Altered Left Ventricular Geometry Changes the Border Zone Temporal Distribution of Stress in an Experimental Model of Left Ventricular Aneurysm: A Finite Element Model Study

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Background—Left ventricular aneurysm (LVA) is a significant complication of myocardial infarction that may lead to global left ventricular (LV) dysfunction. However, the exact mechanism underlying the abnormal function has not been elucidated. In this study we tested the hypothesis that changes in LV geometry cause both an increase in wall stress and a change in the temporal distribution of stress in the LVA border zone (BZ) during systole.

Methods—Transmural anteroapical infarcts were created in adult Dorsett sheep (n=8) and were allowed to mature into LVAs for 10 weeks. Animals were imaged subsequently using MRI with simultaneous recording of intraventricular pressures. Cardiac models were constructed from the MRI images at end-diastole, isovolumic systole, peak-systolic, and end-systole. Two short-axis slices, 1 basal and 1 apical were analyzed. The apical slice included the septal and anterior component of the aneurysm as well as the corresponding BZs and normal myocardium. Regional wall stresses were calculated using finite element analysis and compared with stresses in corresponding regions from normal control sheep (n=7).

Results—In the LVA group, stress was significantly increased in the BZ at the end-diastolic, isovolumic, peak-systolic, and end-systolic instants (P<0.001 for all). In addition the temporal distribution of stress was significantly altered with maximum stress occurring at peak instead of isovolumic systole.

Conclusions—Geometric changes in the LVA hearts increased wall stress and altered its temporal distribution in the BZ region. Correlation of this finding with the corresponding regional blood flow, oxygen consumption, and mechanical systolic performance may help elucidate the mechanism underlying the observed global LV dysfunction. (Circulation. 2002;106[suppl I]:I-168-I-175.)

Key Words: ischemia ■ coronary disease ■ magnetic resonance imaging ■ mechanics ■ computers

Left ventricular aneurysm (LVA) is a significant complication of myocardial infarction that may lead to left ventricular (LV) remodeling with global and regional LV dysfunction, ventricular arrhythmias, or thromboembolic complications. For acutely ischemic myocardium, the pathophysiology of the global LV dysfunction has been linked to regional dysfunction in the border zone (BZ) region of normally perfused but poorly functioning myocardium. Some investigators have estimated increased wall stress in the BZ and attributed the associated global LV dysfunction to increased wall stress. Failure to normalize regionally increased wall stresses results in progressive dilatation, recruitment of BZ myocardium into the scar, and deterioration in contractile function. Consequently, myocardial stress, pathologic cardiac remodeling, and LV decompensation are closely related. An accurate determination of regional ventricular wall stress has considerable potential to characterize and quantify the postinfarction remodeling process and help elucidate the mechanism underlying the global LV dysfunction associated with LVA. However, wall stress cannot be measured directly in the intact, in vivo beating heart. Moreover, the cyclic changes in cardiac geometry with time, add additional complexity, and significantly limit the ability to accurately estimate the regional distribution of stress during the different phases of systole.

Global and regional determination of myocardial wall stress has been significantly enhanced by the application of magnetic resonance imaging (MRI) and sophisticated finite element analysis (FEA). In this investigation both MRI and FEA have been employed to estimate wall stress distribution...
in an experimental model of LVA. The purpose of this study was to quantify the regional and time-varying pattern of stress in an ovine model of LVA and to compare it with corresponding regional stresses in normal animals to help elucidate the mechanisms responsible for associated global LV dysfunction. Specifically, we sought to address the following questions: (1) Is the BZ contractile dysfunction during isovolumic systole accompanied by increased wall stress? (2) Is the increased wall stress limited only to a specific phase of systole such as the isovolumic phase of early systole? (3) Is the temporal distribution of stress different in the LVA versus the normal heart? (4) How does myocardial stress in LVA vary with distance from the aneurysm and is stress normal in regions remote from the aneurysm? We hypothesized that the altered left ventricular geometry in LVA may be associated with changes in the magnitude as well as the temporal pattern of stress distribution, contributing at least partially to the observed late systolic thickening of the BZ myocardium.

To answer these questions and investigate our hypothesis, we used MRI to accurately describe the complex LVA cardiac geometry during systole, and FEA to quantitate the corresponding regional myocardial stress in hearts with LVA.

Methods

Animal Protocol

Creation of Left Ventricular Aneurysm

The ovine model of LVA described by Markovitz and colleagues was used. Nine adult Dorsett sheep were sedated with ketamine (15 mg/kg intramuscularly), masked, and then intubated and ventilated with a mixture of isoflurane and oxygen. Eight animals survived the initial operation (creation of LVA) and to compare it with the corresponding regional stresses in normal animals to help elucidate the mechanisms responsible for associated global LV dysfunction. Specifically, we sought to address the following questions: (1) Is the BZ contractile dysfunction during isovolumic systole accompanied by increased wall stress? (2) Is the increased wall stress limited only to a specific phase of systole such as the isovolumic phase of early systole? (3) Is the temporal distribution of stress different in the LVA versus the normal heart? (4) How does myocardial stress in LVA vary with distance from the aneurysm and is stress normal in regions remote from the aneurysm? We hypothesized that the altered left ventricular geometry in LVA may be associated with changes in the magnitude as well as the temporal pattern of stress distribution, contributing at least partially to the observed late systolic thickening of the BZ myocardium. To answer these questions and investigate our hypothesis, we used MRI to accurately describe the complex LVA cardiac geometry during systole, and FEA to quantitate the corresponding regional myocardial stress in hearts with LVA.

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MRI Acquisition

Imaging was performed in a 1.5-Tesla MR scanner. A series of scout images was obtained to locate the heart and the true long-axis and short-axis planes. Subsequently, a set of sequential short-axis imaging planes (8-mm thick) were obtained parallel to the true short-axis plane and at 8-mm intervals beginning at the level of the mitral valve and ending at a short-axis imaging plane that contained only apical myocardium and no LV or RV endocardium (Figure 1, left). An additional set of 4 long-axis imaging planes was obtained according to the following criteria: (1) orthogonal to the true short-axis imaging plane, (2) intersecting the centroid of the LV, and (3) oriented in a radial fashion with 45-degree separation between long-axis imaging planes (Figure 1, right).
Image acquisition was synchronized to the R wave of the electrocardiogram (ECG) signal. During the actual image data acquisition, the ventilator (Hallowell 2000, Hallowell EMC, Pittsfield, MA) was stopped for 20 to 30 seconds to minimize respiratory motion and the associated motion artifacts in our MR images. During this period, a series of images was acquired at 29-ms intervals until the approximate completion of the entire cardiac cycle. Data acquisition time was about 45 minutes. Imaging variables were a repetition time equal to the cardiac cycle (RR duration), an echo time of 29 ms, an excitation angle of 15 degrees, and an acquisition matrix of 256\times256. The field of view was set to 350\times350 \text{mm}^2 and 400\times400 \text{mm}^2 for the short-axis and long-axis images, respectively.

Hemodynamic Data Acquisition and Analysis

During the scanning interval, the LV pressure, right ventricular pressure, thoracic aortic pressure, and the trigger signal were recorded continuously (Figure 2) using customized data acquisition and manipulation software (LabView 5, National Instruments, Inc, Austin, TX). The MR images resulting from the experiment represented an average over many heartbeats. Therefore, a signal-averaging algorithm was performed on the hemodynamic data set to yield a 20-beat average for each hemodynamic variable. In particular, the average LV, RV and aortic root pressures were calculated at the end-diastolic, isovolumic, peak-systolic and end-systolic instants.

Mathematical Model Construction and Finite Element Model Solutions

A total of 120 accurate nonaxisymmetric mathematical models of both normal and LVA hearts were constructed based on the MRI images at end-diastole, isovolumic systole, peak-systolic and end-systole, and were loaded with the corresponding intracavitary pressures (Figure 2) derived from the intraventricular Millar catheters as previously described. Two short axis slices were selected for analysis, 1 at the base and another at the apex of the heart. The basal slice was selected in the following manner. In a long axis MRI image, the heart was subdivided in 3 equal segments from base to apex. The short axis imaging plane that was closest to the intersection of the basal and the midventricular segments was selected for analysis in both groups. The apical slice in the LVA animals (Figure 3A), included the septal and anterior component of the aneurysm as well as the corresponding septal and anterior BZs and postero-apical myocardium (Figure 3B, lower panel). In the normal animals the apical imaging plane that was located closest to the average apical plane from the LVA animals was used in the analysis. Stresses in aneurysmal, BZ and postero-apical LV myocardium (Figure 3C, lower panel) were calculated using p-version FEA and compared with stresses in corresponding regions at the basal level (Figure 3C, higher panel). Stresses in LVA hearts were also compared with stresses in corresponding regions from normal control sheep in both slices. Details of model construction have been described elsewhere and are only summarized here. Contour points that defined the endocardial and epicardial borders of the heart were selected manually. A continuous mathematical description of the endocardial and epicardial borders of the heart were obtained by use of the contour points as the control points for third order nonuniform B-spline curves. Forward FE solutions were obtained treating the myocardium as a nearly incompressible, linearly elastic, isotropic material with the following material parameters: Modulus of elasticity $E=5\times10^5 \text{dynes/cm}^2$, Poisson's ratio $\nu=0.45$. A typical value was selected for $E$ because it has no effect on the stress distribution. When a linear elastic analysis is performed and traction loads are...
specified, then the stress distribution is independent of the modulus of elasticity, only the deformations are affected by it. Nodal constraints were used to prevent rigid body rotation and translation. After model solution, the average of the maximal principal stress for each element (wall segment) as well as for the entire left ventricle were calculated. Details of the p-version FE formulation may be found in Szabo and Babuska.16,17

Definition of Border Zone and Remote Regions

We identified the BZ from the MR images as the region where the LV wall thickness at end-diastole varied between normal (8 to 12 mm) to very thin (1 to 3 mm). In other words, the BZ was identified as the transition zone between normally thick myocardium and the aneurysm. Thus, the BZ was identified anatomically rather than functionally. More specifically, the LV apical myocardium on the short axis images was subdivided into 3 regions-aneurysm, border zone, and postero-apical regions. The anterior BZ (ABZ) was defined as the region of anterior wall myocardium adjacent to the aneurysm and the septal BZ (SBZ) was defined similarly as the region adjacent to the septal border of the aneurysm (Figure 3C, lower panel). Postero-basal, “aneurysmal,” “ABZ,” and “SBZ” were anatomically specified at the basal level based on the average location and size of the corresponding apical regions. In a similar fashion we identified the corresponding regions in the normal group for both slices.

Statistical Analysis

Continuous data were reported as mean±SD. Normal distribution of the data in the different groups was tested using Lilliefors and Shapiro-Wilks’ tests as well as normal probability and detrended normal plots. Homogeneity-of-variance and sphericity assumptions were tested by Levene’s and Mauchley’s tests respectively. Comparisons between normal and LVA groups were performed by the two-tailed unpaired Student’s t test. Within-subjects statistical comparison among the different wall segments was performed with ANOVA. Differences in the temporal distribution of stress were also tested with ANOVA. A value of P<0.05 was considered significant. Multiple comparisons were corrected with Bonferroni, Scheffe, and Waller-Duncan post hoc procedures. All statistical analyses were performed with Statistica and SPSS statistical packages.

Results

Apical Level

Stress Among the Different Wall Regions Within the Same Animal Group

At the apical level and within the normal animal group (Figure 4A), stress distribution at end-diastole, isovolumic-systole, peak-systole, and end-systole was not significantly different between the different wall regions (P=NS for all). In the LVA animals, the average BZ stress was significantly increased compared with the postero-apical region at peak (498912±163715 versus 277861±94469 dynes/cm², P<0.01) and end-systole (349999±132043 versus 201836±91200 dynes/cm², P<0.05). In addition, there was a significant difference when both BZs were individually compared with the postero-apical region at peak and end-systole (Figure 4B). There was no significant difference in stress between the ABZ and SBZ for any of the systolic instants. The difference in stress between the postero-apical and the aneurysmal region was statistically significant throughout systole (P<0.01 for all) whereas, the difference between the BZs and the aneurysmal
The region was significant at the isovolumic, peak and end-systole (P<0.05) but not at end-diastole (P=0.08).

**Stress in the Corresponding Walls of the Two Animal Groups**

There was no statistically significant difference in stress between the postero-apical region in the LVA group and the corresponding region in the normal animal group at end-diastole or isovolumic-systole (Figure 5A). The difference in stress between the aneurysmal region and the postero-apical region was significant throughout systole (P<0.01, aneurysmal versus postero-apical), whereas, the difference between the aneurysmal region and the individual BZs was significant at the isovolumic, peak and end-systole (†P<0.05, aneurysmal versus ABZ, and §P<0.05, aneurysmal versus SBZ). Note: stress scale is different in (B) to display the significantly higher values in the aneurysmal region.

At the apical level, the time-varying pattern of stress in the normal sheep demonstrated maximal values at the isovolumic-instant (Figure 7A), whereas in the LVA sheep the maximum stress occurred at peak-systole, for all the wall segments (Figure 7B). At the base of the heart, the temporal distribution of stress was similar in both groups, globally and for each of the wall segments, with maximum stress observed, as expected, at the end of the isovolumic contraction.

**Discussion**

Formation of LVAs is common after myocardial infarction and can result in global LV dysfunction and conges-
tive heart failure (CHF) that is not consistently improved by surgical intervention. The pathophysiology of the observed global LV dysfunction has been linked to loss of contractile function attributed to postinfarction LV remodeling. However, the mechanism of this remodeling process remains poorly understood. Lessick and colleagues in 1991, used cine-computed tomography in patients with LVA and demonstrated elevated wall stress and reduced wall thickening in the BZ region. They investigated the possibility that the altered LV geometry could affect local function by increasing the regional myocardial afterload. Their stress calculations were based on the Laplace equation for a sphere and yielded only rough estimates of the regional stresses. However, their study as well as other studies have emphasized the significant role of myocardial stress in the pathologic cardiac remodeling and the associated progression to CHF.

In the current investigation we extensively analyzed for the first time, the regional and temporal variation of LV wall stress in LVA hearts, using MRI and advanced FE modeling techniques. Our results demonstrated a significant increase in stress, in the true LVA BZ region when it was compared with stress in the corresponding “BZ” region in the normal group. This increase was present at end-diastole and persisted throughout systole. In 1988, Nicolosi and Spotnitz using two-dimensional echocardiography to examine regional function in the BZ of LVAs, demonstrated a decrease in BZ thickening during isovolumic-systole. In a similar study, Moulton and colleagues, used MRI tissue-tagging and regional deformation analysis to calculate myocardial wall strains in BZ regions and regions remote from the aneurysm. They demonstrated abnormal circumferential lengthening strains (stretching) in the BZ regions during isovolumic systole, and an overall reduction in fiber shortening during the ejection phase. These results combined with our data support the theory that increased BZ stresses may contribute to the observed abnormal isovolumic stretching of BZ fibers, and reduce the contribution of these fibers to the overall ventricular output. However, we have recently shown that the BZ contractile function is impaired beyond what would be expected due only to changes in geometry and stress distribution. Thus, it appears that regional variation in myocardial wall stress may be responsible for initiation of physiologic and cellular changes that fundamentally alter the BZ myocardium, and also result in the observed dilatation, and overall remodeling of the LV. Indeed, Aikawa et al. studied the relationship between regional wall stress and LV remodeling by application of FEA to end-systolic LV models constructed.
from apical echocardiographic views in patients with anteroseptal MI and normal volunteers. They reported an increase in apical wall stress in patients but no significant difference in stress at the base of the heart. They associated increases in regional stress with LV volume changes and concluded that apical stress was an independent predictor of subsequent LV remodeling. Gaudron et al.,24 studied the relation between LV geometry and global and regional cardiac dysfunction in patients after MI. They identified infarct size and infarct location as significant early predictors of progressive ventricular enlargement and chronic dysfunction. Pfeffer and Braunwald5 have also identified infarct size and ventricular wall stresses as independent factors that influence pathologic ventricular remodeling and clinical outcome, particularly inpatients with large transmural infarcts. The results of these and other studies3,4,25 are consistent with our results and further support the hypothesis that multifactorial early interventions might be necessary to decrease apical wall stress and arrest the process of myocardial remodeling before LV dilatation has occurred.26

Temporal Distribution of Stress
In the current study, in addition to the calculation of the magnitude of stress, we also quantified the time-varying pattern of stress distribution in the different wall regions. In the normal animal group maximal stress was observed as expected at the end of the isovolumic-systole, for both the apical and the basal level. In the LVA group at the apical level, however, stress demonstrated maximum values at peak-systole, most notably in the aneurysmal and BZ areas, and remained at higher than normal levels at the end of systole. The overall decreased contractile function during systolic ejection11 may at least partially explain this phenomenon since the maximum LV pressure recorded at peak-systole, cannot be compensated by an appropriate increase in wall thickness. Postoperative normalization of the temporal distribution of the apical wall stress may be an indirect evidence of improved contractile function associated with favorable prognosis in these patients. However postoperative studies are required to validate this hypothesis. In a recent study Kramer et al.,27 employed MR tagging to analyze regional LV mechanics in human subjects before and after anteroapical aneurysm repair. They demonstrated that LV aneurysm repair was associated with reverse remodeling and an improvement in the extent and orientation of intramyocardial function, especially at the middle and basal LV and inferior wall. Because the authors did not calculate the corresponding wall stresses during systole it is not known if the observed postoperative mechanical improvement is associated with normalization of the temporal distribution of stress.

Finite Element Method
Evaluation of the time-varying structure and function of the heart is technically demanding. The introduction of FE techniques in the 1950s28 has allowed for more accurate estimation of regional myocardial stress. The FE method divides a large, complex object into smaller subdomains. These subdomains, or finite elements, are defined by faces, edges, and vertices, and in aggregate make up the finite element model and approximate the original object. Regional variations in geometry, loading, and material properties can be taken into account. A set of equations describing the relationship between the forces and displacements within each element is derived by applying principles of mechanics. Solving this set of equations subject to the loading and boundary conditions acting on the structure allows calculation of the stresses throughout the structure. This powerful method is probably the best approach for obtaining a realistic quantitative assessment of regional variations in ventricular wall stress.29

Limitations of the Study
In the current investigation we have modeled the myocardium as a homogeneous, isotropic, and linearly elastic material although the myocardium is actually anisotropic and regionally inhomogeneous. With the use of isotropic material properties, the changes in left ventricular stress values are entirely dependent on the regional changes in geometry (remodeling) and the corresponding loads. Unfortunately, our lack of knowledge concerning the specific myocardial fibrous architecture and material properties in the ovine model of LV aneurysm have prevented the inclusion of these important determinants of regional myocardial stress in our finite element model solutions.

An additional limitation was the 2 dimensional nature of the study. Although geometrically accurate, finite element models of the hearts were constructed based on MRI images derived only from short axis imaging planes. Thus, the longitudinal dimensions of BZ and aneurysmal regions were not included in the analysis. In a recent study20 we constructed the complete three-dimensional mathematical model of the heart for I of the LVA animals and calculated stress in the BZ, in an effort to elucidate the mechanism underlying the previously observed BZ contractile dysfunction.10,11 However, application of full three-dimensional regional myocardial stress quantification requires considerable computational time, is currently cumbersome and time consuming, and limits its practical applicability. Clearly, our approach of estimating ventricular wall stress represents a compromise between geometrically simple analytic models and highly complex computational models that incorporate complex myocardial material properties. Nonetheless, this analysis is rapidly applied with currently available technologies and appears to accurately describe the left ventricular stress state.

Clinical Implications
The employment of clinically available techniques for the accurate acquisition of cardiac geometry, the creation of mathematically suitable ventricular representations, and the use of the p-version FEA to obtain reliable analysis results, have important implications for the clinical estimation of regional myocardial stress. Changes in ventricular wall stress are believed to be stimuli for growth and pathologic LV remodeling7,30 that may progress in congestive heart failure despite an adequate amount of normally functioning myocardium immediately after infarction. Thus, it is likely that
surgical aneurysm repair is successful when it results in a reduction in wall stress, and a subsequent improvement in myocardial contractility. Application of the described techniques could allow the creation of patient-specific 3D cardiac models from noninvasively acquired MRI geometric data. A given mathematical representation could then be directly employed for regional myocardial stress estimation. Importantly, the same mathematical model could be modified, with the introduction of morphologic alterations resulting from surgical intervention (proposed or performed), and the subsequent alterations in stress distribution over the modified geometry assessed. In this way insight could be gained into the mechanical consequences of cardiac surgical interventions, and allow the design of new surgical procedures that improve or preserve ventricular function.

In conclusion, in this investigation we used MRI-geometry data sets combined with advanced finite element analysis to extensively characterize not only the regional myocardial distribution of stress in LVA hearts but also for the first time, the time-varying pattern of stress during systole. Our analysis indicates that geometric changes in LVA hearts altered the normal temporal variation of stress and contributed to an increase in the aneurysmal, anterior and septal BZ stress, most notably during peak and end-systole. Correlation of this finding with the corresponding regional blood flow, oxygen consumption, and mechanical systolic performance may help elucidate the mechanism underlying the observed global LV dysfunction.

References
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