Dilatation and distortion of left ventricular (LV) morphologic features after myocardial infarction (MI) is often referred to as “LV remodeling.” Thinning and elongation of the infarcted region commences immediately after coronary occlusion, whereas expansion of noninfarcted regions continues even after the initial infarction is histologically healed and is thought to be responsible for late ventricular dilatation. It has been postulated that increased LV wall stress may be responsible for the morphologic changes that occur in both infarcted and noninfarcted segments. Late hypertrophy of the noninfarcted segment may serve to reduce wall stress and compensate for reduced LV function. Although an increase in wall stress after MI has been presumed to play an important role in ventricular remodeling, this hypothesis has not yet been proved because of the difficulty in measuring regional wall stress in a geometrically complex structure such as the infarcted left ventricle.

LV wall stress has been traditionally assessed by analytic methods that are based on simplified geometric models. We have previously applied the finite element method to end-systolic LV models from patients enrolled in the Healing and Early Afterload Reducing Therapy (HEART) Trial. Individual LV models were constructed from orthogonal apical echocardiographic views obtained at day 14 after anteroseptal MI in 64 patients. Of these, 31 patients received low-dose (0.625 mg) ramipril and 33 patients received full-dose (10 mg) ramipril. LV wall stress was calculated by the finite element method and correlated with change in LV volume from day 14 to day 90 after MI.

Among all patients, increases in apical regional wall stress were associated with LV volume changes (P-trend = 0.15). The relationship between apical regional wall stress and change in LV volume was strongest in the low-dose ramipril group (r = 0.53, P = .002) and remained significant after adjustment for end-diastolic volume, infarct size, ejection fraction, and systolic blood pressure yet was attenuated in the full-dose ramipril group.

Apical regional wall stress is an independent predictor of subsequent LV remodeling after MI. The relationship between increased apical wall stress and LV dilatation appears to be attenuated by full-dose angiotensin-converting enzyme inhibition. (Am Heart J 2001;141:234-42.)
stress after acute MI. The finite element method is a commonly used engineering method for estimation of the stress distribution within a structure and is particularly useful for analysis of complex structures that are difficult to evaluate analytically. These investigations have shown that estimates of global and apical regional wall stress were increased in anterior MI compared with normal and inferoposterior MI.

In this study we estimated global and regional wall stress and analyzed the relationship between these estimates and subsequent changes in LV volume after anteroseptal MI. We used a population of patients from the Healing and Early Afterload Reducing Therapy (HEART) Trial to test the hypothesis that a finite element-based estimate of regional wall stress, particularly in the apex of the infarcted ventricle, is predictive of subsequent LV dilatation after anterior MI.

**Methods**

**Patients**

Sixty-four subjects were selected from patients who were enrolled in the HEART trial, a randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of immediate versus delayed administration of the angiotensin-converting enzyme (ACE) inhibitor ramipril in patients with acute anterior MI. The HEART study randomized 352 patients to receive one of three treatments: (1) low-dose ramipril (0.625 mg daily) for the entire duration of the study, (2) full-dose ramipril (10 mg daily) for the entire duration of the study, and (3) placebo for the first 14 days followed by full-dose ramipril (placebo/full group). Echocardiograms were obtained in the HEART study on days 1, 14, and 90 after MI.

This substudy was designed to test the hypothesis that regional wall stress 2 weeks after MI was predictive of subsequent LV remodeling. This assessment was made at the 2-week point because of the substantial degree of LV functional recovery noted in this population between days 1 and 14 after MI. For this analysis, only the 195 patients receiving a constant dose of medication for the entire study period (the low-dose group and the full-dose group) were eligible for inclusion. Because reperfusion therapy influences LV remodeling and most of the study population (87%) received a similar anatomic region. Because a rotational angle of 0 degrees was assumed for the four-chamber view, and 90 degrees was assumed for the two-chamber view. A midline between the apex and the base of the ventricle was determined by computer and adjusted as necessary. A three-dimensional model of the ventricle was constructed from the orthogonal views with the assumption that the midlines overlapped and represented the central axis of the ventricle.

Digitized curves from the reconstructed ventricle were imported into a computer simulation software package (IDEAS, SDRC, Milford, Ohio) and three-dimensional endocardial and epicardial surfaces were constructed. A finite element mesh composed of five regions was generated. The completed model consisted of a 2500-element, eight-node brick element mesh that was five elements thick throughout. The mesh was constructed in the same manner for each individual ventricular model, ensuring that element and node locations corresponded to similar anatomic regions. The five discrete regions from the mesh represented the anterior wall, lateral wall, inferior wall, septum, and apex. Each mesh was tested for element distortion before model solution and after processing. Loading conditions representing end-systolic LV pressure were applied to individual element faces. Systolic blood pressure obtained at the time of the echocardiographic study was used in lieu of LV end-systolic pressures. The model was restrained at the base and a single node was restrained in all degrees of freedom. A minimal strain linear elastic steady-state finite element solution was used. For simplicity, the myocardial material properties were assumed to be homogeneous, isotropic, and incompressible. A Young's modulus of $1 \times 10^5$ dynes/cm$^2$ was assumed to ensure minimal strain, and a Poisson’s ratio of 0.49 represented near

**Echocardiographic methods**

HEART study echocardiograms recorded on S-VHS tapes included two-dimensional short-axis views at three different levels and apical four- and two-chamber views. Endocardial and epicardial contours from the same frame were digitized from three separate high-quality cardiac cycles from the apical four- and two-chamber views. LV end-diastolic volume was calculated by the modified Simpson’s rule method as part of a separate analysis by an echocardiographer not involved in the finite element modeling. LV infarct size was determined by measuring the mean extent of the akinetic or dyskinetic region in the short axis and apical views and taking the sum of these values, expressed as a percentage of the total endocardial circumference in both short axis and apical views. In addition, wall motion was assessed according to the American Society of Echocardiography wall motion scoring method using a 16-segment model. Reproducibility of the volume measurement was assessed by randomly assigning the echocardiographic reader performing the analysis 50 of the original HEART study echocardiograms for repeated measurement. The upper 95% confidence interval of the difference between original and repeated measurements was 3.8 mL or 5.7%.
incompressibility. Before analyses, a sensitivity study was performed in which it was determined that altering the Young’s modulus by an order of magnitude in either direction would have a minimal effect (<3%) on the model solution. After model solution, the average Von Mises stress on each element and the mean Von Mises stress for the entire ventricle, representing a nondirectional parameter of stress, was calculated (Figure 1).

To assess regional LV wall stress, the mean stress of all elements within each of the five separate regions of the heart was calculated. These regions (anterior wall, lateral wall, inferior wall, septum, and apex) contained 500 elements each and corresponded to the same ventricular locations despite differences in heart size or shape.

Statistical analysis
Data are presented as mean ± SD or SE and are marked accordingly. Differences in means between multiple groups were assessed with analysis of variance (ANOVA) followed by post-hoc comparisons with use of a Bonferroni correction. Linear regression analysis was used to test for trend for categorized variables and multiple regression was used to assess

### Table I. Clinical and echocardiographic data at day 14

<table>
<thead>
<tr>
<th></th>
<th>Low-dose group (n = 31)</th>
<th>Full-dose group (n = 33)</th>
<th>Complete HEART full- and low-dose cohort (n = 195)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>57.0 ± 11.8</td>
<td>60.0 ± 12.6</td>
<td>60.2 ± 12.3</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>81</td>
<td>73</td>
<td>77</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>56.6 ± 8.9</td>
<td>58.3 ± 8.1</td>
<td>57.2 ± 8.5</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>113 ± 13.7</td>
<td>119.1 ± 14.2</td>
<td>117.5 ± 15.1</td>
</tr>
<tr>
<td>LV end-diastolic volume (mL/m²)</td>
<td>55.5 ± 15.9</td>
<td>52.1 ± 14.4</td>
<td>54.7 ± 15.4</td>
</tr>
<tr>
<td>Infarct size (%)</td>
<td>19.1 ± 12.6</td>
<td>19.7 ± 12.0</td>
<td>17.5 ± 12.4</td>
</tr>
<tr>
<td>LV volume change (range ΔmL/m²) day 14 to day 90</td>
<td>-21 ± 25</td>
<td>-23 ± 20</td>
<td>-32 ± 35.6</td>
</tr>
<tr>
<td>Maximal CK</td>
<td>2789 ± 382</td>
<td>2876 ± 284</td>
<td>2471 ± 2021</td>
</tr>
</tbody>
</table>

Expressed in mean ± SD. CK, Creatine kinase.
the ability of wall stress measurements to predict ventricular dilatation independently. A $P$ value of less than .05 was considered statistically significant.

**Results**

**Clinical characteristics**

Clinical and echocardiographic characteristics of the low-dose and full-dose groups included in this study, along with the entire low- and full-dose cohort from HEART, are shown in Table I. There were no significant differences in the day 14 clinical parameters between the two groups and the patients from HEART who were not included in this substudy (ANOVA). Systolic blood pressure was slightly higher in the full-dose group. Overall, LV end-diastolic volume did not change significantly between days 14 and 90 in either low- or high-dose groups, although LV end-diastolic volume change varied from $-21$ to $+25$ mL/m$^2$ in the low-dose group and from $-23$ to $+20$ mL/m$^2$ in the full-dose group. Infarct size on day 14 was 19.1% ± 12.6% in the low-dose group and 19.7% ± 12.0% in the full-dose group ($P = .84$). In this population there is a broad range of LV remodeling; approximately 50% of patients demonstrate some enlargement of the heart during the follow-up period and the distribution of remodeling is normally distributed. The overall mean wall motion score was 1.66 ± 0.38. Wall motion scores $>2.0$ were present only in apical and anteroseptal regions. The mean wall motion score in the apical region was 2.6 ± 0.8. There was no significant difference in wall motion score between low-dose and high dose-groups.

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**Table II. Regional wall stress at day 14**

<table>
<thead>
<tr>
<th>Region</th>
<th>Healthy controls (n = 13)</th>
<th>Low-dose group (n = 31)</th>
<th>Full-dose group (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apical wall (Kdynes/cm$^2$)</td>
<td>144.5 ± 9.1</td>
<td>189.8 ± 7.9*</td>
<td>212.4 ± 8.8*</td>
</tr>
<tr>
<td>Anterior wall (Kdynes/cm$^2$)</td>
<td>88.7 ± 7.0</td>
<td>171.9 ± 10.5*†</td>
<td>215.9 ± 12.8*†</td>
</tr>
<tr>
<td>Lateral wall (Kdynes/cm$^2$)</td>
<td>162.6 ± 9.3</td>
<td>187.6 ± 7.3</td>
<td>207.5 ± 8.5</td>
</tr>
<tr>
<td>Inferior wall (Kdynes/cm$^2$)</td>
<td>156.2 ± 9.3</td>
<td>185.9 ± 8.0</td>
<td>206.6 ± 8.1</td>
</tr>
<tr>
<td>Septal wall (Kdynes/cm$^2$)</td>
<td>133.5 ± 9.6</td>
<td>197.0 ± 8.7</td>
<td>214.8 ± 10.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>161.6 ± 12.8</td>
<td>206.9 ± 9.4</td>
</tr>
</tbody>
</table>

Expressed in mean ± SE.

* $P < .01$ compared with control.
† $P < .05$ compared with other treatment group (ANOVA with post-hoc comparisons).

The relationship between apical wall stress at day 14 after MI and subsequent change in LV size between day 14 and day 90. Patients receiving low-dose and full-dose ramipril are included in these data (n = 64) and are divided into quartiles (16 patients each) on the basis of the apical wall stress measurement.
LV global and regional stress

Global and regional estimates of wall stress from 64 MI patients and 13 healthy controls were assessed by finite element analysis. Average LV wall stress was significantly higher when MI patients were compared with healthy controls (201.5 ± 6.1 Kdynes/cm² vs 144.5 ± 9.1 Kdynes/cm², P < .001). Furthermore, all five predefined segments examined showed increases in wall stress (Table II) with the infarcted apical region showing the most marked differences, from 88.7 ± 7.0 Kdynes/cm² to 194.6 ± 8.7 Kdynes/cm² (P < .0001). The average global and regional LV wall stress values of healthy control subjects and the low-dose and full-dose groups are shown in Table II.

Correlation between LV wall stress and LV end-diastolic volume changes

Neither average stress nor apical wall stress at day 14 was significantly correlated with the LV end-diastolic or end-systolic volume at baseline (day 14) in either group. Among all infarcted patients (n = 64), apical wall stress was significantly related to change in LV volume between day 14 and day 90 because each quartile increase in apical wall stress was associated with increases in LV volume change (Figure 2, P-trend = .015). The relationship between apical wall stress and subsequent ventricular dilatation was strongest in the low-dose group (Figure 3, A; r = 0.53, P = .002). In contrast, this relationship appeared to be attenuated in the full-dose group (Figure 3, B; r = 0.19, P = .29). The slope of the regression between apical wall stress and volume change was significantly different in patients receiving full-dose ACE inhibition from that in patients receiving low-dose ACE inhibition (P < .05). The average wall stress was not related to LV volume change between day 14 and day 90 in either group.

To obtain a measure of wall stress that was independent of LV size, apical regional wall stress was indexed to LV end-diastolic volume in each patient. The correlation between indexed apical wall stress at day 14 and volume change between day 14 and day 90 was strengthened in all patients (r = 0.44, P < .0005) (Figure 4, A), yet was strongest in the low-dose group (r = 0.66, P < .0001) (Figure 4, B) and was not significant in the full-dose group.

To determine the independence of apical wall stress as a predictor of ventricular dilatation, a multiple regression model was used. Apical wall stress remained predictive of subsequent LV dilatation after adjustment for end-diastolic volume, size of the akinetic/dyskinetic segment at day 14, ejection fraction, systolic blood pressure, or drug group, with each 10 Kdynes/cm² increase in wall stress.
associated with a 0.47 mL/m² increase in ventricular volume (adjusted \( r^2 = 0.40, P = .002 \)). Ramipril dose itself is not a predictor of remodeling in this cohort.

**Discussion**

By use of the finite element method, we have previously reported an increase in apical stress after anterior MI. In the current study, we have applied this technique prospectively to demonstrate that an estimate of apical wall stress 2 weeks after anterior MI predicts subsequent LV dilatation during the following 11 weeks. Although it has been postulated that increased wall stress after MI plays an important role in induction of LV remodeling, these results demonstrate in patients a significant association between a measure of global and regional ventricular wall stress and LV remodeling.

**Predictors of LV remodeling**

LV remodeling is influenced by a plethora of clinical variables, including initial infarct size, coronary reperfusion, infarct-related artery patency, acute and chronic hemodynamics, neurohormonal status, and several classes of drugs. ACE inhibitors have been shown to attenuate ventricular remodeling and reduce the mortality rate in acute MI. Late and progressive ventricular dilation still occurs in a significant percentage of patients with MI, despite standard care with thrombolytics, mechanical revascularization, and ACE inhibitors. Global and regional myocardial mechanics and the changes in the myocardial interstitium have been implicated in the secondary changes in ventricular geometry, although the mechanisms by which these factors operate and interact are not fully understood.

According to LaPlace’s law, increases in the radius of curvature and thinning of an infarcted ventricular wall would be expected to result in increases in both diastolic and systolic wall stress. The LV apex has been proposed as the most vulnerable region of the ventricle, because it is the thinnest, and, after anterior MI, has the greatest increase in radius of curvature. Methods that approximate LV shape as a prolate ellipsoid or sphere cannot accurately evaluate the focal increases in stress that occur in the apex and anterior wall after anteroseptal MI, whereas finite element methods are not dependent on geometric assumptions.

**Relationship between wall stress and LV volume change**

In the current study, change in LV volume from day 14 to day 90 after MI rose in proportion to apical regional wall stress 2 weeks after MI. The ventricles with the highest apical wall stress at day 14 were most likely to dilate and ventricles with the lowest apical wall stress at day 14 were most likely to become smaller. Because neither global wall stress nor apical

![Figure 4](attachment:image.png)

The relationship between apical wall stress indexed to LV end-diastolic volume (LVEDV) at day 14 and subsequent change in LV size between day 14 and day 90 among all patients (A) and in patients receiving low-dose (0.625 mg) ramipril (B).
Wall stress and LV end-diastolic volume

The inability of the remaining viable myocardium to compensate for the increased wall stress associated with ventricular dilatation and thinning has been recognized as one of the triggers that promotes ventricular enlargement after MI. We hypothesized that, of two ventricles of the same size after MI, the one with the greatest apical deformation (higher apical regional wall stress) at end-systole will demonstrate the greatest dilatation (Figures 3 and 4). Indeed, when apical wall stress is indexed to diastolic heart size, the relationship between indexed apical stress and LV volume change is strengthened, suggesting the importance of apical deformation in the remodeling process.

The effect of ACE inhibitor on regional wall stress

Numerous studies have demonstrated that ACE inhibition after MI attenuates LV enlargement and improves patient prognosis. The precise mechanism of the beneficial effects of ACE inhibition has not yet been elucidated. All patients in this substudy received ramipril within 24 hours after MI. In addition, all patients in this substudy received reperfusion therapy. However, the relationship between apical stress and LV volume changes was strongest in the group that received low-dose ramipril and was statistically different from the relationship between apical stress and LV volume change in the group that received high-dose ramipril (P < .05), suggesting that higher-dose ACE inhibition attenuated the positive relationship between apical stress and LV remodeling.

Nevertheless, the average wall stress was not significantly different in the low- and full-dose ACE inhibition groups, and systolic blood pressure and apical wall stress were slightly higher in the full-dose group in this substudy. We conclude therefore that in this cohort high-dose ramipril did not reduce wall stress itself but did attenuate the relationship between wall stress and remodeling. These results are consistent with the findings of the Studies of Left Ventricular Dysfunction (SOLVD) investigators, who demonstrated regression of LV hypertrophy with ACE inhibition despite persistent elevation in end-systolic wall stress. One possible explanation for this observation is that ACE inhibition subtly alters the relationship between stress and strain by a direct effect on the material properties of the myocardium. In support of this hypothesis, recent studies have demonstrated that long-term ACE inhibition and AT1 receptor blockade attenuated the development of myocardial interstitial fibrosis in the noninfarcted region and increased the cardiac kinins that also inhibit the interstitial accumulation of collagen in animal models of MI. Alternatively, ACE inhibition might affect mechanotransduction in a way that attenuates the effect of high wall stress on subsequent cellular events that contribute to remodeling. Our observations are also consistent with reports of clinical benefit of ACE inhibition without changing hemodynamic status. Finally, the role played by local inhibition of the renin-angiotensin system in noninfarcted myocardium remains to be elucidated.

Limitations of this study

The design of the HEART study precluded a placebo control group from day 14 to day 90 after MI to compare with the effect of ACE inhibition. Because our outcome variable was change in LV volume between this time period, we chose not to include the group that received placebo for the first 14 days followed by high-dose ramipril because these patients would not have been receiving ACE inhibitor at the time of the 14-day echocardiogram but would have been subject to the effect of high-dose ACE inhibition during the important period between days 14 and 90. Despite the fact that the mean change in end-diastolic volume is relatively small (and negative) in this study population, there is marked heterogeneity of LV remodeling seen in our study population. Indeed, there is marked heterogeneity in 2-week ejection fractions in this population as well. The distribution of LV remodeling in this subset of patients is representative of the HEART study population as a whole, whereas the slightly less remodeling seen in this population may be due to the fact that all patients in this subset underwent reperfusion of some sort, received ACE inhibition (either low or high dose), and survived until 90 days after MI. Many patients were excluded from the current study because of the need for high-quality echocardiograms for this analysis, and we cannot exclude the possibility that selection bias could partially influence our results. However, in our study the major determinant for exclusion was insufficient echocardiographic quality to perform LV reconstruction, and this determination was made by a cardiologist not directly involved in stress measurements and modeling. That clinical baseline char-
acteristics—with the exception of systolic blood pressure, which was slightly but significantly higher in the full-dose group—and the degree of LV volume change were similar in both groups argue against a systematic selection bias. Although we were ultimately able to perform this analysis in approximately 50% of the eligible patients, this type of analysis will become more feasible as more accurate acquisition techniques, including three-dimensional echocardiography and magnetic resonance imaging, become more commonplace.

There are many codeterminants of LV remodeling, including reperfusion status and infarct-related artery patency. Although all the patients in this substudy and the majority in the HEART study as a whole underwent reperfusion therapy, we have no data regarding the adequacy of reperfusion in these patients. We thus cannot exclude the possibility that infarct-related artery patency influences the relationship between wall stress and remodeling.

In any finite element analysis, the quality of the analysis is dependent on the quality of the geometric data and accuracy of the loading conditions. Although we used high-quality echocardiograms for this study, our acquisition method did not allow for true three-dimensional reconstruction. Hence we refer to our modeling as pseudoreconstruction on the basis of two relatively orthogonal views but realize that these views are not truly orthogonal and that more accurate three-dimensional data would improve the quality of our LV volume and wall stress analyses. Ultimately, in our cohort only approximately 50% of eligible patients could undergo finite element modeling. Improved ability to model ventricular geometries, including use of more sophisticated imaging techniques such as three-dimensional echocardiography or magnetic resonance imaging, would certainly enhance this type of analysis. Nevertheless, we believe that this approach is an improvement over wall stress approximations based on arbitrary modeling of the left ventricle as a prolate ellipsoid using minimal measured data. Additionally, a more accurate method of assessing end-systolic pressure, such as carotid tonometry, would likewise improve the accuracy of our results.

Finally, our approach to assessment of LV wall stress is likely to be criticized because of our simplification of myocardial material properties and myocardial isotropy. We have made the assumptions outlined in our method because (1) the material properties of the systolic myocardium are unknown, (2) our sensitivity analyses (data not shown) have suggested that altering the myocardial stiffness in the infarct region by an order of magnitude in both directions has virtually no affect on the model solutions, and (3) the isotropic nature of myocardial tissue is likely to be less important in the contracted state than in the relaxed state. Finally, the results of this study suggest a biologic correlate to this measure. Although this measurement may not be the most accurate assessment of wall stress possible, we believe it is more appropriate and more clinically relevant in the post-MI population than commonly used analytic approaches. Nevertheless, approaches to assessing myocardial material properties during systole are essential to an improved understanding of the relationship between contractility and myocardial morphologic features. McPherson et al44 have used the finite element approach to assess diastolic elastic modulus by determining the global elastic modulus that best predicted diastolic deformations in ventricular geometry after coronary occlusion. It is conceivable that this approach might be used in a systolic model.

Conclusions
Apical regional LV wall stress 2 weeks after anteroseptal MI predicts subsequent changes in LV volume during the ensuing 11 weeks. This relationship remains significant after ventricular size is controlled, suggesting that the extent of apical deformation may play a critical role in LV remodeling. High-dose ACE inhibition appears to attenuate the positive relationship between left ventricular apical wall stress and remodeling while not affecting apical wall stress itself directly. That the relationship between regional wall stress and remodeling is attenuated by ACE inhibition suggests an important role for the local renin-angiotensin system in the sequence of events that leads from the alteration in mechanical forces to changes in ventricular morphologic features that occur after MI.

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