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Intracoronary Enalaprilat to Reduce Microvascular Damage During Percutaneous Coronary Intervention (ProMicro) Study

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Objectives This study investigated the influence of intracoronary enalaprilat on coronary microvascular function and peri-procedural outcome measures in patients with stable angina undergoing percutaneous coronary intervention (PCI).

Background Intracoronary angiotensin-converting enzyme inhibitors have been shown to relieve myocardial ischemia in stable patients and to improve epicardial flow in patients with ST-segment elevation myocardial infarction. Yet, it is still unclear whether these effects are mediated by a modulation of the coronary microcirculation.

Methods We randomly assigned 40 patients to receive either an intracoronary bolus of enalaprilat (50 μg) or placebo before elective PCI. The index of microvascular resistance was measured at baseline, 10 minutes after study drug administration, and after PCI. High-sensitivity cardiac troponin T was measured as a marker of myocardial injury.

Results Infusion of enalaprilat resulted in a significant reduction in index of microvascular resistance (27 $\pm$ 11 at baseline vs. 19 $\pm$ 9 after drug vs. 15 $\pm$ 8 after PCI), whereas a significant post-procedural increase in index of microvascular resistance levels was observed in the placebo group (24 $\pm$ 15 at baseline vs. 24 $\pm$ 15 after drug vs. 33 $\pm$ 19 after PCI). Index of microvascular resistance levels after PCI were significantly lower in the enalaprilat group ($p < 0.001$). Patients pre-treated with enalaprilat also showed lower peak values (mean: 21.7 ng/ml, range: 8.2 to 34.8 ng/ml vs. mean: 32.3 ng/ml, range: 12.6 to 65.2 ng/ml, $p = 0.048$) and peri-procedural increases of high-sensitivity cardiac troponin T (mean: 9.9 ng/ml, range: 2.7 to 19.0 ng/ml vs. mean: 26.6 ng/ml, range: 6.3 to 60.5 ng/ml, $p = 0.025$).

Conclusions Intracoronary enalaprilat improves coronary microvascular function and protects myocardium from procedure-related injury in patients with coronary artery disease undergoing PCI. Larger studies are warranted to investigate whether these effects of enalaprilat could result into a significant clinical benefit. (J Am Coll Cardiol 2013;61:615–21) © 2013 by the American College of Cardiology Foundation

Angiotensin-converting enzyme (ACE) inhibitors improve clinical outcomes in patients with coronary artery disease (1–4). Beyond the long-term protective effect of the oral treatment, intracoronary administration of ACE inhibitors may be beneficial in patients undergoing percutaneous coronary intervention (PCI). Pretreatment with intracoronary enalaprilat of patients with stable coronary artery disease relieved myocardial ischemia during PCI, as assessed by intracoronary electrocardiogram and chest pain score (5). Moreover, in patients undergoing primary PCI for ST-segment elevation myocardial infarction, enalaprilat injection in the infarct-related artery reduces the adhesion of inflammatory cells and improves epicardial flow (6). Possible mechanisms underlying these protective effects include an improvement of the endothelium-dependent epicardial coronary vasodilation mediated by an increase in endogenous bradykinin activity (7). In addition, preliminary findings from experimental models suggest that enalaprilat also may lead to an improvement of coronary blood flow and coronary flow reserve (CFR) (8). Yet, it is still unclear whether this latter effect is exerted mainly at the level of the coronary microcirculation.

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme

CFR = coronary flow reserve

FFR = fractional flow reserve

hs-cTnT = high-sensitivity cardiac troponin T

IMR = index of microvascular resistance

PCI = percutaneous coronary intervention

PMI = periprocedural myocardial infarction

In the present study, we investigated whether enalaprilat improves coronary microvascular function, as assessed with the index of microvascular resistance (IMR), and we assess its relative impact on peri-procedural outcomes in patients undergoing elective PCI.

Methods

This was a prospective, randomized, double-blind, controlled study carried out at the Cardiovascular Center Aalst OLV Clinic, Aalst, Belgium, between February and September 2011.

Patient population. We enrolled 40 patients with stable coronary disease referred for elective PCI of an isolated, functionally significant (fractional flow reserve [FFR]: <0.80) lesion located in the proximal two-thirds of a major coronary artery. Patients were excluded in the presence of the following conditions: treatment with oral ACE inhibitors in the previous 15 days, previous myocardial infarction, left ventricle ejection fraction less than 50%, left ventricle wall-motion abnormalities, left ventricular hypertrophy, in-stent restenosis, bifurcation with side branch of more than 2 mm, ostial lesion, and contraindications to adenosine. The study protocol was approved by the institutional ethics committee, and patients gave informed consent for participation and data collection.

Adjunctive medications. All patients were administered a loading dose of 600 mg clopidogrel and 500 mg aspirin the day before the procedure. During catheterization, all patients received a weight-adjusted intravenous heparin bolus (100 IU/kg) to maintain an activated clotting time of between 250 and 300s.

Study protocol. Patients were assigned randomly to receive either an intracoronary bolus of enalaprilat or placebo before PCI. Assignment to 1 of the 2 treatments was determined by a computer-based randomization system, and randomization assignment for each patient was kept in a sealed envelope. Enalaprilat 50 μg in 5 ml NaCl 0.9% was administrated to the study patients (9); 5 ml NaCl 0.9% was administrated to the placebo patients. Both the patient and the catheterization laboratory team (operator and scrub nurse) were blinded to the assigned treatment. An independent study nurse not involved in the procedure was responsible of opening the sealed envelope and preparing the solution of enalaprilat (active drug) or placebo (pure saline) to be administered according to treatment allocation. Enalaprilat or placebo was infused in the target coronary artery through the guiding catheter over a 2-min period, followed by a 10-ml 0.9% NaCl solution flush. The dosage of enalaprilat was chosen on the basis of previous studies (9). Coronary physiological indexes (CFR, IMR, and FFR) were measured in each patient at baseline (before study drug administration), 10 min after study drug administration, and after PCI, as previously described (10–18). Briefly, an intracoronary pressure and temperature sensor-tipped guidewire (PressureWire Certus, RADI, St. Jude Medical, Uppsala, Sweden) was used to measure distal coronary pressure and to derive thermodilution curves. Thermodilution curves were obtained (in triplicate) from a hand-held, 3-ml rapid (<0.25 s) injection of room temperature saline at baseline and during maximal hyperemia, which was achieved by infusion of 140 μg/kg per minute of adenosine via the femoral vein. Mean transit time (T_{mn}) at baseline and during maximal hyperemia was derived from thermodilution curves. Simultaneous recordings of mean aortic pressure (guiding catheter, P_a) and mean distal coronary pressure (distal pressure sensor, P_d) also were obtained at baseline and during maximal hyperemia. The CFR was calculated from the ratio of hyperemic to baseline T_{mn}. The IMR was calculated using the following equation: $IMR = P_a \times T_{mn}\,[(P_d - P_w) / (P_a - P_w)]$, where P_w is the coronary wedge pressure. P_w was measured as the distal coronary pressure (from the distal pressure and temperature sensor) during complete balloon occlusion of the vessel obtained during PCI. The FFR was calculated from the ratio of distal to proximal pressures at maximal hyperemia. The PCI procedures were performed by standard technique. In all cases, balloon pre-dilatation was performed before stent implantation.

Peri-procedural myocardial necrosis. High-sensitivity cardiac troponin T (hs-cTnT) (Roche Diagnostics, Mannheim, Germany) was determined in blood samples taken before and 8 and 24 h after intervention. Peri-procedural myocardial infarction (PMI) was defined as a post-procedural increase in hs-cTnT more than 3 times the 99th percentile of the upper reference limit (i.e., 14 ng/ml) for patients with baseline negative myocardial necrosis markers, consistent with the joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation task force consensus statement on the redefinition of myocardial infarction for clinical trials on coronary intervention (19). In patients with increased baseline levels of hs-cTnT, a subsequent increase of more than 50% of the baseline value fulfilled the criteria for PMI (20).

Statistical analysis. At the time the ProMicro (EnalaPrilat to Reduce MICROvascular Damage During Percutaneous Coronary Intervention) (ProMicro) trial was conceived, no studies were available specifically reporting on the impact of enalaprilat on microvascular function. However, we based our sample size calculation on our previous studies showing that a strategy of direct stenting resulted in a significant impact on microvascular function with a 45% reduction in IMR after PCI compared with conventional balloon angioplasty followed by stent implantation (as performed in the present study) (21,22). Assuming a 33% reduction in IMR

after PCI in the enalaprilat group, a total of at least 17 patients per group was needed to achieve an 80% power at a 2-sided alpha of 0.05 to detect the expected difference. Therefore, we aimed at enrolling a total of 40 patients (20 per group). Continuous variables are expressed as mean ± SD or as median (interquartile range), as appropriate. Categorical variables are reported as frequencies and percentages. Normal distribution was tested with the D'Agostino-Pearson omnibus K^2 test. Comparisons between continuous variables were performed using the Student *t* test or Mann-Whitney *U* test. These tests were corrected for repeated measures where appropriate. The IMR at baseline, after drug administration, and after PCI was compared with an analysis of variance (ANOVA) for repeated measures or with the Friedman test, as appropriate. Comparisons between categorical variables were evaluated using the Fisher exact test or the Pearson chi-square test, as appropriate. Correlations between continuous variables were assessed using the Spearman rank correlation test. A 2-way ANOVA for repeated measures was used to detect changes in IMR levels over time in the 2 study groups. Statistical analyses was performed using STATA/IC software version 10 (STATA Corp., College Station, Texas) and p values <0.05 (2-tailed) were considered significant.

Results

Patient population. A total of 40 patients were enrolled in this study: 20 randomized to the enalaprilat group and 20 randomized to the placebo group. Baseline clinical and procedural characteristics are shown in Tables 1 and 2, respectively. No significant differences were found between the 2 study groups for any of the variables reported.

Measurements of coronary physiological indices. Measurements of the physiologic indices in the 2 groups at the 3 time points are reported in Figure 1 and Table 3. In the enalaprilat group, a significant change in IMR ($p < 0.0001$, ANOVA) was observed after drug administration and after PCI, whereas no significant variations were observed in the placebo group ($p = 0.058$, Friedman test).

At baseline, FFR, CFR, and IMR were similar in 2 study groups. After drug administration, a significant reduction in IMR was detected in the enalaprilat group (27 ± 11 at baseline vs. 19 ± 9 after drug administration, $p < 0.001$), whereas no significant variations were observed in the placebo group (24 ± 15 at baseline vs. 24 ± 15 after drug administration, $p = 0.899$). Likewise, CFR increased significantly in the enalaprilat group (2.2 ± 1.4 at baseline vs. 2.7 ± 1.3 after drug administration, $p = 0.004$), whereas it did not change significantly in the placebo group (2.4 ± 0.9 at baseline vs. 2.4 ± 1.0 after drug administration, $p = 0.870$). The FFR decreased significantly after drug administration in the enalaprilat group ($p = 0.023$ after drug administration vs. baseline), but did not change in the placebo group ($p = 0.527$ after drug administration vs. baseline). After PCI, procedural success was achieved in all patients: FFR values increased to more than the ischemic threshold of 0.80 (enalaprilat: $p < 0.001$ vs. baseline, placebo: $p < 0.001$ vs. baseline), with no significant differences in FFR values after PCI between the 2 study groups (Table 3). However, patients in the enalaprilat group showed significantly lower IMR values after PCI compared with those who received placebo (15 ± 8 vs. 33 ± 19, $p < 0.001$) (Table 3). In particular, although in the enalaprilat group a further reduction in IMR was observed ($p < 0.001$ vs. baseline, $p = 0.027$ vs. after drug administration), a significant increase in IMR values was detected in the placebo group after PCI ($p = 0.017$ vs. baseline, $p = 0.018$ vs. after drug administration) (Fig. 1). Using a 2-way ANOVA, a significant interaction between study group and IMR at the 3 study time points (baseline, after drug administration, and after PCI) was found in determining IMR values ($p = 0.003$). Consistently, in the enalaprilat group, a significant increase in CFR after PCI was observed ($p < 0.001$ vs. baseline, $p = 0.008$ vs. after drug administration), whereas in the placebo

Table 1 Clinical Characteristics

	Enalaprilat (n = 20)	Placebo (n = 20)	p Value
Age (yrs)	64 ± 10	64 ± 11	0.926
Male	14 (70)	18 (90)	0.235
BMI (kg/m^2)	27.9 ± 3.6	27.1 ± 4.0	0.593
Hypertension	14 (70)	11 (55)	0.327
Diabetes mellitus	5 (25)	3 (15)	0.695
Dyslipidemia	16 (80)	14 (70)	0.716
Smoking habit	7 (35)	5 (25)	0.731
Previous PCI	6 (30)	4 (20)	0.716
LVEF (%)	61 ± 9	63 ± 9	0.739
Serum creatinine (mg)	0.96 ± 0.25	0.97 ± 0.13	0.891
C reactive protein (mg/l)	3.5 ± 2.6	2.1 ± 1.3	0.317
Beta blockers	13 (65)	10 (50)	0.337
Calcium channel blockers	5 (25)	5 (25)	1.000
Statins	18 (90)	17 (85)	1.000

Value are mean ± SD or n (%).
BMI = body mass index; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

Table 2 Procedural Characteristics

	Enalaprilat (n = 20)	Placebo (n = 20)	p Value
Target vessel			0.507
LAD	11 (55)	14 (70)	
LCx	3 (15)	3 (15)	
RCA	6 (30)	3 (15)	
Percent stenosis (%)	65 ± 11	64 ± 13	0.964
Number of stents	1.3 ± 0.6	1.2 ± 0.5	0.545
Drug-eluting stent,	11 (55)	10 (50)	0.752
Stent diameter (mm)	3.08 ± 0.44	3.07 ± 0.34	0.924
Stent length (mm)	24 ± 7	21 ± 7	0.235
Maximal inflation pressure (mm Hg)	15 ± 2	13 ± 5	0.153
Post-dilatation	14 (70)	13 (65)	0.736

Values are n (%) or mean ± SD.
LAD = left anterior descending artery; LCx = left circumflex artery; RCA = right coronary artery.

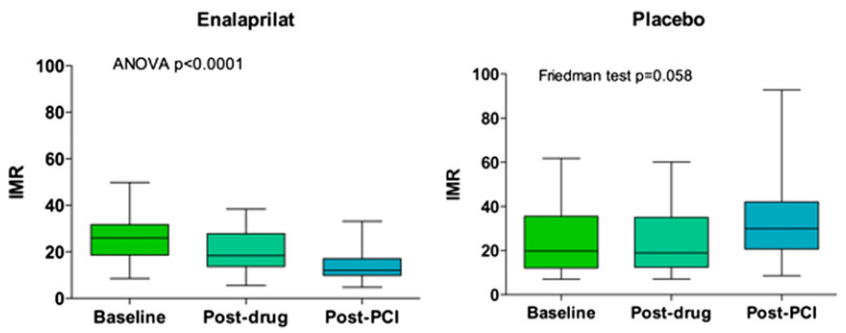

Figure 1 Variations of Microvascular Function During Percutaneous Coronary Intervention

The index of microvascular resistance (IMR) at baseline, after drug administration (either enalaprilat or placebo), and after percutaneous coronary intervention (PCI). **(Left)** Patients treated with enalaprilat. **(Right)** Patients treated with placebo. **Boxes** extend from the 25th to the 75th percentile, with a line at the 50th percentile (median). **Whiskers** show the highest and the lowest values. ANOVA = analysis of variance.

group, CFR did not change significantly (p = 0.352 vs. baseline, p = 0.287 vs. after drug administration). A trend toward higher CFR values was observed in the enalaprilat group as compared with the placebo group (3.6 ± 1.8 vs. 2.7 ± 1.2, p = 0.100).

Peri-procedural myocardial necrosis. Baseline levels of hs-cTnT were similar in the 2 study groups (mean: 7.0 ng/ml, range: 3.0 to 15.6 ng/ml in the enalaprilat group vs. mean: 4.1 ng/ml, range: 3.0 to 8.1 ng/ml in the placebo group, p = 0.259). The peri-procedural increase in hs-cTnT was significantly lower in the enalaprilat group compared with the placebo group (mean: 9.9 ng/ml, range: 2.7 to 19.0 ng/ml vs. mean: 26.6 ng/ml, range: 6.3 to 60.5 ng/ml, p = 0.025) (Fig. 2A). A total of 12 (30%) patients demonstrated PMI; of these, 3 (15%) were in the enalaprilat group and 9 (45%) were in the placebo group (p = 0.034) (Fig. 2B).

Correlation between IMR and myocardial necrosis. A significant correlation was found between IMR after PCI and peri-procedural hs-cTnT increase, both in patients in the enalaprilat group (rho = 0.463, p = 0.040) and in those of the placebo group (rho = 0.457, p = 0.045) (Fig. 3). Furthermore, patients who had PMI showed significantly higher IMR values after PCI compared with those who did not have PMI (33 ± 22 vs. 20 ± 13, p = 0.023) (Fig. 4).

Table 3 Physiological Measurements

	Enalaprilat (n=20)	Placebo (n=20)	p value
Baseline			
SBP	126 ± 16	130 ± 23	0.412
DBP	66 ± 7	69 ± 11	0.321
HR	65 ± 9	67 ± 10	0.522
FFR	0.70 ± 0.13	0.71 ± 0.14	0.944
IMR	27 ± 11	24 ± 15	0.513
CFR	2.2 ± 1.4	2.4 ± 0.9	0.534
After drug administration			
SPB	127 ± 20	129 ± 23	0.783
DBP	66 ± 8	68 ± 12	0.436
HR	66 ± 9	68 ± 10	0.500
FFR	0.69 ± 0.13	0.71 ± 0.14	0.749
IMR	19 ± 9	24 ± 15	0.270
CFR	2.7 ± 1.3	2.4 ± 1.0	0.550
After PCI			
SBP	133 ± 21	133 ± 24	0.989
DBP	68 ± 9	70 ± 13	0.534
HR	65 ± 8	67 ± 10	0.472
FFR	0.89 ± 0.06	0.89 ± 0.07	0.652
IMR	15 ± 8	33 ± 19	<0.001
CFR	3.6 ± 1.8	2.7 ± 1.2	0.100

Values are mean ± SD.

CFR = coronary flow reserve; DBP = diastolic blood pressure; FFR = fractional flow reserve; HR = heart rate; IMR = index of microvascular resistance; SBP = systolic blood pressure.

Discussion

In this randomized, controlled, double-blind study conducted in patients with stable coronary artery disease, we found that intracoronary enalaprilat improves coronary microvascular function and prevents the occurrence of microvascular impairment related to PCI. This beneficial effect of enalaprilat on the microcirculation was associated with a reduced PCI-related myocardial injury.

In patients with coronary atherosclerotic disease, ACE inhibitors have been associated with a significant reduction in mortality and adverse cardiovascular events (1–4). One of the proposed mechanisms underlying this beneficial effect was attributed to an improvement in endothelial function (23,24). In chronically instrumented dogs with dilated cardiomyopathy, enalaprilat improved transmural myocardial perfusion and restored impaired coronary flow (8). In patients with endothelial dysfunction, the improvement of brachial flow-mediated dilation with ACE inhibitors was by far superior to that achieved by other antihypertensive drugs (25,26). This effect also has been observed acutely and locally in patients with mild coronary atherosclerosis, as demonstrated by the selective improvement of the

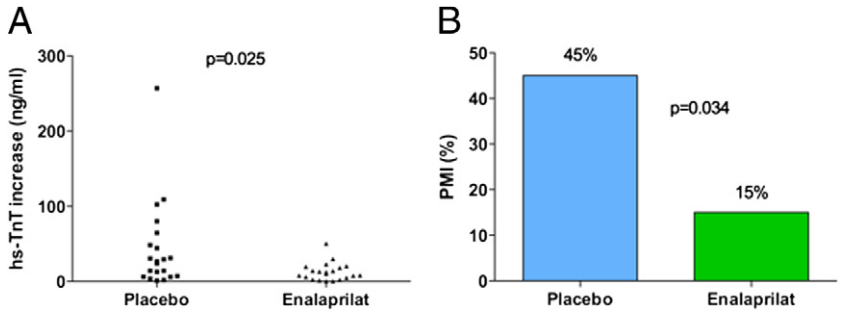

Figure 2 **Peri-procedural Myocardial Necrosis**

(A) Peri-procedural increase in high-sensitivity cardiac troponin T (hs-cTnT) and **(B)** incidence of peri-procedural myocardial infarction (PMI) in the 2 study groups.

endothelium-dependent epicardial vasomotion induced by intracoronary enalaprilat, an effect mediated at least in part through an increase in endogenous bradykinin activity (7). In addition, intracoronary enalaprilat in patients with chronic stable angina undergoing PCI attenuated chest pain and ST-segment changes during balloon inflation (5). Moreover, a significant increase in coronary blood flow was observed in 6 patients, as measured with an intracoronary Doppler wire after enalaprilat infusion. Of note, this effect was not accompanied by a significant epicardial coronary vasodilation, suggesting that mostly coronary microvasculature could be involved in determining flow augmentation (5). In ST-segment elevation myocardial infarction patients undergoing primary PCI, intracoronary enalaprilat after reopening the infarct-related artery improved coronary blood flow, as assessed by corrected thrombolysis in myocardial infarction frame counts, and prevented the increase in L-selectin, P-selectin, and endothelin-1 observed during reperfusion (6).

Our findings confirmed and further extended the available evidence. We confirmed that intracoronary enalaprilat significantly increased CFR (from 2.2 ± 1.4 to 2.7 ± 1.3, p = 0.004), as measured with intracoronary thermodilution. Had we based our indication for PCI on a CFR cutoff for functional significance of coronary stenosis (27), this might have had an impact on clinical decision making. According to published guidelines (28), we based our indication for PCI on symptoms, noninvasive functional tests available, and positive value of FFR. Unlike FFR, which is a specific index of the epicardial coronary stenosis severity, CFR does not enable distinguishing between the contribution of the epicardial and microvascular component to the flow reduction. Whether this increase in CFR could be sustained and is sufficient to relieve completely patient's symptoms, myocardial ischemia, or both is unknown, although this seems unlikely because FFR values showed only minor changes (from 0.70 ± 013 to 0.69 ± 0.13, p = 0.023) that remained always less than the ischemic threshold of 0.80.

We extended the available data by demonstrating that this effect mainly was the result of an improvement in microvascular function, as assessed by the IMR, specifically evaluating the presence of microvascular dysfunction (12–15). We also found that microvascular dysfunction related to PCI was prevented by the administration of enalaprilat. In fact, IMR increased after PCI in the placebo group, whereas it was found to be decreased significantly in the enalaprilat group, therefore suggesting a protective role of ACE inhibition on coronary microvasculature during PCI.

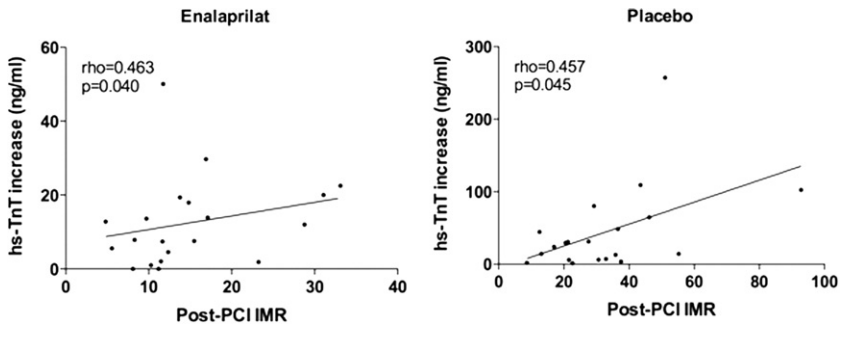

Figure 3 **Microvascular Function and Peri-procedural Myocardial Necrosis**

Correlation between index of microvascular resistance (IMR) after PCI and peri-procedural increase in hs-cTnT in the 2 study groups. Abbreviations as in Figures 1 and 2.

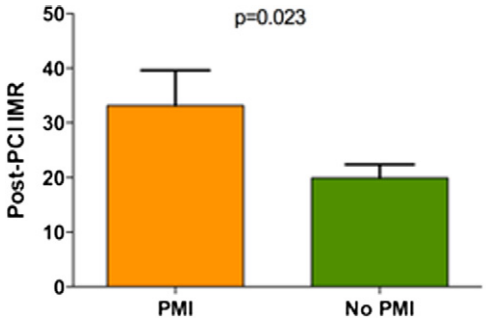

Figure 4 **Microvascular Function and PMI**

IMR after PCI in patients with and without PMI. Abbreviations as in Figures 1 and 2.

Of note, microvascular resistance in the enalaprilat group was found to be even lower after PCI compared with 10 min after drug administration. We can speculate that the effect of enalaprilat on IMR did not reach the peak 10 min after drug infusion, but was prolonged over time. Alternatively, we cannot exclude an interaction between enalaprilat and PCI effects on microvascular resistance.

We cannot provide a mechanistic explanation for these results, but we can speculate, based on previous data (6), that the beneficial effect of enalaprilat on coronary microcirculation could be related to the reduction of neurohormonal and inflammatory markers, such as endothelin-1 and norepinephrine, and the increased availability of bradykinin and nitric oxide induced by this drug. Moreover, bradykinin is a well-known inducer of cardiac preconditioning; therefore, we also may be able to attribute to enalaprilat a protective effect from PCI-related myocardial damage that is mediated by the potentiation of bradykinin.

In our patients, we noted a slight, albeit significant, FFR reduction after enalaprilat administration (from 0.70 ± 0.13 to 0.69 ± 0.13, p = 0.023). Similarly to other pharmacologic agents (i.e., alpha-blockers) (29,30), this may be explained by the ability of enalaprilat to vasodilate and unmask some residual microvascular resistance. Yet, this did not have any clinical impact in our study because all patients recruited had a significant FFR of less than 0.80 and therefore already were candidates for percutaneous coronary revascularization. Whether this drug always should be administrated to all patients undergoing FFR assessment, especially to those close to threshold value for functional significance (i.e., an FFR value of 0.80), is unknown and goes beyond the scope of our study.

In placebo patients, despite an effective PCI, only a trend toward an increase in CFR after PCI was observed. This is explained partly by the limited sample size and partly by the fact that CFR accounts for changes in both epicardial and microvascular resistance. However, FFR accounts for changes in flow of the epicardial coronary artery and can be considered as an index of epicardial coronary resistance, whereas IMR accounts for changes in microvascular resistance. In placebo patients: 1) there are no changes in epicardial resistance (FFR) after drug administration, whereas a significant reduction of epicardial resistance occurs after PCI; 2) no significant changes are observed in microvascular resistance (IMR) after drug administration, whereas a moderately increase occurs after PCI; and 3) consistently with changes occurring in both epicardial and microvascular resistance, CFR does not change after drug administration, whereas only a slight increase, although not statistically significant, occurs after PCI.

This beneficial effect of enalaprilat on the microcirculation translated into a reduced PCI-related myocardial injury. In fact, patients pretreated with enalaprilat showed a significantly lower post-procedural hs-cTnT release as compared with patients receiving placebo. The observation of a moderate correlation between IMR after PCI and post-procedural hs-cTnT level suggests that the myocardial injury that occurs at the time of PCI is reflected by an immediate increase in IMR and a subsequent increase in hs-cTnT. This is in line with our previous findings demonstrating, in stable patients undergoing PCI, a correlation between post-procedural troponin T elevation and IMR values obtained in patients with conventional balloon dilatation followed by stent implantation versus a direct stenting technique (21).

Our findings may be clinically relevant if considering that even small elevations of troponin T after PCI have been associated with subsequent adverse cardiovascular events (31,32). Even if the issue of peri-procedural myocardial leakage is being reappraised (33), strategies aiming at reducing myocardial damage in the context of coronary intervention should be welcomed in patients undergoing coronary revascularization. In this perspective, pretreatment with enalaprilat could be considered as an adjunctive treatment in patients with stable coronary artery disease undergoing PCI.

Study limitations. The investigators were not blinded to the IMR results. We measured IMR only once after PCI, immediately after the end of the procedure; therefore, potential further variations in microvascular function could not be detected.

Only a low dose of enalaprilat was used in the present study. Therefore, whether higher doses could result in an even larger improvement in microvascular function could not be investigated. In addition, enalaprilat was administrated selectively through the guiding catheter into the ostium of the left or right coronary artery. In most of the cases, the study vessel was the left coronary artery (either the left anterior descending or the left circumflex artery). Therefore, we cannot exclude that an even more pronounced effect of enalaprilat on the microcirculation could have been unmasked, had the injection been performed subselectively, that is, directly into a study vessel (that is, left anterior descending or left circumflex artery).

The sample size of this study was relatively small. Although no significant differences were detected in baseline characteristics, potential unbalance between the 2 study groups is not to be excluded entirely.

Conclusions

This randomized, controlled, double-blind study showed for the first time that intracoronary enalaprilat is able to improve coronary microvascular function and to protect myocardium from procedure-related injury in patients with coronary artery disease undergoing PCI. Further larger studies with long-term follow-up are warranted to investigate whether these effects of enalaprilat could result in a significant clinical benefit.

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