Anti-Ischemic Effects of Angiotensin-Converting Enzyme Inhibition in Hypertension

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OBJECTIVES
We investigated whether augmentation of bradykinin (BK) bioavailability with angiotensin-converting enzyme (ACE) inhibition is associated with reduced exercise-induced myocardial ischemia in hypertension.

BACKGROUND
Bradykinin responses are depressed in hypertension, and endothelial dysfunction contributes to myocardial ischemia by promoting abnormal coronary vasomotion during stress.

METHODS
Fourteen hypertensive (HT) and 17 normotensive (NT), mildly symptomatic patients with coronary artery disease (CAD) and ST-segment depression during exercise were studied before and after seven days of oral enalapril (EN), which was titrated from 2.5 to 20 mg daily. Patients underwent two treadmill exercise tests and determination of forearm vasodilator response to BK.

RESULTS
Despite receiving a lower dose of EN (7.8 vs. 14.8 mg, p < 0.001), NT patients had a significant reduction in blood pressure compared to HT patients. Compared to pre-EN, the ischemic threshold, defined as the rate-pressure product at the onset of 1-mm ST depression (p = 0.045), the duration of exercise to 1-mm ST depression (180 ± 54 s, p = 0.007) and the maximum exercise duration (94 ± 18 s, p < 0.001) were greater after EN in HT patients, but not in NT subjects (all p ≥ 0.3). Patients with a greater drop in blood pressure experienced no improvement in exercise-induced ischemia. Forearm blood flow responses to BK were improved with EN in all patients to a similar extent. Moreover, no correlation was observed between the basal response to BK or the magnitude of its improvement with EN and with either the dose of EN or the improvement in exercise ischemic threshold.

CONCLUSIONS
Exercise-induced myocardial ischemia is ameliorated in HT patients with CAD by ACE inhibition. (J Am Coll Cardiol 2001;38:1116–22) © 2001 by the American College of Cardiology

Exercise dilates human coronary epicardial arteries and microvessels in normal individuals, and the resulting augmentation in blood flow serves to meet the increased myocardial oxygen requirements. The vascular endothelium is pivotal in regulating this vasomotion by releasing a variety of relaxing and constricting factors in response to increased shear stress (1). One important endothelium-derived relaxing factor is nitric oxide (NO) or an adduct of NO that contributes almost entirely to flow-mediated 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, which may contribute to the pathogenesis of myocardial ischemia in these patients (2–4). Endothelial cell dysfunction associated with reduced NO activity is believed to be the major underlying cause for this abnormal vasomotion. In humans, bradykinin (BK) is an endogenous mediator of basal coronary tone and flow-mediated dilation (5). Endothelial dysfunction resulting in impaired BK-mediated responses, as observed in patients with hypertension (6), may contribute to reduced NO bioavailability.

Angiotensin-converting enzyme (ACE) inhibitors act in part by increasing BK activity. In recent experiments, we and others have demonstrated that ACE inhibition reverses abnormal coronary vasomotion by ameliorating endothelial dysfunction and increasing NO bioavailability (7–10). Based on these observations, and acute experiments suggesting that ACE inhibition may have anti-ischemic actions (11–13), we hypothesized that ACE inhibition may reduce myocardial ischemia in patients with hypertension. Thus, the aims of this study were to investigate whether: 1) ACE inhibitor therapy reduces exercise-induced myocardial ischemia in hypertensive (HT) patients with coronary artery disease (CAD), and 2) whether any observed improvement in exercise capacity correlates with vasomotor responses to BK. Normotensive (NT) patients with CAD were also investigated and served as the control group.

METHODS
Patients. We studied 14 HT and 17 NT asymptomatic or mildly symptomatic patients with stable symptoms and angiographically documented CAD (>50% stenosis in one or more epicardial arteries). All patients had exercise-induced ST-segment depression. The presence of ischemia was confirmed by demonstrating reversible defects on stress thallium scintigraphy. There were no differences in age,
Patient Characteristics

Following the forearm study, patients were
endothelium-dependent vasomotor function with intra-
during treadmill exercise and measurement of forearm blood
flow was measured during the last 2 min of the
infusion. Data were analyzed after blinding for the treat-
mant phase.

The study was conducted on two separate days,
before and after treatment with oral enalapril (EN). On
each patient as described previously (10). Patients gave informed
consent and the protocol was approved by the Investigative
Review Board of the National Heart, Lung and Blood
Institute.

Protocol. The study was conducted on two separate days,
before and after treatment with oral enalapril (EN). On
each study day, an intra-arterial cannula was introduced
under local anesthesia into the brachial artery of the non-
dominant arm for accurate measurement of blood pressure
during treadmill exercise and measurement of forearm blood
flow. After 1-h rest, patients had determination of forearm
endothelium-dependent vasomotor function with intra-
arterial BK. Following the forearm study, patients were
exercised on the treadmill on two occasions separated by a
duration of 3 h, employing the National Institutes of Health
Combined protocol (14). Blood pressure, heart rate and a
12-lead electrocardiogram (ECG) were recorded every 30 s
to determine with accuracy the ischemic threshold (heart
rate \times blood pressure at the onset of 1-mm ST-segment
depression). Mean values from the two exercise tests for all
parameters were used for the final analysis. The rate-
blood pressure product (RPP) was calculated as mean arterial
pressure \times heart rate. Exercise was terminated for
moderate-intensity chest pain, limiting dyspnea, 3-mm
ST-segment depression or excessive fatigue. The tests were
analyzed after blinding for treatment phase.

Following the pretreatment exercise tests and forearm
infusion study, patients were discharged on EN, starting at
2.5 mg. Subsequently, the dose was increased to 5 mg,
7.5 mg, 10 mg, 12.5 mg, 15 mg and then 20 mg each day,
except when systolic blood pressure decreased to
\leq 100 mm Hg or any side effects occurred. Each subject
coordinated blood pressure measurements at home with a
study nurse. After 7 to 10 days of treatment with the
maximum tolerated dose, the patients returned for a repeat
forearm vascular function study and two treadmill exercise
tolerance tests as previously described.

MEASUREMENT OF FOREARM BK-MEDIATED VASODILA-
TION. All studies were performed in a quiet room with a
temperature of approximately 22°C. Patients were asked to
refrain from drinking alcohol or beverages containing caff-
eine and from smoking for 24 h before the studies. Forearm
blood flow was measured using strain gauge plethysmogra-
phy, as previously described (15). Basal measurements were
obtained during intra-arterial infusion of 5% dextrose solu-
tion at 1 ml/min. Forearm blood flow was then measured
during infusion of intra-arterial BK at 6.25, 25, 100 and
400 ng/min. Each dose was infused for 5 min and forearm
blood flow was measured during the last 2 min of the
infusion. Data were analyzed after blinding for the treat-
ment phase.

Plasma ACE levels and genotype for the ACE gene
insertion-deletion (I/D) polymorphism were determined for
each patient as described previously (10).

Statistical analysis. Data are expressed as mean ± SEM.
The difference between means was tested with either the
paired or unpaired Student t test as appropriate. All tests
were two-sided, and a p < 0.05 was considered statistically
significant. The dose-response curves with BK before and
after EN were compared using a two-way repeated measures
analysis of variance (ANOVA) with appropriate interaction
terms (16). Correlations were performed using the Pearson
correlation coefficient.

RESULTS

Effects of EN on exercise testing. RESTING HEMODYNA-
MICS. The maximum tolerated dose of EN after titration was
higher in the HT patients (Table 1). At rest, significant

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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<tbody>
<tr>
<td>Hypertensives</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Men (n, %)</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
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<tr>
<td>LDL (mg/dl)</td>
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<tr>
<td>Triglycerides (mg/dl)</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
</tr>
<tr>
<td>Smokers (n)</td>
</tr>
<tr>
<td>No. of diseased vessels</td>
</tr>
<tr>
<td>ACE level (U/l)</td>
</tr>
<tr>
<td>Deletion allele (%)</td>
</tr>
<tr>
<td>Enalapril dose (mg)</td>
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</tbody>
</table>

ACE = angiotensin-converting enzyme; HDL = high density lipoprotein; LDL = low density lipoprotein; NS = p < 0.1.
differences were seen in systolic (p = 0.002) and diastolic (p = 0.02) blood pressures, and rate-pressure product (mean arterial pressure × heart rate, p = 0.06), but not heart rate (p = 0.9) between the HT and NT patients (Table 2). Treatment with EN produced a small but significant decrease in heart rate in NT patients. Mean arterial pressure fell significantly in NT patients (95 ± 3 to 88 ± 3 mm Hg, p = 0.02), but the change in HT patients was not significant (111 ± 5 to 105 ± 5 mm Hg, p = 0.13). Resting RPP was lower in both groups (Table 2).

**ISCHEMIC THRESHOLD.** In HT patients, the RPP at 1-mm ST-segment depression (ischemic threshold) increased by 1.1 ± 0.5 × 10³ mm Hg-beats/min (p = 0.045 compared to pretreatment) after EN. The increase was attributable to a significantly higher heart rate achieved (p = 0.007) (Table 2). The duration of exercise to 1-mm ST-segment depression also increased by 180 ± 54 s (p = 0.005) in HT patients (Fig. 1). In comparison, RPP (0.5 ± 0.7 × 10³ mm Hg-beats/min, p = 0.5) and the duration of exercise (78 ± 66 s, p = 0.3) to 1-mm ST-segment depression did not change significantly with EN in the NT patients (Fig. 1; Table 2).

**PEAK EXERCISE.** Enalapril therapy did not alter the heart rate, blood pressure or RPP achieved at peak exercise in HT patients (Table 2). In contrast, in NT patients, a significant decrease occurred in diastolic blood pressure and RPP, but not heart rate or systolic blood pressure at peak exercise (Table 2). In HT patients, following treatment with EN, the maximum exercise duration and workload increased by 94 ± 18 s (p = 0.0003 compared to pretreatment) and 0.7 ± 0.4 metabolic equivalents (METs) (p = 0.056), respectively (Fig. 2). In contrast, there was no improvement in NT patients: 4.8 ± 12 s (p = 0.7) and 0.2 ± 0.1 METs (p = 0.4) change in duration and workload, respectively.

**Table 2.** Systemic Hemodynamics at Rest, 1-mm ST-Depression and at Peak Exercise, Before and After Treatment With Enalapril

<table>
<thead>
<tr>
<th></th>
<th>Hypertensives</th>
<th>Normotensives</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Heart Rate</td>
<td>SBP</td>
</tr>
<tr>
<td></td>
<td>(beats/min)</td>
<td>(mm Hg)</td>
</tr>
<tr>
<td>Resting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>77 ± 3</td>
<td>164 ± 7</td>
</tr>
<tr>
<td>Enalapril</td>
<td>74 ± 3</td>
<td>159 ± 6</td>
</tr>
<tr>
<td>p Value</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>1-mm ST-Depression</td>
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<td></td>
</tr>
<tr>
<td>(Ischemic Threshold)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>111 ± 3</td>
<td>191 ± 6</td>
</tr>
<tr>
<td>Enalapril</td>
<td>120 ± 4</td>
<td>198 ± 5</td>
</tr>
<tr>
<td>p Value</td>
<td>0.007</td>
<td>0.3</td>
</tr>
<tr>
<td>Peak Exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>123 ± 4</td>
<td>207 ± 6</td>
</tr>
<tr>
<td>Enalapril</td>
<td>120 ± 5</td>
<td>199 ± 10</td>
</tr>
<tr>
<td>p Value</td>
<td>0.19</td>
<td>0.04</td>
</tr>
</tbody>
</table>

p values compare control vs. enalapril.

DBP = diastolic blood pressure; RPP = rate-pressure product; SBP = systolic blood pressure.

Figure 1. Change in ischemic threshold (rate-pressure product [RPP]) and duration of exercise at the onset of 1-mm ST-depression in hypertensive and normotensive patients before (open bars) and after (solid bars) treatment with enalapril.
Maximum ST-segment depression also tended to decrease \((p = 0.069)\) in patients with HT, but not in NT subjects \((p = 0.4)\).

**DETERMINANTS OF RESPONSES TO EXERCISE.** There was no significant correlation between the percent change in ischemic threshold and the cholesterol level, age, presence of diabetes, smoking, the ACE I/D genotype, ACE level and the dose of EN, in the entire population.

We also investigated whether the effect of EN on resting blood pressure or RPP correlated with the magnitude of improvement in exercise capacity. A significant negative correlation existed among the change in resting systolic blood pressure \((r = 0.45, p = 0.02)\), diastolic blood pressure \((r = 0.52, p = 0.005)\), and RPP \((r = 0.52, p = 0.005)\), and the change in ischemic threshold with EN, suggesting that patients with a little or no decrease in resting blood pressure with EN had a greater improvement in ischemia, and vice versa.

Because some patients not known to have a history of hypertension either had elevated resting blood pressure \((>140/90 \text{ mm Hg})\) at the time of the study or had an HT response to exercise where systolic blood pressures exceeded 200 mm Hg, we reanalyzed the group with known hypertension and those with resting hypertension or exercise-induced HT responses together (HTs, \(n = 19\)) and compared them with the remaining NT patients \((n = 11)\) who had a normal resting blood pressure and a normal blood pressure response to exercise. The mean resting and peak exercise blood pressures were higher in HT patients than in the NT cohort (resting 162/83 vs. 131/67 mm Hg, and peak exercise 206/85 vs. 172/72 mm Hg, both \(p < 0.01\)).

Hypertensive patients had a significant increase in peak exercise duration \((57 \pm 14 \text{ s, } p = 0.001)\) and exercise duration to ischemic threshold \((204 \pm 66 \text{ s, } p = 0.009)\), whereas these changes were insignificant in NT patients. The workload to the ischemic threshold also improved in HT patients \((1.1 \pm 0.1 \text{ mm Hg-beats/min, } p = 0.04)\) compared to pretreatment, but not in the NT cohort. Finally, peak ST-segment depression was also significantly lower in HT patients after EN \((p = 0.03)\) but not in NT patients.

**Effects of EN on BK responses.** No change occurred in arterial pressure during administration of BK in the control study. After EN therapy, BK administration also did not alter blood pressure, except at the peak dose \((105 \pm 3 \text{ vs. } 95 \pm 5 \text{ mm Hg, baseline compared to BK 400 ng/min, } p = 0.02)\) in HT patients and NT patients \((89 \pm 2 \text{ vs. } 80 \pm 3 \text{ mm Hg, } p = 0.003)\).

Enalapril did not alter resting forearm blood flow and vascular resistance in the two groups (Fig. 3). Bradykinin produced similar dose-dependent forearm microvascular dilation in both groups \((p = \text{NS, ANOVA})\), HT compared to NT patients). The EN augmented BK responses measured as flow and resistance changes in both patient groups by ANOVA (Fig. 3). A significant interaction was seen between the dose of BK and drug (pre- and post-EN), suggesting a differential effect of EN at different doses of BK. Therefore, the effects of enalapril on the flow and resistance changes were investigated at each dose of BK after Bonferroni’s adjustment. This analysis revealed that, in HT patients, both flow and resistance changes were significantly different at all doses of BK \((p < 0.01)\), but in NT patients, significant flow enhancement \((p = 0.013)\) was observed at the lower two doses of BK only. There was no difference in the percent change in BK-mediated vasodilation with EN between HT and NT patients \((p = \text{NS, ANOVA})\). There was no correlation between the dose of EN and the magnitude of improvement in the BK response.
with EN. Moreover, no correlation existed between the magnitude of change in exercise ischemic threshold and the change in BK responses with EN.

**DISCUSSION**

The ACE inhibitors have several beneficial effects on cardiovascular function in HT patients. In this study, we evaluated the effects of ACE inhibition on exercise hemodynamics in HT patients with stable CAD and documented myocardial ischemia and compared them to NT patients. Our data show that ACE inhibition reduces ischemia in HT patients, but this beneficial effect was not observed in NT patients despite an equivalent level of ACE inhibition in both patient groups. The magnitude of improvement in exercise tolerance did not correlate with the improvement in vasodilator response to BK with EN. The NT patients had a greater reduction in blood pressure, and the magnitude of reduction in blood pressure correlated inversely with the degree of improvement in exercise-induced ischemia.

**Improvement in exercise hemodynamics and exercise tolerance by ACE inhibition.** Improvement in HT patients was manifested by a reduction in maximum ST-segment depression and an increase in ischemic threshold, measured as an increment in the RPP and duration of exercise at 1-mm ST-segment depression. Moreover, ACE inhibition was accompanied by a significant increase in exercise tolerance measured as the final duration of exercise or the peak workload achieved. These findings are consistent with a previous study demonstrating that two weeks of treatment with captopril improved duration of exercise and decreased maximal ST-segment duration in patients with hypertension (17). Unlike the present study, however, an increase in RPP at the ischemic threshold was not reported.

Enalapril did not improve myocardial ischemia in NT patients. Previous studies have also demonstrated a variable effect of ACE inhibition on myocardial ischemia. Daly et al. (18) observed in patients with and without HT that captopril reduced resting coronary blood flow and RPP by reducing blood pressure. Gibbs et al. (19) reported an increase in exercise capacity in NT patients; however, two patients experienced significant worsening, possibly from a marked reduction in resting blood pressure. We observed a significant correlation between the decrease in resting blood pressure with EN and the lack of improvement in ischemia. This indicated that patients who experienced the greatest decrease in blood pressure with EN had worsening of their exercise-induced ischemia. Indeed, 5 of the 17 NT patients who had a ≥10% reduction in mean arterial pressure also had a >10% decrease in ischemic threshold. The mechanism for this deterioration is unknown, though a reduction...
in coronary perfusion pressure may be responsible (20). Finally, it is possible that a benefit on ischemia would have been observed in a larger group of NT patients, and possibly after a longer duration of therapy.

Two trials have examined the incidence of recurrent ischemia during exercise in patients treated with ACE inhibitors after either myocardial infarction or bypass surgery (21,22). One year of double-blind treatment with captopril in patients after a myocardial infarction produced no difference in exercise capacity or the frequency of ST-segment depression between the treated and placebo groups (21). Use of a tissue-specific ACE inhibitor, quinapril, in patients after coronary artery bypass grafting also failed to demonstrate a reduction in the incidence of exercise-induced ST-segment depression or ambulatory myocardial ischemia when compared to placebo (22). Unlike our study, these investigations were examining the onset of new ischemia and not the effect of ACE inhibition on current ischemia.

Mechanisms underlying the reduction in myocardial ischemia. Antianginal therapy relieves myocardial ischemia via several differing mechanisms. Some agents, such as nitroglycerin, act as coronary vasodilators that dilate coronary stenoses and augment myocardial blood flow delivery. Others, such as beta-receptor antagonists, lower resting RPP and RPP during exercise, thus reducing myocardial oxygen demands during stress. However, the RPP at ischemia is often lower with these agents, indicating that they may cause vasoconstriction. Other agents, such as calcium antagonists, can also reduce peripheral vascular resistance and afterload, leading to reduced myocardial oxygen demand during stress. When a drug or intervention leads to an improvement in ischemic threshold, defined as the RPP at onset of ischemia, as observed with ACE inhibition in our HT patients, it is likely to be indicative of improved coronary blood flow delivery during stress. This enhancement of coronary blood flow may be due either to reduced epicardial constriction during stress, increased collateral blood flow or a combination of these processes.

Alternatively, ACE inhibition may reduce myocardial oxygen consumption by reducing myocardial contractility and left ventricular wall stress. As observed in this and previous studies, the resting RPP was lower with EN, indicating a reduction in resting oxygen consumption (18,19). However, at peak exercise, there was no reduction in RPP in the HT patients.

A large body of evidence indicates that coronary vasomotion importantly modifies the ease with which myocardial ischemia occurs in patients with coronary atherosclerosis. Vasoconstriction, or failure of normal vasodilation during physiologic stress of the coronary vasculature in the presence of atherosclerosis, is believed to be secondary to the development of endothelial dysfunction and reduced NO bioavailability during stress (3,4). The ACE inhibition improves endothelial dysfunction and augments NO bioavailability (7–9) by two important mechanisms. First, by reducing vascular angiotensin II, a powerful stimulus for reduced nicotinamide adenine dinucleotide/reduced nicotinamide adenine dinucleotide phosphate oxidase-dependent vascular superoxide anion generation, it can increase bioavailability of NO (23). Increased vascular oxidant level inactivates endothelial NO, a mechanism that appears to be instrumental in precipitating endothelial dysfunction in atherosclerosis. Second, ACE degrades BK, and inhibition of the enzyme elevates vascular BK activity (24). Bradykinin is a locally synthesized polypeptide that directly stimulates the NO pathway and regulates flow-mediated vasodilation in the normal human coronary circulation (5). Additionally, we demonstrated that pacing-induced coronary constriction was reversed by acutely inhibiting ACE with enalaprilat, an effect that was mimicked by low-dose infusion of BK (8). Augmentation of BK responses may be particularly relevant in hypertension where endothelial dysfunction is associated with impaired vasodilator response to BK (14).

Also, ACE inhibition may enhance coronary and peripheral vasodilator function by inhibiting generation of angiotensin II, reducing synthesis of endothelin and inhibiting sympathetic activity. The latter mechanism is supported by our observation that treatment with EN resulted in a significant reduction in resting heart rate and blood pressure, suggesting that there may have been a concomitant reduction in sympathetic tone. In those with a greater hypotensive effect with ACE inhibition, reflex baroreceptor activation may enhance sympathetic activity and thus negate some of the beneficial effects of ACE inhibition.

ACE inhibition, BK-mediated vasodilation and myocardial ischemia. We performed BK infusions into the forearm to explore the relationship between the anti-ischemic effect of EN and the augmentation of BK-mediated vasodilation by ACE inhibition. Although enhancement of BK responses was significant at all doses of BK in HT patients but at the lower doses in NT patients, perhaps due to the lower dose of EN used in this subset, there was no difference in the degree of augmentation between the two groups. Thus, BK-dependent vasodilation was augmented by EN to a similar extent in HT patients whose exercise tolerance improved compared to NT patients in whom exercise capacity remained unchanged. Finally, our data indicate that the magnitude of enhancement in BK activity with EN in the peripheral microcirculation does not correlate with the improvement in blood flow in atherosclerotic coronary arteries in HT patients.

Study limitations. This is not a randomized-blinded study; however, observer bias was minimized by blinding the individuals to the treatment phase during analysis of the exercise ECGs and forearm blood flow data, and by choosing objective end points such as ischemic threshold. We elected to titrate the dose of EN to maximize the ACE inhibition in each patient. This strategy helped avoid excessive hypotension in some patients that might have resulted had we used a fixed dose in all patients. We are
unable to determine from our study whether a lower dose of EN, one that did not lower blood pressure in NT patients, or a longer duration of treatment would have improved ischemia, or that a higher dose, as received by the HT patients, would have been beneficial. This needs to be studied further.

We are unable to comment whether ACE inhibition reduces spontaneous ischemic episodes and symptoms of angina. Further studies in moderately symptomatic patients are required to address this question. It is also clear that ACE inhibition improves outcome, free of acute coronary syndromes in both NT and HT patients (25). Finally, we investigated changes in endothelial function with EN in the peripheral microvasculature but not conductance vessels. Because improvement in coronary epicardial rather than microvascular endothelial function may have contributed to EN’s anti-ischemic action, study of the conductance vessels either in the coronary or the brachial circulations may have correlated better with the enhancement in exercise capacity.

Conclusions and implications. Our study demonstrates that ACE inhibition with EN reduces myocardial ischemia during stress and increases exercise tolerance in HT patients with stable CAD. These findings are consistent with our observation from acute studies that ACE inhibition improves endothelial dysfunction and reverses abnormal flow-mediated coronary vasomotion (8). Thus, in addition to their antiatherogenic effect, ACE inhibitors may possess clinically significant anti-ischemic properties in this population. The lack of benefit and potential worsening in a subset of NT patients who experienced significant reduction in blood pressure should raise caution with their use in this population in an era where ACE inhibitors are being advocated for improving outcome in all patients with atherosclerosis.

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