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Angiotensin-Converting Enzyme Inhibitor Therapy Affects Left Ventricular Mass in Patients With Ejection Fraction >40% After Acute Myocardial Infarction

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Objectives. **We tested the hypothesis that angiotensin-converting enzyme (ACE) inhibitor therapy decreases left ventricular (LV) mass in patients with a left ventricular ejection fraction (LVEF) >40% and no evidence of heart failure after their first acute Q wave myocardial infarction (MI).**

Background. **Recently, ACE inhibitor therapy has been shown to have an early mortality benefit in unselected patients with acute MI, including patients without heart failure and a LVEF >35%. However, the effects on LV mass and volume in this patient population have not been studied.**

Methods. **Thirty-five patients with a LVEF >40% after their first acute Q wave MI were randomized to titrated oral ramipril (n = 20) or conventional therapy (control, n = 15). Magnetic resonance imaging (MRI) performed an average of 7 days and 3 months after MI provided LV volumes and mass from summated serial short-axis slices.**

Results. **Left ventricular end-diastolic volume index did not change in ramipril-treated patients (62 ± 16 [SD] to 66 ± 17 ml/m^2) or in control patients (62 ± 16 to 68 ± 17 ml/m^2), and stroke volume index increased significantly in both groups. However, LV mass index decreased in ramipril-treated patients (82 ± 18 to 73 ± 19 g/m^2, p = 0.0002) but not in the control patients (77 ± 15 to 79 ± 23 g/m^2). Systolic arterial pressure did not change in either group at 3-month follow-up.**

Conclusions. **In patients with a LVEF >40% after acute MI, ramipril decreased LV mass, and blood pressure and LV function were unchanged after 3 months of therapy. Whether the decrease in mass represents a sustained effect that is associated with a decrease in morbid events requires further investigation.**

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Large trials have demonstrated a significant reduction in cardiovascular morbidity and mortality with long-term use of angiotensin-converting enzyme (ACE) inhibitors in patients with left ventricular (LV) dysfunction, heart failure or acute myocardial infarction (MI), or a combination of these (1–3). This benefit included an ~24% reduction in the risk of MI, the need for revascularization and a reduction in the likelihood of hospital admission for unstable angina. This effect was independent of LV ejection fraction (LVEF) and greater than expected for the small reduction in blood pressure (1). The recent Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) and Fourth International Study of Infarct Survival (ISIS-4) results have demonstrated a mortality benefit of ACE inhibitor therapy in unselected patients, including patients without LV dysfunction (4,5). Furthermore, captopril had a favorable effect on ischemic burden and functional capacity, as well attenuation of LV dilation in post-MI patients with only mild LV dysfunction (6). Taken together, these studies suggest that ACE inhibitor therapy benefits a wider group of post-MI patients, including those with well-preserved LV function.

The effects of ACE inhibitors on LV function have been extensively studied in selected patients with documented LV dysfunction (LVEF <40%). Therapy with ACE inhibitors have been shown to attenuate the increase in LV volumes, to decrease myocardial mass and to preserve LVEF (7–13). These beneficial effects of ACE inhibitors in patients with LV dysfunction are presumably mediated by decreasing preload and afterload, but ACE inhibitor therapy may also exert tissue

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Abbreviations and Acronyms

ACE	=	angiotensin-converting enzyme
GISSI	=	Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico
ISIS	=	International Study of Infarct Survival
LV	=	left ventricular
LVEF	=	left ventricular ejection fraction
MI	=	myocardial infarction
MRI	=	magnetic resonance imaging
PTCA	=	percutaneous transluminal coronary angioplasty
SAVE	=	Survival and Ventricular Enlargement trial
SOLVD	=	Studies of Left Ventricular Dysfunction

effects on the myocardium and vasculature by blunting the trophic effect of angiotensin II on myocytes and fibroblasts in the heart (14,15) and by preventing the degradation of endogenous kinins (e.g., bradykinin) to inactive metabolites (16,17).

The impetus for the current investigation was generated because of the ongoing large-scale clinical trials evaluating the prevention of atherosclerosis-related events using ACE inhibitors in all patients with coronary artery disease, including those with well-preserved LV function (18). The Survival And Ventricular Enlargement (SAVE) trial included patients with LVEF <40%; however, no study has evaluated the effects of ACE inhibitors on LV mass and volumes in patients with preserved LV function (LVEF >40%) and coronary atherosclerosis. Thus, the current investigation examines the effects of the ACE inhibitor ramipril on LV volumes and mass in patients with LVEF >40% after acute MI using geometry-independent calculations of mass and volume from summated serial short-axis slices obtained from magnetic resonance imaging (MRI).

Methods

Patient selection. Forty-four patients who had their first acute Q wave MI and had a LVEF >40% were enrolled between April 1993 and September 1994. All patients were in normal sinus rhythm and had evidence of an acute transmural MI with new abnormal Q waves in at least two contiguous electrocardiographic (ECG) leads, ST segment elevation ≥2 mm above baseline in at least two contiguous ECG leads, creatine kinase–MB isoenzyme elevation and a clinical history of angina lasting longer than 30 min. Exclusion criteria included previously documented MI, presence of significant valvular heart disease, symptomatic congestive heart failure, atrial fibrillation, suspected renal artery stenosis, renal insufficiency with serum creatinine >2.0 mg/dl, child-bearing potential, prior use or known allergy to ACE inhibitors and any contraindication to MRI. Conventional therapy, thrombolytic agents or primary percutaneous transluminal coronary angioplasty (PTCA), nitrates, beta-blockers, calcium entry blockers and revascularization were offered to all patients as determined by their primary physician. Before entry into the research protocol, each potential subject signed an informed consent and underwent a history and physical examination conducted by one of the investigators. Subsequently, initial MRI was performed in each patient within 16 days of acute MI. This protocol was reviewed and approved by the Institutional Review Board for Human Use at the University of Alabama, Birmingham.

Magnetic resonance imaging. MRI was performed using a 1.5-tesla nuclear MRI/spectroscopy system (ACS Philips) using a gradient echocardiographic imaging approach acquiring serial short-axis slices of 8 mm thickness with a slice gap of 1.0 mm as previously described in our laboratory (19,20). The MASS version 1.0 cardiac software package (Laboratory of Clinical and Experimental Imaging Processing, University Hospital at Leiden) was used to measure LVEF, LV volumes and LV mass from the summated serial short-axis slices using the Simpson rule as previously validated in our laboratory (19,20). Circumferential wall thickness was assessed at the base of the heart from a slice that was not involved in the MI. Assessment of the MRI scans was performed by a technician (R.O.) who had no knowledge of the patients' treatment group.

Randomization and treatment. After documenting a LVEF >40% by MRI, patients were randomized to conventional therapy as dictated by their primary physician or conventional therapy plus titrated dose ramipril. All patients were evaluated by a history and physical examination by one of the investigators at baseline, at 2 weeks and at 3 months after their MI. An ECG, blood urea nitrogen and creatinine levels, urinalysis and a complete blood cell count were obtained at these visits. All patients in both groups had their blood pressure measured by a physician every 7 days for 2 weeks after discharge. All patients randomized to receive ramipril were started on 2.5 mg twice daily and titrated upward to 5 mg and then to 10 mg twice daily at 7 and 14 days if systolic blood pressure remained >110 mm Hg. The same approach was used in the patients receiving conventional therapy with nitrates, beta-blockers and calcium channel blocking drugs. The starting dose of 2.5 mg of ramipril was chosen based on the documented effect of this oral dose in decreasing cardiac ACE activity by 35% in tissue extracts of human hearts obtained at the time of surgery (21).

Data analysis. The data are presented as mean value ± SD. Differences in baseline characteristics, hemodynamic variables and LV volumes and LV mass were determined by the unpaired Student *t* test. Baseline and 3-month follow-up data were analyzed using the paired Student *t* test. Although this is a randomized trial, the degree of change for any given variable may be correlated with the magnitude of baseline hemodynamic variables and LV volume and mass values and with other factors, including age, gender, history of hypertension, location of MI and use of thrombolytic therapy. Therefore, the significance of treatment effect (ramipril vs. conventional therapy) was determined by analysis of covariance, adjusting for potential baseline differences between the groups. The covariates included those listed in Tables 1 and 2. Because of the small sample size, potential covariates were determined by

Table 1. Baseline Patient Characteristics

Variable	Control (n = 15)	Ramipril (n = 20)
Age (mean ± SD, yr)	60 ± 11	58 ± 11
Gender (male/female)	13/2	18/2
HTN	4 (27)	5 (25)
Angina	2 (13)	3 (15)
Anterior MI	6 (40)	11 (55)
Inferior MI	9 (60)	9 (45)
Beta-blockers	12 (80)	15 (75)
Nitrates	13 (86)	16 (80)
Calcium entry blockers	1 (7)	0
Thrombolytic agents	9 (60)	10 (50)
Open infarct-related artery	12 (92)	19 (95)
PTCA	9 (60)	16 (80)
CABG	0	1 (5)

Data presented are number (%) of patients, unless otherwise indicated. CABG = coronary artery bypass grafting; HTN = hypertension; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

backward stepwise regression with $p \leq 0.10$. Any change in LV mass or volume during the study was then adjusted for the significant covariates. These adjusted changes were considered significant between the two groups with $p < 0.05$.

Results

Patient group (Table 1). Forty-four patients underwent baseline MRI and randomization at a mean of 7 ± 4 days (range 2 to 16) after their MI. Twenty-one patients were randomized to conventional therapy and 23 to conventional therapy plus ramipril. Thirty-five patients completed their baseline and 3-month follow-up MRI studies. Three patients receiving ramipril did not complete the study: one developed angioedema, one developed hyperkalemia and one had persistent nausea. A control patient was inadvertently started on an ACE inhibitor by the clinic physician and was therefore excluded from the study. Five control patients did not complete the study owing to their refusal to return for the final MRI study. Patients who did not have the 3-month MRI study were omitted from the analysis.

The baseline clinical data for patients completing the study are presented in Table 1. There were no significant differences between treatment groups regarding age, gender, history of hypertension and angina, MI location, use of thrombolysis/PTCA or concomitant drug therapy. Ramipril was initiated within an average of 7 days of MI, and after 3 months of therapy the titrated mean dose of ramipril was 7 mg/d (range of 1.25 to 10). Coronary angiography was performed in 87% of the patients who had conventional therapy and in all ramipril-treated patients at the discretion of the primary physician as part of post-MI risk stratification. Patency of the infarct-related artery was documented in 92% and 95% of the conventional therapy and ramipril-treated groups, respectively, as a result of thrombolysis or PTCA, or both. The extent of coronary artery disease in the ramipril-treated patients (defined as diameter stenosis >70%) was single-vessel (55%), two-vessel (30%) and three-vessel (10%) disease and no significant disease (5%). The extent of coronary artery disease in the patients who had conventional therapy (defined as diameter stenosis >70%) was single-vessel (69%), two-vessel (15%) and three-vessel (8%) disease and no significant disease (8%).

Hemodynamic variables and volumes and mass (Table 2). At the time of randomization there were no differences in heart rate or systemic arterial pressure between the control and ramipril groups. Although there was no significant change in systolic blood pressure from baseline to the 3-month follow-up in either group, systolic blood pressure was greater in the control versus the ramipril-treated patients at 3-month follow-up (128 ± 13 vs. 118 ± 13 mm Hg, $p = 0.02$). Baseline LVEF, end-diastolic volume index, end-systolic volume index and mass index did not differ between the control and ramipril groups. In patients treated with conventional therapy alone, LV end-diastolic volume index, mass index, mean circumferential wall thickness and mass to end-diastolic volume ratio remained unchanged. However, LVEF increased from the baseline to the 3-month follow-up study.

Patients treated with conventional therapy plus ramipril demonstrated no change in LV end-diastolic volume index or end-systolic volume index. However, LV mass index and mean circumferential wall thickness of noninfarcted myocardium decreased significantly with ramipril therapy (Fig. 1). The decrease in LV mass was accompanied by a decrease in mass to end-diastolic volume ratio. The decrease in LV mass index, mean circumferential wall thickness and mass to end-diastolic volume ratio in the ramipril-treated group persisted after performing analysis of covariance, adjusting for potential differences in baseline patient characteristics (Table 1), hemodynamic variables and LV mass and volumes (Table 2) in both groups.

The percent change in LV end-diastolic volume index, mass index and mass to end-diastolic volume ratio for the ramipril and control groups is depicted in Figure 2. Left ventricular

Table 2. Hemodynamic and Left Ventricular Volume Data

	Control (n = 15)		Ramipril (n = 20)	
Variable	Baseline	3 mo	Baseline	3 mo
SBP (mm Hg)	120 ± 16	128 ± 13	123 ± 13	118 ± 13
DBP (mm Hg)	76 ± 8	78 ± 7	74 ± 8	70 ± 10
HR (beats/min)	76 ± 10	69 ± 12	75 ± 9	72 ± 11
LVEDVI (ml/m^2)	62 ± 16	68 ± 17	62 ± 16	66 ± 17
LVESVI (ml/m^2)	30 ± 10	30 ± 14	32 ± 12	33 ± 13
SVI (ml/m^2)	32 ± 7	38 ± 4†	30 ± 6	33 ± 7*
LVEF (%)	52 ± 6	57 ± 8*	50 ± 8	52 ± 9
LV mass index (g/m^2)	77 ± 15	79 ± 23	82 ± 18	73 ± 19†
LV wall thickness (cm)	1.15 ± 0.18	1.10 ± 0.21	1.14 ± 0.14	1.00 ± 0.12†
LV mass/LVEDV ratio	1.30 ± 0.37	1.17 ± 0.27	1.34 ± 0.21	1.13 ± 0.24†

*$p < 0.05$. †$p < 0.005$. Data are presented as mean value ± SD. DBP = diastolic blood pressure; HR = heart rate; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; SBP = systolic blood pressure; SVI = stroke volume index.

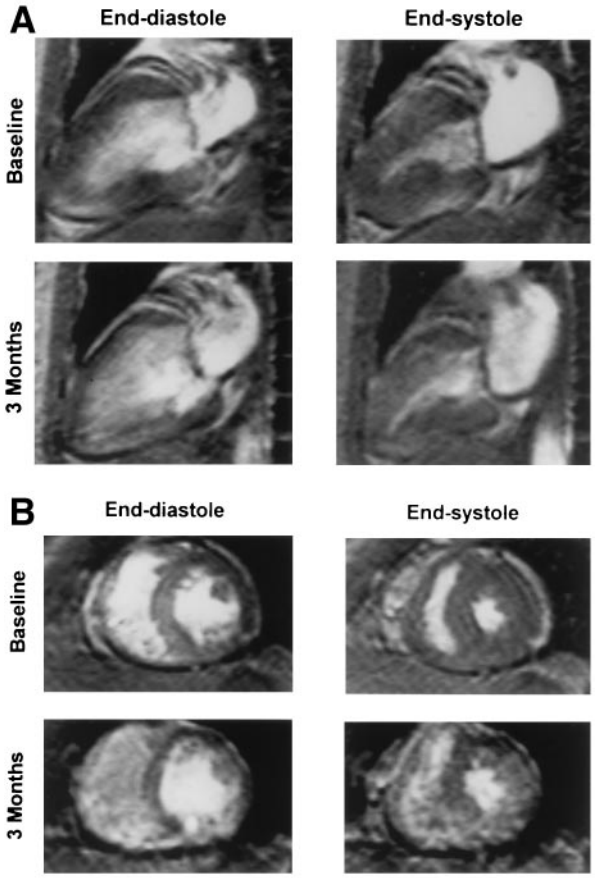

Figure 1. Long-axis (**A**) and short-axis (**B**) end-diastolic and end-systolic magnetic resonance images of the heart at baseline and 3 months after an anterior myocardial infarction in a patient randomized to receive ramipril. There is decreased wall thickening in the interventricular septum on the short-axis images. Note the decrease in LV wall thickness in noninfarcted myocardium at end-diastole, the increase in LV end-diastolic chamber size and the decrease in the LV mass/end-diastolic volume ratio as systolic wall thickening remains well preserved at the 3-month study in both long- and short-axis images.

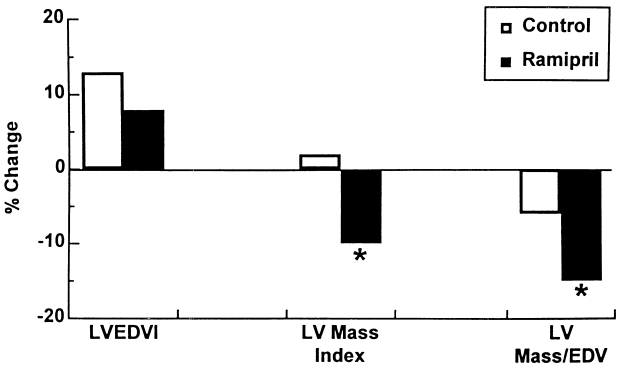

Figure 2. Bar graph depicting the changes in left ventricular end-diastolic volume index (LVEDVI), LV mass index and LV mass/end-diastolic volume (EDV) ratio in control and ramipril-treated groups. (See text for details.) *$p < 0.001$ for change compared with baseline.

mass decreased significantly in the ramipril group (10%, $p < 0.001$) and did not change in the conventional therapy group (2%). Thus, the decrease in the mass to end-diastolic volume ratio in the ramipril-treated patients was mediated by the decrease in LV mass rather than by an increase in end-diastolic volume.

Discussion

In the current investigation, patients with a LVEF >40% after their first acute Q wave MI were randomized to conventional therapy or conventional therapy plus ramipril. Ramipril decreased LV wall thickness and mass, whereas LV volumes and blood pressure did not change in either group. The changes in mass and wall thickness with ramipril persisted after analysis of covariance, correcting for any potential baseline differences in patient characteristics, hemodynamic variables and LV mass and volumes. To our knowledge, this is the first investigation to evaluate the effects of ACE inhibitor therapy on LV volumes and mass in patients with well-preserved LV systolic function after MI.

Results of the current study. Our patients did not have increased LV mass or systolic hypertension at baseline. This may reflect the low incidence of hypertension and the frequent use of nitrate and beta-blocker therapy in our patients. Ramipril therapy decreased LV mass by 11% and wall thickness of noninfarcted myocardium by 9% in our post-MI patients, despite a lack of change in blood pressure. These relatively small changes in LV mass and wall thickness are within the resolution of the images obtained by MRI and can be obtained with high interobserver and intraobserver reproducibility (22). With regard to LV mass determination, the post-MI ventricle does not conform to simple geometry owing to the presence of regional ischemia or infarction, or both. Magnetic resonance imaging can be used to tomographically section the entire heart, providing accurate measurements of ventricular volume and mass, as well as wall thickness independent of geometric assumptions (19,20).

The decrease in LV mass, without significantly changing systolic pressure, is in keeping with studies of pressure overload in the rat, which demonstrated hypertrophy regression without changes in carotid (23,24) or LV systolic pressure (25,26), suggesting a tissue effect of ACE inhibitors. In our patients, however, a late systolic pressure peak at the root of the aorta from reflected waves may have been moderated by ACE inhibitor therapy, thus decreasing afterload not detected in the simple measurement of blood pressure (27). Furthermore, a single measurement of blood pressure at one point in time may not provide an overall impact of these agents on ventricular afterload over the 3-month follow-up period. Although there are no data in normal human subjects, ACE inhibitor therapy has been demonstrated to decrease LV mass in the normal rat (28–31). In these studies, the decrease in LV mass was proportional to the decrease in blood pressure, suggesting that the normal left ventricle is capable of downward regulation of its mass in response to a reduced hemody-

namic load. In support of this mechanism, the lower systolic blood pressure achieved in patients receiving ramipril versus conventional therapy alone could explain the decrease in LV mass in the ramipril-treated patients. However, our patients had an acute MI, and whether this provides a stimulus for hypertrophy in noninfarcted myocardium in the early post-MI period, even when LV function is well preserved, remains an open question.

Results of other work. Gintzon et al. (32) demonstrated a significant increase in LV mass of noninfarcted myocardium in patients with both small and large MIs over a 9-month period of observation. In addition, McDonald et al. (33) demonstrated a 22% increase in LV mass in dogs 1 week after experimentally induced myocardial damage involving only 17% of the myocardium. Kramer et al. (34) reported a 43% increase in LV mass 1 week after 26% myocardial damage in sheep. These last two animal studies demonstrate an early hypertrophic response within 1 week after small- to moderate-sized MIs.

The mechanical stimulus for hypertrophy in small- to moderate-sized MIs could result from elevated diastolic filling pressures. Gottlieb et al. (35) demonstrated that approximately half of the patients who presented with mild to moderate pulmonary congestion had LVEFs >40%. In addition, previous studies demonstrated that patients with an acute MI had marked activation of all neurohormonal systems, many of which are growth factors (36). Plasma renin and angiotensin II levels were shown to increase twofold on the third day after MI in patients without heart failure (37). Furthermore, rat models of MI demonstrated increased ACE activity and ACE gene transcript levels in noninfarcted myocardium in small and large MIs (38). Taken together, increases in diastolic load as well as circulating and local neurohormonal factors could stimulate hypertrophy in noninfarcted myocardium within 1 week after MI.

Whether there was an actual increase in wall thickness in noninfarcted myocardium after MI that was reversed by ramipril and whether a decrease from a normal LV mass and wall thickness represent a beneficial effect cannot be answered by this study. In ramipril-treated patients, LVEF remained unchanged despite the decrease in mass/volume ratio. In contrast, echocardiographic studies in humans (32) and dogs (39) after MI have suggested that hypertrophy in the noninfarcted myocardium normalizes wall stress and has a beneficial effect on LV function. However, in the rat model of MI, there is increased collagen accumulation (40), decreased capillary density (41) and altered epicardial to endocardial flow ratios (42) in noninfarcted myocardium, suggesting that this process represents a "pathologic" hypertrophy that may result in long-term LV dysfunction. Therapy with ACE inhibitors in rats with experimentally induced MI decreases LV mass, preserves function and prolongs survival compared with untreated rats (43–46).

Conclusions. Reductions in acute ischemic events (e.g., MI, unstable angina and need for revascularization) in the Studies of Left Ventricular Dysfunction (SOLVD) and the SAVE trials were independent of LVEF in patients treated with ACE inhibitors (15). In addition, the mortality benefit of ACE inhibitor therapy in the unselected patient groups of GISSI-3 and ISIS-4 included patients with well-preserved LV function. Our results must be interpreted with caution owing to the small number of patients studied. Furthermore, it is questionable whether there is any benefit from the small decrease in LV mass in our patients because there was relatively little evidence of LV remodeling, as demonstrated by no change in LV volume and LVEF in both groups receiving standard therapy after MI. This finding may be related to a patent infarct-related artery in the majority of the patients in this study. There are many published reports suggesting that an open artery may well influence ventricular remodeling both by curtailing infarct expansion and by potentially influencing remodeling in viable myocardium (47,48). Alternatively, the beneficial effect of ACE inhibitor therapy may be in the vasculature by preventing endothelial dysfunction, progression of coronary atherosclerosis and MI (49). This potential mechanism is currently being tested in clinical trials to determine whether ACE inhibitors should be continued long term in patients with normal or near normal LVEFs after MI and in patients with documented coronary atherosclerosis with no prior history of MI.

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