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J. Am. Coll. Cardiol. 2004;43;1511-1514
doi:10.1016/j.jacc.2003.09.069

This information is current as of November 12, 2009

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<http://content.onlinejacc.org/cgi/content/full/43/9/1511>

JACC

JOURNAL of the AMERICAN COLLEGE of CARDIOLOGY



CLINICAL RESEARCH

Coronary Artery Disease

Angina Pectoris Prior to Myocardial Infarction Protects Against Subsequent Left Ventricular Remodeling

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OBJECTIVES	To investigate the hypothesis that prior angina pectoris confers protection from remodeling occurring after myocardial infarction (MI), we analyzed echocardiograms from the Healing and Early Afterload Reducing Therapy (HEART) trial.
BACKGROUND	Ischemia occurring before MI has been shown to reduce infarct size in experimental models and to improve outcomes in patients. The extent to which ischemia occurring before MI influences subsequent changes in ventricular size and function is unclear.
METHODS	We studied 283 patients enrolled in the HEART trial who had echocardiograms at days 1 and 90 after MI. Left ventricular (LV) dilation from days 1 to 90 was used as a measure of LV remodeling. We explored the relationship between symptomatic angina occurring before infarction and subsequent LV remodeling.
RESULTS	In patients who reported angina ($n = 111$) during the three months preceding MI, LV volume change was -0.73 ± 2.6 ml over the 90-day post-MI period, compared with 6.8 ± 2.6 ml for patients ($n = 172$) without angina ($p = 0.017$). In contrast, there were no differences in changes in ejection fraction based on prior angina. Maximal creatine kinase was significantly lower in patients with prior angina ($2,119 \pm 1,729$ vs. $2,701 \pm 2,088$, $p = 0.016$). In a multivariate model, prior angina remained protective for ventricular remodeling after adjusting for age, gender, baseline ejection fraction, Killip class, baseline end-diastolic volume, and drug treatment group ($p = 0.042$). However, the protective effect of pre-infarction angina appeared to be attenuated in diabetic patients.
CONCLUSIONS	Ischemic symptoms occurring before MI may protect against LV remodeling. These protective effects may be secondary to recruitment of collaterals or ischemic preconditioning of the myocardium, and they appear to be attenuated in diabetic patients. (J Am Coll Cardiol 2004;43:1511-4) © 2004 by the American College of Cardiology Foundation

Left ventricular (LV) remodeling—changes in the size and shape of the LV—is associated with increased morbidity and mortality post-myocardial infarction (MI) (1). The extent of LV remodeling can be influenced by initial infarct size, reperfusion therapy, and post-MI medical treatment (2). Episodes of ischemia occurring before MI (ischemic preconditioning) have been shown in a number experimental models to reduce infarct size (3). Furthermore, angina

versus late ramipril therapy after MI (5). We have utilized data from HEART to test the hypothesis that symptomatic ischemic episodes occurring before MI influence the extent of LV remodeling occurring after MI.

METHODS

Patients. The HEART study was a double-blind randomized trial of immediate versus delayed ramipril in 352 patients with anterior Q-wave MI. Patients underwent echocardiographic examinations before randomization (within 24 h of MI) and at 14 and at 90 days after MI and were randomly assigned to receive one of three dosing regimens of ramipril (placebo for 14 days, followed by full-dose [10 mg] ramipril; low-dose [0.625 mg] ramipril for 90 days; or full-dose [10 mg] ramipril for 90 days). Inclusion and exclusion criteria and the details of the titration scheme and patient characteristics have been previously described (5).

Serial echocardiographic data were available for 286 patients. Patients with initial echocardiograms of insufficient quality or patients who were alive at 90 days but in whom 90-day echocardiograms were not available were excluded from these analyses. Of the 352 patients enrolled in the original study, 48 did not have echocardiograms of

See page 1515

occurring before MI has been associated with improved in-hospital outcome (4). The extent to which clinical episodes of ischemia occurring before MI influence subsequent LV function and remodeling is unknown.

The Healing and Early Afterload Reducing Therapy (HEART) trial was a randomized controlled trial of early

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Manuscript received July 18, 2003; revised manuscript received September 12, 2003, accepted September 23, 2003.

Abbreviations and Acronyms

CK	= creatine kinase
HEART	= Healing and Early Afterload Reducing Therapy trial
LV	= left ventricle/ventricular
MI	= myocardial infarction

sufficient quality for analysis, and 18 (including 13 deaths) did not have all three echocardiograms.

Assessment of ischemic episode. At enrollment in HEART, the local investigator administered a baseline intake questionnaire asking whether the patient had experienced angina within the past three months. An additional question determined whether angina occurred at rest or had awakened the patient from sleep. Determination of symptomatic ischemia was made in 283 patients who had echocardiograms performed at days 1 and 90.

Echocardiographic analysis. Echocardiographic measurements were made in triplicate on a Nova Microsonics workstation as previously described. Endocardial borders from end-diastolic and end-systolic frames were digitized manually, and LV volumes were assessed with the modified Simpson's rule method. Infarct segment size was assessed by manually tracing the akinetic or dyskinetic segment, which was expressed as a percentage of endocardial perimeter. The reproducibility of the echocardiographic measurements has been previously reported (5).

Statistical analyses. Patients were categorized into two groups depending on whether or not they experienced clinical angina during the three months preceding MI. Patients were further categorized depending on whether they had rest or exertional angina. Left ventricular remodeling was defined as the increase in ventricular end-diastolic volume between days 1

and 90 and treated as a continuous variable. Differences between means when normally distributed were compared with the Student *t* test and with the Wilcoxon rank sum test when not normally distributed. Comparison of groups was performed with analysis of variance. Multivariate linear regression was used to assess the relationship between stable angina preceding MI and post-MI ventricular remodeling. Values are expressed as mean \pm SD. A value *p* < 0.05 was considered statistically significant.

RESULTS

Clinical and echocardiographic characteristics of patients with (n = 111) and without (n = 172) stable angina in the three months preceding MI are shown in Table 1. Previous history of MI and use of anti-anginal medications, including aspirin, nitrates, beta-blockade, and calcium channel blockers, were more common in patients with a history of angina in the three months preceding MI. Stable angina preceding MI was associated with both reduced maximal creatine kinase (CK) (2,701 \pm 2,088 vs. 2,119 \pm 1,729, *p* = 0.016) and decreased infarct segment length (26.9 \pm 11.2% vs. 24.6 \pm 9.8%, *p* = 0.08), although ejection fractions were similar in the two groups (52.6 \pm 9.4% vs. 52.4 \pm 9.8%, *p* = 0.81). There were no differences in medication use between groups at 90 days.

Left ventricular end-diastolic volume from days 1 to 90 increased by 6.8 \pm 2.6 ml in patients without prior stable angina, compared with a 0.73 \pm 2.6 ml decrease in patients with prior stable angina (*p* = 0.017) (Table 1). There was no difference in change in ejection fraction over the 90-day period in the two groups. Patients with angina at rest or during sleep demonstrated less remodeling than either patients with exertional angina or patients with no angina (analysis of variance, *p* = 0.049) (Fig. 1).

Table 1. Clinical and Echocardiographic Characteristics of Patients With and Without Prior Angina

	No Angina (n = 172)	Angina (n = 111)	p Value
Age	59.4 \pm 12.4	59.4 \pm 12.2	0.97
Male	138 (80%)	85 (77%)	0.46
Female	34 (20%)	26 (23%)	0.46
Prior MI	20 (11%)	24 (21%)	0.02
Diabetes	36 (21%)	22 (20%)	0.82
Beta-blocker	16 (9%)	27 (24%)	0.001
Ca-blocker	18 (10%)	20 (18%)	0.07
Nitrates	4 (2%)	13 (11%)	0.001
Aspirin	34 (20%)	39 (35%)	0.004
Thrombolysis	156 (88%)	97 (87%)	0.20
Primary PTCA	49 (28%)	29 (26%)	0.51
Maximum CK	2,701 \pm 2,088	2,119 \pm 1,729	0.016
Baseline LV end-diastolic volume (ml)	103.1 \pm 35.6	107.3 \pm 36.0	0.32
Baseline LV end-systolic volume (ml)	49.9 \pm 24.7	52.3 \pm 26.0	0.42
Baseline ejection fraction (%)	52.6 \pm 9.4	52.4 \pm 9.8	0.81
Baseline infarct segment length (%)	26.9 \pm 11.2	24.6 \pm 9.8	0.08
Change in end-diastolic volume (days 1 to 90)	6.8 \pm 25.7	-0.73 \pm 26.1	0.017
Change in ejection fraction (days 1 to 90)	4.4 \pm 9.1	4.5 \pm 10.6	0.96

CK = creatine kinase; LV = left ventricular; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

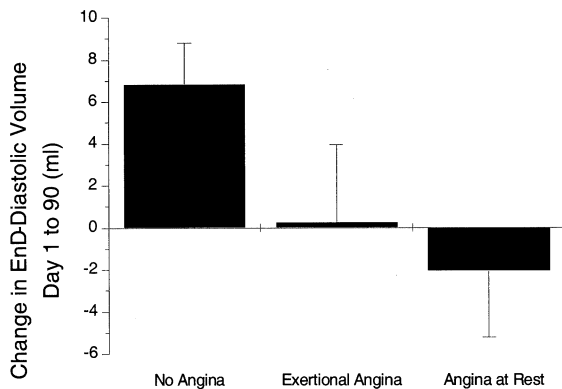


Figure 1. Change in end-diastolic volume between days 1 and 90.

In a multivariate model, prior stable angina remained predictive of less remodeling after adjusting for age, gender, baseline ejection fraction, Killip class, history of diabetes, baseline end-diastolic volume, and drug treatment ($p = 0.042$), but not after including maximal CK in the model. To determine whether patients with prior stable angina were more likely to obtain medical treatment early, we compared the time until thrombolysis in the 205 patients in this cohort who received thrombolytic therapy. Patients with prior stable angina had slightly longer times to thrombolysis (3.9 ± 6.0 vs. 3.4 ± 2.8 h, $p = 0.41$), although these were not significantly different.

The prevalence of diabetes was similar in both groups. We tested the hypothesis that decreased reporting of ischemic episodes in diabetic patients might account for increased remodeling in the group that did not report prior angina. There were no differences in the extent of remodeling in diabetics with and without stable angina (4.1 ± 2.6 vs. 4.7 ± 2.5 , $p = 0.86$). Thus, the protective effect of stable angina preceding MI appeared to be attenuated in diabetics (Table 2). There was no interaction between stable angina and remodeling amongst diabetics ($p = 0.19$).

DISCUSSION

The results of this analysis demonstrate that patients with symptomatic stable angina preceding MI demonstrate less ventricular remodeling than do patients without prior symptomatic stable angina. Furthermore, patients with rest angina appear to be more protected than patients with exertional angina. In addition, stable angina preceding MI appears to be associated with decreased infarct size, as measured by peak CK and echocardiographic estimates of infarct segment length, suggesting that angina preceding

Table 2. Left Ventricular Dilatation From Days 1 to 90 in Diabetics and Non-Diabetics With and Without Angina

	No Angina Δ in Volume (ml)	Angina Δ in Volume (ml)	p Value
Diabetics (n = 58)	4.1 ± 2.6 (n = 36)	4.7 ± 2.5 (n = 22)	0.86
Non-diabetics (n = 227)	7.8 ± 2.1 (n = 89)	-1.9 ± 2.1 (n = 138)	0.007

MI may confer protective benefits on remodeling by limiting the size of the infarct itself. Although previous studies have demonstrated improvement in hospital outcome in patients with symptomatic ischemia occurring before MI, this study demonstrates that structural changes in the LV may be affected by prior symptomatic ischemia in humans.

A reduction in infarct size as a result of previous exposure to brief episodes of ischemia has been referred to as ischemic preconditioning (6) and this phenomenon is supported by numerous experimental models (2,3). The cardioprotective effects of this phenomenon have been attributed to reduced energy demand in ischemic preconditioned myocardial tissue (6). The mechanisms eliciting these changes are complex and still unclear. Adenosine, bradykinin, and opioids have all been documented to accumulate during episodes of ischemia and are associated with preconditioning effects via interaction with second messenger systems, specifically protein kinase C and K_{ATP} channels (6-8). Brief episodes of ischemia are often associated with protein kinase C activation, which stimulates opening of mitochondrial K_{ATP} channels (9). A consistent finding has been that the cardioprotective manifestations appear to be independent of coronary collateral flow (2).

Stable angina preceding MI represents a clinical correlate of ischemic preconditioning. Several clinical studies have suggested that stable angina occurring before MI may confer cardioprotective effects. Both the Thrombolysis In Myocardial Infarction (TIMI)-4 and -9 thrombolytic trials demonstrated that angina might reduce infarct size, improve survival, improve left ventricular function and reduce arrhythmias (4,10). Of 153 patients, of whom 100 had stable angina preceding infarction, angina was associated with a lower incidence of ventricular arrhythmia, pump failure, cardiac rupture, and a lower in-hospital mortality rate (10). In addition, peak CK was also lower in patients with angina, and in a subset of 65 patients who underwent left ventriculography, patients with angina showed improved function and reduced ventricular volumes (10). Although this assessment was performed early after infarction, our data suggest that symptomatic ischemia occurring before infarction confers sustained benefit as well. Although the maximal peak CK in the angina group in the present study was less when compared to the non-angina group, ejection fractions were similar. This may be explained by the fact that early ejection fraction may be more strongly influenced by the extent of myocardial stunning than by the extent of necrosis (11).

In the current study, exertional angina was associated with less of a protective effect than rest or sleep angina. It is possible that individuals experiencing rest or sleep angina may be having these events quite proximal to infarction; additionally, these individuals may have an overall greater ischemic burden (12). Alternatively, patients experiencing exertional angina may have elevated circulating levels of catecholamines that may overcome any benefits of preconditioning (13,14).

Although stable angina preceding MI offered protection from subsequent ventricular remodeling in the overall cohort, this effect was not apparent in diabetic patients. We cannot rule

out the possibility that this finding was due to reporting bias, as diabetic patients may be less likely to report ischemic symptoms even though they may have more total ischemic episodes. If this were the case in our diabetic cohort, the relationship between angina and remodeling might be obscured. Similar differential findings between diabetics and nondiabetics were shown in a recent post-MI study of 121 diabetic patients in which there were no significant differences in peak CK, LV ejection fraction, or in-hospital mortality observed between groups with or without prodromal angina (15). Although the differential findings may have been partly explained by delayed hospital presentation in diabetics, evidence from various animal based studies suggests that diabetic hearts are less sensitive to the effects of preconditioning (16,17). Diabetes is thought to interfere with the biochemical pathways of preconditioning (18,19), rendering the diabetic myocardium more vulnerable to repeated bouts of ischemia (20). Sulphonylureas are documented to antagonize K_{ATP} channels and this may also contribute to preconditioning insensitivity (9,21). Other confounding factors include impaired perception of ischemia associated with high ischemic burden and resulting in late presentations and more complete infarctions. A combination of reporting bias, delayed presentations, and reduced sensitivity to preconditioning may explain our findings within the diabetic group.

Some potential limitations of this analysis must be noted. Our ability to determine whether a patient had prior angina was dependent on an accurate history and recording of this information by the site investigator. We considered two potential biases that might have influenced the relationship between prior stable angina and remodeling. First, we considered the possibility that patients who had experienced prior stable angina were more likely to seek and receive prompt medical attention. This did not appear to be the case in patients who received thrombolysis; the time to thrombolysis was in fact shorter in patients who had not had prior angina (3.9 ± 6.0 h vs. 3.4 ± 2.8 h). Second, individuals with impaired pain perception might be expected to demonstrate greater remodeling owing to unrecognized multiple events and late presentation for treatment; this could have confounded the results observed amongst diabetics, although it apparently did not. Additionally, we cannot exclude the possibility that the relationship between prior angina and remodeling may be different in patients with larger, more extensive infarcts.

In summary, stable angina preceding MI appears to protect against subsequent ventricular remodeling. This effect appears to be attenuated in diabetic patients. Whether this finding is due to reporting bias or an intrinsic resistance to preconditioning in the diabetic heart requires further study.

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