Pretreatment With Intracoronary Enalaprilat Protects Human Myocardium During Percutaneous Coronary Angioplasty

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Objectives
We tested the hypothesis that enalaprilat induces preconditioning (PC)-mimetic actions in patients with stable coronary artery disease.

Background
Angiotensin-converting enzyme (ACE) inhibitors increase the bioavailability of bradykinin, which induces cardiac PC.

Methods
Twenty-two patients undergoing coronary angioplasty were randomized to an intracoronary infusion of enalaprilat or placebo, followed 10 min later by a PC protocol.

Results
In control patients, the ST-segment shift was greater during the first inflation than during the second and third inflations, both on the intracoronary electrocardiogram (ECG) (21.0 ± 2.8 mm vs. 13.0 ± 2.0 mm and 13.0 ± 2.0 mm, p < 0.05) and the surface ECG (16.0 ± 4.0 mm vs. 10.0 ± 2.0 mm and 9.0 ± 2.0 mm, p < 0.05). In contrast, enalaprilat-pretreated patients showed no change in ST-segment shift during inflations on either the intracoronary or the surface ECG. During the first inflation, the ST-segment shift was significantly smaller in treated versus control patients. The chest pain score during the first inflation was also significantly smaller in treated patients versus control patients (33.0 ± 6.0 mm vs. 64.0 ± 6.0 mm) and did not change in treated patients during the second and third inflations, whereas it decreased significantly in control patients. In a subset of 6 patients, enalaprilat increased coronary blood flow during infusion, but this effect dissipated before the beginning of angioplasty.

Conclusions
Pretreatment with enalaprilat attenuates the manifestations of myocardial ischemia during angioplasty. This is the first in vivo evidence showing that an ACE inhibitor protects human myocardium, possibly via PC-mimetics actions, a novel property that might explain the cardioprotective actions of these drugs. (J Am Coll Cardiol 2007;49:1607–10) © 2007 by the American College of Cardiology Foundation

Inhibitors of the angiotensin-converting enzyme (ACE) have been shown to exert beneficial actions in patients with ischemic heart disease (1). In particular, several studies have documented a reduction in the occurrence of myocardial infarction and ischemic events among patients receiving these drugs (1,2). Although the mechanism responsible for these salutary actions remains unclear, inhibition of bradykinin degradation (which is catalyzed by the ACE) has been proposed as a plausible mechanism (3).

Because ACE inhibitors potentiate bradykinin, which induces cardiac preconditioning (PC), one would expect that these drugs would elicit a PC-mimetic state. However, thus far, no evidence has been reported to suggest that ACE inhibitors are capable of inducing PC in humans. The goal of this study was to determine whether enalaprilat, the active metabolite of enalapril, exerts PC-mimetic actions in the human heart.

Methods
We enrolled 22 patients with chronic stable angina and preserved left ventricular function who were referred for elective angioplasty of an isolated coronary obstructive lesion. Criteria for inclusion and exclusion have been detailed previously (4). Patients on oral ACE inhibitors were excluded from this study.

The protocols for drug infusion, angioplasty, and data collection have been previously reported (4). Patients were assigned to receive intracoronary enalaprilat or normal saline before percutaneous transluminal coronary angioplasty (PTCA). Enalaprilat (Merck, North Wales, Pennsylvania; 0.75 mg in 50 ml saline) was infused over 15 min at 0.05 mg/min directly into the stenotic artery (total dose 0.75 mg). The placebo group received an equivalent volume of saline. The intracoronary electrocardiogram (ECG) and surface ECG leads were recorded, as previously reported (5). Coronary blood flow (CBF) measurements were performed in a subset of 6
enalaprilat-treated patients using a 0.014-inch Doppler guidewire (4). The study was approved by the institutional review board.

All data are reported as mean ± SEM. The ST-segment shift, chest pain score, coronary flow, and vessel diameter were analyzed with a 2-way repeated-measures analysis of variance for time and treatment. Post hoc contrasts between groups at various time points or between time points within 1 group were performed with a 2-tailed Student t test using the Bonferroni correction. Other continuous or dichotomous variables were compared between the 2 groups using Student t tests or chi-square tests, respectively.

Results

The baseline and demographic characteristics of the patients are summarized in Table 1. Enalaprilat administration did not produce appreciable changes in heart rate (73 ± 4 beats/min vs. 71 ± 3 beats/min in control patients), arterial blood pressure (127 ± 6 mm Hg vs. 131 ± 8 mm Hg) or rate-pressure product (9.8 ± 10^3 vs. 9.3 ± 10^3 ± 0.8 ± 10^3).

Electrocardiographic signs of ischemia. In the placebo group, the ST-segment shift was significantly greater during the first balloon inflation than during the second and third inflations, both on the intracoronary ECG (21.0 ± 2.8 mm vs. 13.0 ± 2.0 mm and 13.0 ± 2.0 mm, respectively, p < 0.05) and on the surface ECG (16.0 ± 4.0 mm vs. 10.0 ± 2.0 mm and 9.0 ± 2.0 mm, respectively, p < 0.05) (Fig. 1). In contrast, the enalaprilat-pretreated group showed no change in the ST-segment shift during any of the 3 balloon inflations on either the intracoronary ECG (10.0 ± 2.0 mm vs. 10.0 ± 2.0 mm and 9.0 ± 2.0 mm, p = NS) or the surface ECG (8.0 ± 2.0 mm vs. 8.0 ± 2.0 mm and 8.0 ± 2.0 mm, p = NS) (Fig. 1). The ST-segment shift recorded on the intracoronary ECG was significantly smaller in the enalaprilat-pretreated group compared with the placebo group during the first balloon inflation (10.0 ± 2.0 mm vs. 21.0 ± 2.8 mm, −11 mm, p < 0.05), but did not differ significantly between groups during the second and third inflations (13.0 ± 2.0 mm vs. 10.0 ± 2.0 mm and 13.0 ± 2.0 mm vs. 9.0 ± 2.0 mm in control and treated patients, respectively, p = NS) (Fig. 1). Similarly, the ST-segment shift recorded on the surface ECG was significantly smaller in the enalaprilat group compared with placebo during the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and Clinical Characteristics of the Patients</th>
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<tr>
<td></td>
<td>Placebo (n = 11)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>50 ± 3</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>7/4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
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<td>Smoking</td>
<td>5</td>
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<tr>
<td>Diabetes mellitus</td>
<td>4</td>
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<tr>
<td>Previous CAGB</td>
<td>0</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>0</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>58 ± 1</td>
</tr>
<tr>
<td>CCS anginal syndrome on admission</td>
<td>1–2</td>
</tr>
<tr>
<td>3–4</td>
<td>4</td>
</tr>
<tr>
<td>Interval between most recent angina and PTCA (days)</td>
<td>3.8 ± 1.1</td>
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<tr>
<td>Antianginal medications</td>
<td>Long-acting nitrates</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
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<td>10</td>
<td>11</td>
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CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; PTCA = percutaneous transluminal coronary angioplasty.
first balloon inflation (8.0 ± 2.0 mm vs. 16.0 ± 4.0 mm, p < 0.05), but not during the second and third inflations (10.0 ± 2.0 mm vs. 8.0 ± 2.0 mm and 9.0 ± 2.0 mm vs. 10 vs. 8.0 ± 2.0 mm in control and treated patients, respectively, p = NS) (Fig. 1).

Chest pain. The chest pain score in the placebo group was significantly greater during the first than during the second and third balloon inflations (64.0 ± 6.0 mm vs. 49.0 ± 8.0 mm and 40.0 ± 8.0 mm, p < 0.05) (Fig. 1). In contrast, in the enalaprilat-pretreated group the chest pain score did not differ significantly among inflations (33.0 ± 6.0 mm vs. 34.0 ± 7.0 mm and 34.0 ± 6.0 mm, p = NS). The chest pain score was significantly smaller in the enalaprilat group compared with control patients during the first (33.0 ± 6.0 mm vs. 64.0 ± 6.0 mm, p < 0.05) and second (34.0 ± 7.0 mm vs. 49.0 ± 8.0 mm, p < 0.05) balloon inflations, but not during the third balloon inflation (34.0 ± 6.0 mm vs. 40.0 ± 8.0 mm, p = NS).

CBF. The average CBF increased significantly during enalaprilat infusion (77.8 ± 10.3 ml/min vs. 188.8 ± 31.0 ml/min, p = 0.006) but returned to baseline levels shortly after the end of the infusion (within <10 min) (80.2 ± 8.9 ml/min, p = 0.8) (Fig. 2). Enalaprilat did not produce epicardial coronary vasodilation, because no significant changes in minimal coronary luminal diameter were observed before, during, or after the intracoronary infusion (3.06 ± 0.11 mm vs. 3.25 ± 0.12 mm vs. 3.14 ± 0.12 mm, p = NS) (Fig. 3).

Discussion

The results of this study show that pretreatment with enalaprilat results in less ST-segment shift and less chest pain during the first balloon inflation in patients undergoing elective PTCA. Although in control patients, the electrocardiographic and subjective manifestations of ischemia were attenuated during the second and third balloon inflations compared with the first (a manifestation of ischemic PC), in enalaprilat-pretreated patients there was virtually no change in any of these parameters, indicating that the superimposition of ischemic PC to enalaprilat pretreatment did not provide additional protection beyond that provided by the drug (i.e., the myocardium was maximally protected by enalaprilat). The augmented tolerance to ischemia conferred by enalaprilat was observed after the CBF returned to baseline and was not influenced by concomitant medical therapy.

Although we did not measure blood enalaprilat levels, it seems plausible that the protection afforded by enalaprilat represents a form of pharmacological PC rather than a direct anti-ischemic effect of the drug, because such an effect was observed 10 min after the end of the infusion, when the coronary vasodilatory effects of the drug had completely resolved. If biologically active levels of enalaprilat were still present during balloon inflation, one would have expected the coronary vasodilation to persist. The mechanism whereby enalaprilat induces PC may involve potentiation of bradykinin, which is known to precondition myocardium experimentally (5) and to induce PC in the setting of PTCA (4). Theoretically, it is also possible that the protective effect of enalaprilat may have been triggered by the transient increase in CBF, possibly via endothelial shear-mediated mechanisms. However, ACE inhibitors potentiate PC in isolated human cardiac tissue (6), suggesting that the PC effect of enalaprilat is independent of coronary flow changes.

Previous studies have shown the ability of ACE inhibitors to alleviate experimental myocardial ischemia/reperfusion injury (5) and to extend the duration (but not the magnitude) of the “warm up” phenomenon in patients...
undergoing exercise tolerance tests (7). However, to our knowledge, this is the first in vivo evidence that ACE inhibitors protect human myocardium against ischemia.

An inevitable limitation of studies of PTCA is that in contrast to animal experiments in which infarct size has been used as the end point to assess the role of bradykinin or ACE inhibitors in PC (8), in the present study the main end point was the magnitude of the ST-segment shift. The ST-segment elevation is a surrogate marker of ischemia, and as such its reliability has been questioned (9). However, the attenuation of ST-segment elevation during PTCA is concordant (in both direction and magnitude) with changes in other parameters of ischemia (lactate production, H+ release, echocardiographic measurements of systolic and diastolic function), suggesting that ST-segment shifts are a useful marker of the severity of ischemia in humans (10). Similar conclusions have been reached in experimental models (reviewed by Leesar et al. [10]).

Our results are consistent with numerous experimental studies that have documented cardioprotective effects of various ACE inhibitors in animal models (11,12). In addition, we (4) have shown that pretreatment with bradykinin alleviates ischemia in the same clinical setting (PTCA) used in the present study. Both adenosine and bradykinin (whose bioavailability is enhanced by ACE inhibitors) can trigger PC experimentally (13), and ACE inhibitors potentiate ischemic PC in human atrial trabeculae through activation of bradykinin receptors (6).

Our infusion rate of enalaprilat was based on previous studies (14). We were concerned that higher doses could have induced hypotension and/or ischemia, which in turn may have triggered PC and confounded the analysis.

In conclusion, this study reveals a novel action of ACE inhibitors in humans that, if confirmed in larger trials, may have broad implications for the treatment of coronary artery disease. The demonstration of the cardioprotective properties of enalaprilat in PTCA provides a mechanism for explaining the anti-ischemic actions of ACE inhibitors in patients with coronary artery disease. The present results warrant further investigation to determine whether ACE inhibitors precondition the myocardium in settings associated with more severe ischemia (e.g., cardiac surgery, acute myocardial infarction) and whether these actions translate into tangible benefits.

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REFERENCES