unopposed myogenic constriction (2,3,5,11). In a previous study, we observed that acute ACE inhibition improves acetylcholine-mediated, endothelium-dependent dilation and that this is in part achieved by increased NO bioavailability (27). In this study, we evaluated the effects of ACE inhibition and BK on coronary vasomotion during stress. Our data show that: 1) ACE inhibition improves endothelial dysfunction and abolishes abnormal epicardial coronary artery constriction during cardiac pacing, 2) low-dose BK also abolishes coronary constriction during pacing, and 3) ACE inhibition did not influence microvascular dilation during stress.

Improvement in flow-mediated epicardial vasomotion by ACE inhibition. As previously reported, cardiac pacing produced a heterogenous epicardial coronary arterial response where some segments dilated and others either constricted or remained unchanged. Often constriction and dilation in different segments of epicardial coronary arteries occurred in the same patients. This heterogenous response of epicardial coronary arteries to endothelium-dependent stimuli has been observed previously (28,29) and highlights the patchy nature of vascular endothelial dysfunction in coronary conductance vessels of patients with atherosclerosis or its risk factors.

In order to evaluate endothelial function of segments that constricted or dilated during pacing, we assessed the effects of BK, an endothelium-dependent vasodilator, and sodium nitroprusside, an endothelium-independent agonist. Segments that constricted with pacing did not dilate with BK, whereas those that reacted normally to pacing by dilating also dilated with BK. In contrast, both dilating and constricting segments relaxed equally with sodium nitroprusside, indicating that endothelial, but not smooth muscle function, was abnormal in segments which constricted with pacing. This is in keeping with animal studies where

endothelial damage following balloon injury to the canine coronary arteries resulted in marked vasoconstriction during exercise (30). Similarly, in humans, an attenuated vasodilator response to acetylcholine in patients with endothelial dysfunction is associated with a depressed dilator response to pacing (31).

The effect of enalaprilat was specific for the endothelium-dependent vasodilator, BK, and was greater in segments that initially did not dilate with BK (endothelial dysfunction) compared to those that dilated (normal endothelial function). Thus, after ACE inhibition, both segments dilated to a comparable degree. Similar changes were observed with ACE inhibition during cardiac pacing. The beneficial effect of ACE inhibition was restricted to segments with endothelial dysfunction, where pacing after enalaprilat abolished epicardial constriction. In contrast, segments which initially dilated normally with pacing remained unchanged after enalaprilat. However, there was no difference in the magnitude of increase in flow and, hence, shear stress between the two groups to account for the observed difference in epicardial arterial response. These findings are in agreement with a previous study where acute infusion of the ACE inhibitor, perindoprilat, improved cold presser-mediated epicardial coronary constriction (32).

Improvement in coronary endothelial function by ACE inhibition. As reported previously, acute ACE inhibition with enalaprilat did not alter basal coronary vascular tone (22,32,33). However, it is not possible to conclude from this observation that local generation of angiotensin II by vascular ACE or enalaprilat-mediated increased endogenous BK availability do not contribute to resting tone. Since resting coronary vascular tone is tightly autoregulated, it is possible that reduced angiotensin II-mediated constriction and BK-mediated dilation is offset by changes in other endogenous dilators and constrictors.

In the present study, enalaprilat potentiated epicardial and microvascular dilation in response to BK, but not to sodium nitroprusside, suggesting that it can selectively improve endothelium-dependent but not -independent vasodilation. Potentiation of BK responses also confirms that acute administration of enalaprilat achieved adequate inhibition of coronary ACE. Because BK is metabolized by kininase II or endothelial ACE, improvement of the BK response by enalaprilat would be expected and would not necessarily indicate global improvement in endothelial function. However, in a previous study, we have also demonstrated improved acetylcholine responses with enalaprilat, an effect that was due to increased NO bioactivity (27), a finding confirmed by the TREND investigators using oral quinapril (34). Data from studies in the human forearm circulation of patients with mild heart failure (35) and the femoral circulation of patients with atherosclerosis (36) confirms a similar action of ACE inhibition on peripheral vascular endothelial dysfunction.

Mechanism underlying the improvement in flow-mediated epicardial vasomotion by ACE inhibition: role of BK. There are at least two important mechanisms whereby ACE inhibition may improve endothelial NO activity. By reducing vascular angiotensin II production, it can increase bioavailability of NO as angiotensin II is a powerful stimulus for NADH/NADPH oxidase-dependent vascular superoxide anion generation (17,18). Increased vascular oxidant level inactivates endothelial NO, a mechanism that appears to be instrumental in precipitating endothelial dysfunction in hypercholesterolemia, atherosclerosis, hypertension and diabetes (37–40). The second possible mechanism underlying the beneficial effects of ACE inhibition is by elevation of vascular BK levels that will directly stimulate the NO pathway.

Although the precise mechanism whereby the endothelium senses and transduces the stimulus of flow and shear stress is unknown, the possibility that BK may play a key role in mediating tonic basal and flow-stimulated release of NO was suggested by recent studies. Epicardial constriction and inhibition of flow-mediated epicardial dilation in the human coronary circulation was observed during inhibition of endogenous BK activity with icatibant, a specific B2 receptor antagonist (12). In our study, we investigated whether the observed improvement in flow-mediated constriction by ACE inhibition was a result of increased BK activity by repeating pacing during a low-dose infusion of BK that in itself did not change epicardial diameter in the segments with dysfunction. Pacing-induced constriction was abolished by low-dose BK, whereas segments that initially dilated with pacing, and, hence, had normal endothelial function, had no effect. These observations allow us to speculate that coronary endothelial dysfunction results in diminished endogenous kinin activity during stress, which can be overcome by either exogenous BK or by ACE inhibition, and that the beneficial effect of ACE inhibitors is, at least partly, due to enhanced BK activity. This is further supported by a recent study in normal volunteers which demonstrated that B2 receptor inhibition abolishes the potentiation of flow-mediated dilation of the radial artery by quinaprilat (41).

The observation that BK and ACE inhibition does not affect epicardial diameter in constricting segments at rest, yet improves flow-mediated dilation with pacing, needs explanation. One explanation is that there is up-regulation of vascular ACE in these segments as described in animal models of atherosclerosis and in humans (42,43). Thus, low dose BK is metabolized rapidly resulting in no baseline effect; however, during increasing shear, there is likely to be increased availability of BK as a result of its shear-mediated production. This increased endogenous production in the setting of either ACE inhibition or low-dose BK infusion is able to reverse the flow-mediated constriction. In the dilating segments, there is no up regulation of ACE and, thus, no limitation in BK production during stress. Thus, enhancement does not occur. Alternatively, basal and shear-

mediated NO production by the BK pathway may have different thresholds and are affected differentially by atherosclerosis and its risk factors, a possibility that is worthy of further study.

Angiotensin-converting enzyme inhibition and microvascular coronary dilation during stress. Cardiac pacing significantly reduced coronary vascular resistance, but this was not altered by enalaprilat in either patients with, or those without, depressed pacing-induced microvascular dilation. Our data indicates that, unlike epicardial vasomotion, microvascular metabolic dilation is not potentiated by ACE inhibition in patients with atherosclerosis or its risk factors. This was observed despite improvement in BK-mediated microvascular responses in these patients, and, therefore, deserves explanation.

That metabolic coronary microvascular dilation is, at least partly, dependent on endothelium-derived NO activity has been demonstrated by us in a previous study (1). 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 of NO was reduced in those with endothelial dysfunction. In contrast to its partial 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 only partially dependent on endothelial NO (44). Coronary microvascular dilation during pacing in addition to NO is also mediated by release of local metabolites including adenosine, prostaglandins, carbon dioxide, hypoxia and is partly due to circulating catecholamines and withdrawal of sympathetic tone (44). 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 (25,26,44). Furthermore, cardiac pacing is not a maximal shear stress-producing stimulus, as coronary blood flow on average only increases by 50% with cardiac pacing. It is possible that during conditions where blood flow increases are near the maximum vasodilatory capacity of the human coronary microvessels, the importance of an intact NO pathway will become evident. Thus, unlike BK or acetylcholine-mediated dilation, which is predominantly endothelium-dependent, pacing-induced microvascular dilation is only in a small part NO-dependent. Since ACE inhibition selectively improves endothelium-dependent vasodilation, these differences may explain the lack of potentiation of microvascular dilation in the present study compared to previous studies in which augmentation of endothelium-dependent acetylcholine-mediated microvascular dilation has been observed (27,45).

Limitations. In this study we did not use a BK receptor antagonist to investigate the contribution of kinins in the action of ACE inhibitors. Though this would have been the most desirable approach, no suitable agent was available for clinical use. Our study did not include vessels with >50% stenosis and thus we cannot conclude from our data whether ACE inhibition would also improve flow-mediated vasomotion in vessels with more severe atherosclerosis. Results from trials in progress examining the effect of ACE inhibitors in myocardial ischemia will help clarify this issue (46). Our study was also not designed to evaluate whether an increase in NO activity is responsible for the beneficial effect of ACE inhibition on flow-mediated dilation, but the finding that improvement in acetylcholine- and BK-mediated coronary and peripheral dilation is due to increased NO activity in our previous studies suggests that this is the most likely explanation for the observed changes (27,36). Due to limited number of patients studied, we are unable to investigate whether the beneficial effects of ACE inhibitors are more likely to occur in patients with one or other of the specific risk factors for atherosclerosis. This issue needs to be tested in specific subsets of patients.

Conclusions. Abnormal epicardial flow-mediated vasomotion is associated with endothelial dysfunction in patients with atherosclerosis and its risk factors. Angiotensin-converting enzyme inhibition selectively improves endothelium-dependent, but not -independent dilation. Furthermore, ACE inhibition abolishes abnormal flow-mediated epicardial vasomotion in patients with endothelial dysfunction, but it does not influence microvascular dilation during pacing in patients with diffuse but nonstenotic epicardial coronary artery disease. This improvement in epicardial constriction with ACE inhibition is likely to be mediated, in part, by an increase in endogenous BK activity.

Improvement in abnormal coronary vasomotion during stress with ACE inhibitors may result in amelioration of myocardial ischemia in patients with coronary artery disease. Their long-term effects in enhancing vascular NO activity provides a pathophysiologic basis for the observed antithrombotic effect of ACE inhibitors and point to a potential role of these agents in arresting the progression of atherosclerosis.

Acknowledgments

We thank Gloria Zalos, R.N., William H. Schenke, B.S., Rita Mincemoyer, R.N. for their technical assistance.

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