Transmural Myocardial Deformation in the Ischemic Canine Left Ventricle

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The myocardium is a complex three-dimensional structure consisting of myocytes interconnected by a dense collagen weave that courses in different directions. Regional ischemia can be expected to produce complex changes in ventricular deformation. In the present study, we examined the effects of ischemia on two- and three-dimensional finite strains during acute transmural myocardial ischemia in 13 open-chest anesthetized dogs. In contrast to systolic deformation observed during the control period in which circumferential shortening exceeded longitudinal shortening, our results indicate that after 5 minutes of acute ischemia, end-systolic in-plane lengthening across the left ventricular wall occurs in approximately equal amounts in the circumferential and longitudinal directions. Along with these changes in extensional strains, there were significant negative transverse shearing deformations during ischemia. Myocardial ischemia also resulted in a loss of the normal end-systolic transmural gradients of shortening and thickening. Three-dimensional end-diastolic strains indicate that the left ventricular wall undergoes a significant passive reconfiguration that varies transmurally with lengthening in the epicardial tangent plane and wall thinning increasing from the epicardium toward the endocardium. The large systolic changes in shearing deformations with ischemia could potentially influence collateral blood flow and certainly indicate that uniaxial measurements of deformation in the ischemic myocardium, which do not account for shearing deformation, are incomplete and must be interpreted with caution. Moreover, normal transmural systolic gradients in deformation, which would be anticipated on geometric grounds, are lost during ischemia, implying that the material properties of ischemic tissue or the loading conditions imposed on the ischemic region by partially impaired adjacent myocardium vary transmurally. (Circulation Research 1991;68:368–381)

During acute transmural myocardial ischemia, systolic shortening deteriorates within several beats and is replaced by holosystolic lengthening and wall thinning.1–5 Although alterations in regional ventricular deformations during acute ischemia have been partially characterized, most studies have used measurements obtained along fixed directions, usually in line with or at a known angle from the local muscle fibers.2–8 However, the myocardium is a complex structure with muscle fibers coursing in different directions and a dense connective tissue network between the fibers. Recent studies,9–13 in which multidimensional measurements of finite strain components and their corresponding principal deformations were made, indicate that the principal directions associated with the greatest deformations are not necessarily aligned with local fibers and that there are significant positive transverse shears. In the ischemic myocardium, both transmural and regional gradients in blood flow may produce complex three-dimensional variations in myocardial function. Moreover, histological studies14 indicate that the extracellular matrix is disrupted early in ischemia, suggesting that major changes in local deformation may occur away from the local fiber direction. Thus, it seems unlikely that measurements along fixed directions would quantitatively reflect the changes in deformation seen with ischemia. Therefore, the major objective of this study was to determine regional three-dimensional finite strains in the acutely ischemic left ventricle.

To characterize transmural deformation in the ischemic left ventricular wall, a set of experiments was performed to measure regional three-dimensional finite strains.12 Data were acquired during a control period and at 5 and 10 minutes after total occlusion of the left anterior descending coronary
FIGURE 1. Schematic diagram of the preparation used in this study. The diagram shows the ventricular site in the anterior free wall where the bead columns were inserted, the coordinate system to which the strains are referred, and the site of coronary occlusion (snare). The other two diagrams show an expanded view of the transmural markers and a representative tetrahedron. LA, left atrial.

artery (LAD). The degree and uniformity of the reduction in blood flow was documented by myocardial blood flow measurements using radioactive microspheres. To measure the temporal sequence of early (less than 5 minutes) changes after LAD occlusion, a second set of experiments was performed in which strain was monitored continuously during ischemia. For this purpose, we used the two-dimensional ultrasonic crystal triangle technique described recently. This technique has substantially better spatial and temporal resolution than the three-dimensional technique.

Results from this study demonstrate that along planes parallel to the epicardial surface, the acutely ischemic myocardium lengths during systole in approximately equal amounts along the minor and major axes of the heart. In addition, there is a loss of the normal transmural gradient of circumferential shortening and radial thickening, with transverse shear strains becoming negative during ischemia. In diastole, there is a substantial reconfiguration of the ischemic region, with lengthening predominantly in the circumferential direction, and greater lengthening and wall thinning occurring in the inner third of the wall.

Materials and Methods

Thirteen mongrel dogs were anesthetized with intravenous pentobarbital (30 mg/kg) and ventilated with a respirator (Harvard Apparatus, South Natick, Mass.) on room air. Additional anesthetic was administered as necessary (approximately 20 mg every 2 hours). The heart was exposed through a median sternotomy and bilateral fifth intercostal space thoracotomy and placed in a pericardial cradle. A P-6 micromanometer (Konigsberg Instruments Inc., Pasadena, Calif.) was inserted into the left ventricle through an apical stab wound and was calibrated with a fluid-filled catheter introduced from the femoral artery into the left ventricle. Once matching pressures were obtained, the fluid-filled catheter was withdrawn into the aortic root to monitor aortic pressure. A short, fluid-filled catheter was introduced into the left atrial appendage. Both fluid-filled catheters were attached to Statham P23-Dt pressure transducers (Gould Instruments, Cleveland, Ohio) with a zero reference at the level of the mid–right atrium. Limb leads for an electrocardiogram were placed. A section of the proximal LAD was dissected free, and a snare was placed around it, as shown in Figure 1.

In the first group of experiments (group 1, n=7), three-dimensional finite strains were measured by the radiopaque bead column technique as described previously. For this purpose, a 1-cm-thick Plexiglas template was sutured to the anterior free wall of the left ventricle at about 50–70% of the distance from base to apex and well within the perfusion area of the LAD. Three columns of five lead beads (1.0–1.2 mm o.d.) were implanted into the left ven-
tricular wall using holes in the template to aid in positioning a needle trocar containing the beads. The Plexiglas template then was removed, and five 2-mm reference markers were sutured to the epicardial surface (apex, bifurcation of the main left coronary artery, and at the entry hole of each of the implanted columns) to define a local cardiac coordinate system. Calibration distances in both film views were obtained by placing a 1-cm calibration bar on the epicardium. The animal was positioned on the operating table to avoid an overlap of beads on the biplane radiographic images (anterior–posterior and lateral views). During each run, high-speed biplane cineradiography (120 frames/sec) was performed to record the bead positions during the cardiac cycle.

In the second group of dogs (group 2, n=6), regional left ventricular two-dimensional finite strains were measured with three piezoelectric crystals (2 mm in diameter) placed in a triangular array. Each crystal was inserted through an epicardial stab wound into the midwall of the myocardium approximately 5 mm below the epicardial surface and within the perfusion area of the LAD. The three crystals formed a triangle in the midwall, with each segment of the triangle approximately 1.5 cm in length. One leg of each crystal triangle was aligned along the long axis of the left ventricle. The ultrasonic crystals were excited with 5 MHz sound and received signals amplified with a system from Triton Technology, Inc., San Diego. Because three separate dimensions are recorded with only three crystals (not the usual six), each piezoelectric crystal must function alternately as a transmitter or receiver in more than one dimension. To accomplish this, wires from each crystal were led in parallel to an excitation or receiver amplifier on at least one other channel, with the sequential activation of channels assuring that each measurement was independent. The transit time of 5 MHz ultrasound in tissue was assumed to be 1.55 μsec/mm. To determine the precise orientation of the crystal triangle, five reference beads (2 mm in diameter) were sutured to the epicardial surface in a manner similar to that described above. High-speed biplane cineradiograms were obtained for the purpose of analyzing the crystal positions with respect to the long axis and their depth in the myocardium at end diastole. The electrocardiogram, aortic pressure, high and low gain left ventricular pressure, left atrial pressure, the three segment lengths, and the cine camera shutter correlation pulses were recorded on an eight-channel polygraph (Brush-Clevite, model 2000 Gould, Cerritos, Calif.) at a paper speed of 200 mm/sec and on FM magnetic tape for subsequent analog-to-digital conversion.

Myocardial Blood Flow Measurements

Because the objective of these studies was to determine finite deformation in transmurally ischemic myocardium, the degree of reduction in blood flow and the relation of the marker beads to the ischemic area was estimated in all group 1 animals by using the radioac-
tive microsphere reference withdrawal method. To ensure that the microspheres were adequately dispersed, the vial was placed for 5 minutes in a vortex agitator before injection. One to three million microspheres (to provide a minimum of 400 per tissue sample) labeled with either 46Sc, 99Nb, or 131I were injected through the catheter placed in the left atrium at approximately 12–15 minutes after LAD occlusion. A reference sample of blood was withdrawn at a constant known rate starting seconds before the microsphere injection and continuing for 2.5 minutes.

After the dog was killed with an overdose of pentobarbital, the heart was excised and placed in formalin to facilitate tissue sectioning. After 5 days of formalin fixation, the left ventricle was excised from the rest of the fixed heart, and 1-cm slices were cut in planes perpendicular to the long axis, forming a ring. Each ring was cut into several full-thickness wedges around the circumference. The three surface beads were contained in one wedge. Then, each wedge was subdivided into the three representative layers of the heart (endocardium, midwall, and epicardium). The sections with bead columns were cut under fluoroscopy to individually identify the layer of each section in which a bead was localized. Thus, we were able to determine the blood flow at the site of the strain measurement. Blood flows then were computed by using the equation Qm=(CmXQr)/Cr, in which Qm is myocardial blood flow (milliliters per minute), Cm equals counts in the tissue sample (counts per minute), Qr is, the withdrawal rate of the reference arterial sample (milliliters per minute), and Cr equals counts in the reference arterial sample. Flow per gram of tissue was calculated by dividing blood flow by sample weight, with control blood flow measurements obtained from tissue samples from nonischemic areas.

In all experiments, measurements were obtained for approximately five to 10 cardiac cycles, with the respirator suspended at end-expiration. In the group 1 experiments, data were collected during a control period and at 5 and 10 minutes after total LAD occlusion. These data will be referred to as three-dimensional transmural strains. Lateral and anterior–posterior films were projected separately onto a digitizing pad (HIPAD, Houston Instruments, Austin, Tex.) to obtain the two-dimensional coordinates of the centroids of the bead shadows for one full cardiac cycle from end diastole to end diastole. The three-dimensional coordinates were reconstructed from corresponding film frames in the lateral and anterior–posterior views. A local cardiac coordinate system (circumferential, longitudinal, and radial coordinate directions) was constructed. The coordinate data were used to compute the end-diastolic and end-systolic three-dimensional deformation across the left ventricular wall.

In the two-dimensional group 2 experiments, data were collected during control and 30 seconds, 1 minute, and 5 minutes after total LAD occlusion and will be referred to as two-dimensional midwall
strains. Analog data were played back from FM tape for analog-to-digital conversion at 5-msec intervals, and 10 cardiac cycles were averaged. Strains were calculated from the average of dimension signals. From the biplane films, the three-dimensional positions of the three crystals and the five reference beads were reconstructed to determine the depth and orientation of the crystals. The depth of all crystals from the epicardium averaged 5.3 mm, and the greatest difference in depth between any two crystals was 1.2 mm. The angle between the local longitudinal coordinate direction and the reference leg of the crystal triangle also was computed. If this angle deviated by more than 10° from longitudinal, the computed two-dimensional strains were corrected by the appropriate tensor transformation. The timing of end diastole was determined from the peak of the R wave on the electrocardiogram. The timing of aortic valve closure (end systole) was determined by transposing the central aortic pressure at the dicrotic notch onto the high-fidelity left ventricular pressure tracing.

Strain Analysis

In the three-dimensional transmural (group 1) experiments, the coordinate data of four noncoplanar markers forming small tetrahedrons of muscle were used to compute the three-dimensional finite strains at various transmural locations. This method is described briefly here and in detail in previous publications concerning the normal heart. From the 15–18 beads available in each animal, several tetrahedra that met the following criteria were available for analysis: from the end-diastolic frame before ischemia (control), three beads at a similar depth (varying by no more than 1.5 mm), and the height of the fourth bead from the triangular base formed by the other three between 2 and 4 mm; also, the product of the stretch ratios at end systole were between 0.9 and 1.1. Seventy-one tetrahedrons met these criteria in the control state. All data from these tetrahedrons during ischemia are included. Fifty-six tetrahedrons from end-diastolic data met the geometric criteria (base and height of the tetrahedrons) and were used to examine end-diastolic strains. Strains from tetrahedrons whose centroids were located 0–30% of the distance from the epicardium were averaged to represent epicardial data. Data from tetrahedrons 31–60% deep and 61–90% deep were averaged for midwall and endocardial data, respectively. Percent depth was based on the total wall thickness measured postmortem and the end-diastolic distance of the centroid of the tetrahedron from the epicardial tangent plane.

Finite strains (normal and shear strains) were calculated from an equation that defines a symmetric strain tensor (Eij) in terms of small line segments and their orientations. This equation was applied to the coordinate data from a reference configuration (e.g., end diastole) and a subsequent configuration (e.g., end systole) that had deformed relative to the reference frame. Finite strains occurring in the epicardial tangent plane (or parallel to it) are circumferential strain (E11), longitudinal strain (E22), and in-plane shear (in the circumferential–longitudinal plane or E12). Strains that occur in planes perpendicular to the epicardial tangent plane are the radial strain (E33, wall thickening) and the transverse shear strains E13 (circumferential–radial) and E23 (longitudinal–radial). Normal strains (E11, E22, and E33) are extensional, with negative values representing segment shortening and positive values representing segment lengthening. In continuum mechanics, the shear strains (E12, E13, and E23) also can be expressed as the change in angle between two line segments. For convenience, shear strain data also will be presented in this manner and will be referred to two line segments initially oriented at right angles (90°). A standard convention will be used to define the sign of each shear strain, that is, acute angles (<90°) during deformation represent positive shears, whereas obtuse angles (>90°) represent negative shears. For example, \( \cos \theta_{12} = 2E_{13}/[(1+2E_{11})(1+2E_{22})]^{1/2} \). For the two-dimensional midwall experiments (group 2), finite strains were computed by applying the three segment lengths to the described equation in its two-dimensional form.

Three principal strains can be computed from the normal strains. The three principal strains have three associated principal directions or axes. These are the eigenvectors that, along with their corresponding eigenvalues, complete the eigenspairs and provide an equivalent representation of the six cardiac strains at a given location and time. The principal axes indicate the directions relative to an end-diastolic cardiac coordinate system along which the principal stretches occur. These data are conveniently given as a three-by-three modal matrix \( Z_{ij} \), \( i,j = 1,3 \) in which each column is a unit vector with three components, that is, the direction cosines of a chosen eigenvector in cardiac coordinates (circumferential, longitudinal, and radial in order down each column). An additional property of the eigenvectors is that they are mutually orthogonal. If one arbitrarily ranks the three principal strains (eigenvalues) in increasing order, the first eigenvector corresponds to the direction associated with the most negative strain (greatest shortening), and the third eigenvector is associated with the most positive strain (greatest lengthening). In the simplest case, the modal matrix would be the identity matrix \( Z_{ij} = I_{ij} \). Here, the greatest shortening would be purely circumferential, whereas the greatest lengthening would be purely radial or transmural (wall thickening). In previous investigations, we have computed a principal angle associated with the greatest systolic shortening as follows: principal angle = \( \arctan(Z_{23}/Z_{13}) \). This calculation gives the direction of the most negative strain projected on the epicardial tangent plane in a manner similar to fiber angles. In ischemia, the principal directions change markedly, and comparing principal strains ranked in this fashion with control is
difficult. For example, during ischemia the most negative principal strain is oriented primarily in the wall thickness direction rather than the in-plane direction as in the normal heart. Thus, in the present study we have elected to present data on the whole modal matrix calculated from averaged normal and shear strains at three locations.

For end-diastolic strain calculations in group 1, we used the coordinate data at end diastole during the control period as a reference configuration to compute the deformation at the end-diastolic frame after 5 and 10 minutes of acute ischemia.

Statistical Analysis

Results

End-systolic Strains

Three-dimensional transmural strains (group 1). A total of 71 tetrahedrons collected from all seven dogs fulfilled the selection criteria from the control end-diastolic frame in each study. There were 23 tetrahedrons located in the epicardium, 26 in the midwall, and 22 in the endocardium. The number of selected tetrahedrons in each layer in each animal varied between two and five. Heart rate for control and 5 and 10 minutes of ischemia were 126±17, 123±14, and 124±15 beats/min, respectively; peak left ventricular systolic pressures were 121±22, 121±28, and 123±23 mm Hg, respectively. No significant changes were observed in heart rate or peak systolic pressure during ischemia compared with control conditions. During ischemia, there was a significant increase in left ventricular end-diastolic pressure (LVEDP) from 2.3±1.5 mm Hg during control to 4.1±1.1 and 4.6±1.0 mm Hg after 5 and 10 minutes of occlusion, respectively.

Blood flow in the area of the beads was compared with the averaged flows in the circumflex perfused bed (control area). Blood flow in the area of the beads was reduced to 21±23% (0.19±0.20 ml/min/g) of the control area in the epicardium, 10±6% (0.11±0.06 ml/min/g) in the midwall, and 6±4% (0.06±0.04 ml/min/g) in the endocardium.

Figure 2 shows the three-dimensional normal and shear strain data for a full cardiac cycle in one experiment. Control data are shown in open circles and data after 10 minutes of ischemia are shown in closed circles. In this example, finite strains were computed from the coordinate data of a tetrahedron whose centroid was located at a 50% depth into the left ventricular wall. LVEDP was 4 mm Hg, and end diastole is at time zero and end systole at 265 msec.

During the control period there was greater segment shortening in the circumferential (−0.13) than longitudinal (−0.08) direction. There were positive radial strains (E13), indicating wall thickening of about 40% by end systole. After 10 minutes of myocardial ischemia, there were nearly equal positive circumferential (0.09) and longitudinal (0.10) strains (segment lengthening or bulging) and negative radial strains (wall thinning). In-plane shear (E12) was small during control and did not change with ischemia. However, the transverse shearing deformations (E13 and E23) went from positive (control, 0.05 and 0.08, respectively) to negative (−0.07 and −0.10, respectively) with acute myocardial ischemia.

Figure 3 represents a typical example of the end-systolic strains observed at several sites across the left ventricular wall during control (open circles) and after 10 minutes of ischemia (closed circles) in a single experiment. Each data point represents the computed end-systolic strain from one tetrahedron plotted as a function of the percent depth of the centroid of that tetrahedron from the epicardium. The top panels plot the normal strains and the bottom panels the shear strains. During the control period, the end-systolic circumferential strains were negative and in this case demonstrated a significant transmural gradient, as illustrated by the regression line (greater circumferential shortening in the endocardium than epicardium). After 10 minutes of ischemia, E13 became positive across the left ventricular wall, and there were no significant transmural differences. The longitudinal strain (E22) was negative during the control period but showed no transmural gradient. During ischemia, E22 became positive and demonstrated a transmural gradient with more lengthening toward the endocardium. Radial strains were positive during the control period and increased substantially deeper into the left ventricular wall. During ischemia, E33 became uniformly negative at all levels (wall thinning). During the control period, shearing deformations (E12, E13, and E23) tended to be small and positive and became negative after acute myocardial ischemia.

These results are summarized for all experiments in Table 1. During the control period, circumferential strains (E11) were significantly more negative than the longitudinal strains (E22) in the endocardium but not in the midwall or epicardial levels. With 10 minutes of acute myocardial ischemia, both E11 and E22 were positive in approximately equal magnitudes at all levels. Radial strains (E13) were positive during control and became negative (wall thinning) with ischemia. No significant differences were observed in finite strains between 5 and 10 minutes of acute ischemia. The in-plane shear (E12) and the circumferential–radial (E11) and longitudinal–radial (E23) transverse shears were small to moderate and positive during the control period and became negative with ischemia. The end-systolic shear angles (computed from the shear strains) did not differ across the left ventricular wall during the control period or after ischemia.
ischemia. The mean end-systolic shear angles during the control period were 86° for $E_{12}$, 87° for $E_{13}$, and 85° for $E_{23}$ and changed with ischemia to 91°, 95°, and 97°, respectively. The change in shear angle computed from $E_{23}$ with ischemia was statistically significant for all three different depths.

Figure 4 plots the averaged normal strains for all animals at three levels across the wall. $E_{11}$ increased significantly from the epicardium to the midwall and endocardial layers during the control period. After 5 and 10 minutes of ischemia, $E_{11}$ became positive across the left ventricular wall, and there were no significant transmural differences. The longitudinal strain ($E_{22}$) was negative during control, and there were no significant differences across the left ventricular wall. However, after 5 and 10 minutes of ischemia, $E_{22}$ became positive and tended to develop a gradient across the left ventricular wall (statistically significant only at the endocardial layer after 10 minutes of ischemia). Radial strains ($E_{33}$) were positive during the control period (wall thickening) and increased significantly deeper into the left ventricular wall. After ischemia, $E_{33}$ became uniformly negative at all levels (wall thinning) without any significant transmural gradient.

Table 2 shows principal strains and directions (eigenvectors) computed from the average normal and shear strains (Table 1). During control, the principal direction associated with the greatest negative principal strain at all sites across the wall has a radial component close to zero, indicating that the greatest shortening occurs in planes parallel to the epicardial tangent plane. The principal direction associated with the greatest positive strain, on the other hand, has radial components close to one, indicating that thickening occurs predominantly in the radial direction. Note that the eigenvector corresponding with the greatest shortening has an orientation projected in the epicardial tangent plane that corresponds to a negative angle of $-52^\circ$ (arctan $-0.792/0.609$) in the epicardium and $-26^\circ$ in the endocardium. After 10 minutes of ischemia, the eigenvectors are no longer oriented close to the reference system. The greatest lengthening now has substantial components in the longitudinal and circumferential directions ($Z_5$ in Table 2, ischemia),

![Image](http://circres.ahajournals.org/content/376/10/2141/F2.large.jpg)
indicating substantial lengthening in the epicardial tangent plane.

Figure 5 shows a graphic representation of these data from an endocardial tetrahedron in one experiment. Each panel represents a three-dimensional perspective plot of the cardiac coordinate system (unit cube represented by dotted lines) and a deformed (end-systolic) parallelepiped. The three mutually orthogonal edges that intersect at each vertex of the solid parallelepipeds are oriented along each of the three principal axes and are scaled by the respective stretch ratios. As reflected by the control data in Table 2 at end systole (Figure 5, panel A), there is substantial lengthening in the radial direction and in-plane shortening deformation. In contrast, with 10 minutes of ischemia (Figure 5, panel B), lengthening occurs in the epicardial tangent plane and shortening occurs in the radial direction. Note that in ischemia, the parallelepiped is tipped away from the epicardial tangent plane, reflecting the influence of significant shearing deformation; that is, in ischemia, the principal direction associated with

**TABLE 1. Changes in End-systolic Finite Deformation Variables with Total Occlusion of the Left Anterior Descending Coronary Artery**

<table>
<thead>
<tr>
<th></th>
<th>E₁₁</th>
<th>E₂₂</th>
<th>E₃₃</th>
<th>E₁₂</th>
<th>E₁₃</th>
<th>E₂₃</th>
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<tbody>
<tr>
<td><strong>Control</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Epi</td>
<td>-0.04±0.05</td>
<td>-0.06±0.03</td>
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<td>0.04±0.02</td>
<td>0.02±0.03</td>
<td>0.03±0.03</td>
</tr>
<tr>
<td>Mid</td>
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<td>-0.09±0.02</td>
<td>0.23±0.08*</td>
<td>0.02±0.03</td>
<td>0.04±0.04</td>
<td>0.03±0.03</td>
</tr>
<tr>
<td>Endo</td>
<td>-0.14±0.05*</td>
<td>-0.09±0.02</td>
<td>0.38±0.14*</td>
<td>0.03±0.03</td>
<td>0.02±0.09</td>
<td>0.07±0.04</td>
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<tr>
<td><strong>5-Minute ischemia</strong></td>
<td></td>
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<tr>
<td>Epi</td>
<td>0.06±0.05</td>
<td>0.04±0.04</td>
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<td>-0.02±0.02</td>
<td>-0.08±0.04</td>
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<tr>
<td>Mid</td>
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<td>0.06±0.04</td>
<td>-0.10±0.03</td>
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<td>-0.05±0.03</td>
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<tr>
<td>Endo</td>
<td>0.05±0.06</td>
<td>0.07±0.06</td>
<td>-0.07±0.10</td>
<td>-0.01±0.03</td>
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<td><strong>10-Minute ischemia</strong></td>
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<td>0.07±0.03</td>
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<td>-0.06±0.06</td>
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<tr>
<td>Mid</td>
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<td>-0.01±0.07</td>
<td>-0.03±0.08</td>
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Values are mean±SD. Significant differences from epicardium denoted by an asterisk. Statistical analysis indicates that both normal and shear strains were significantly different from control at 5 and 10 minutes of acute ischemia in all cases except the in-plane shear (E₁₂) at 10 minutes of ischemia (p<0.10). E₁₁, circumferential strain; E₂₂, longitudinal strain; E₃₃, radial strain; E₁₂, circumferential-radial shear; E₂₃, longitudinal-radial shear; epi, epicardium; mid, midwall; endo, endocardium.
CIRCUMFERENTIAL STRAIN (E11)

LONGITUDINAL STRAIN (E22)

RADIAL STRAIN (E33)

TABLE 2. Average Eigenvectors

<table>
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<th>Control</th>
<th>10-Minute ischemia</th>
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<tr>
<td></td>
<td>Z1</td>
<td>Z2</td>
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<tr>
<td>Epicardium</td>
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<tr>
<td>Circumferential</td>
<td>0.609</td>
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<tr>
<td>Longitudinal</td>
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</tr>
<tr>
<td>Radial</td>
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</tr>
<tr>
<td>Principal strain</td>
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</tr>
<tr>
<td>Midwall</td>
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<tr>
<td>Circumferential</td>
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<tr>
<td>Longitudinal</td>
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<td>−0.862</td>
</tr>
<tr>
<td>Radial</td>
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<td>0.132</td>
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<tr>
<td>Principal strain</td>
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<td>−0.082</td>
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<tr>
<td>Endocardium</td>
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<td></td>
</tr>
<tr>
<td>Circumferential</td>
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<td>−0.439</td>
</tr>
<tr>
<td>Longitudinal</td>
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</tr>
<tr>
<td>Radial</td>
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<td>0.159</td>
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<tr>
<td>Principal strain</td>
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<td>−0.087</td>
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</table>

Principal strains and directions (eigenvectors Z1–Z3) computed from data shown in Table 1. Data shown are for epicardial, midwall, and endocardial layers in the circumferential, longitudinal, and radial directions (see “Materials and Methods, Strain Analysis”).

Wall thinning (Z1) is tipped away from the radial direction, and the principal direction associated with the greatest lengthening (Z3) is tipped out of the epicardial tangent plane (Table 2).

Two-dimensional midwall strains (group 2). No significant changes were observed in heart rate or peak systolic pressure during ischemia when compared with control conditions. Heart rate values for control and 30 seconds, 1, and 5 minutes of ischemia were 111±28, 112±28, 110±27, and 108±27 beats/min, respectively; peak systolic pressure values were 111±23, 108±22, 102±16, and 100±22 mm Hg, respectively. Significant increases occurred in end-diastolic pressure from 5.6±3.0 mm Hg during control to 8.6±4.6 and 9.3±4.1 mm Hg during 1 and 5 minutes of ischemia, respectively.

Typical plots of the midwall end-systolic normal and in-plane shear strains for control and 5 minutes of ischemia in one animal are shown in Figure 6. During the control period at end systole, there was greater segment shortening in the circumferential than the longitudinal direction. With acute myocardial ischemia, segment lengthening (bulging) was present, and at end systole the longitudinal strain (E22) became more positive than E11. In-plane midwall shear or E22 was small, positive, and not different between control and 5 minutes of ischemia.

Midwall end-systolic strain data for all six animals are shown in Figure 7. During the control period, E11 was significantly more negative than E22. By 30 seconds of ischemia, E11 was still negative (wall shortening), and E22 was akinetic. After 1 minute of acute myocardial ischemia, E11 was akinetic, and E22 was dyskinetic (demonstrating positive strains). By 5 minutes of ischemia, both normal strains were dyskinetic, with E22 and E11 becoming very similar in magnitude. Five-minute data obtained from the three-dimensional measurements for E11 and E22 (group 1 data) are shown next to the corresponding two-dimensional results and illustrate similar magnitudes of local deformation by the two techniques. In-plane shearing deformation (E12) during control was 0.03±0.02 and did not change significantly with ischemia. In-plane shear strains were 0.01±0.01 at 30 seconds, 0.02±0.02 at 1 minute, and 0.04±0.04 at 5 minutes of ischemia.

End-diastolic Strains

Twenty tetrahedrons in the epicardium, 18 in the midwall, and 18 in the endocardium met the geometric selection criteria. End-diastolic strains were calculated as the change in end-diastolic configuration from the control period (“undeformed,” reference
FIGURE 5. Schematic representation of principal deformation computed from an endocardial tetrahedron in one experiment. The dotted cube shows the cardiac coordinate system (C, circumferential; L, longitudinal; R, radial). In each panel the solid parallelepipeds represent principal data in a deformed configuration relative to a reference configuration; that is, each edge is oriented along a principal direction and is scaled by the corresponding principal stretch. End-systolic deformation obtained during the control period is shown in panel A. End-systolic deformation obtained at 10 minutes of ischemia is shown in panel B. In panel C, the control end-diastolic frame has been used as the reference configuration and the ischemic end-diastolic frame has been used as the deformed configuration. This diastolic deformation is illustrated by the dashed-dot deformed cube. In panel D, the control end-diastolic frame has been used as the reference configuration, and the ischemic end-systolic frame has been used as the deformed configuration. Thus, panel D represents the combined effect of both diastolic and systolic deformations present in the endocardium.

FIGURE 6. Representative data from one animal showing two-dimensional strains (E_{12}, circumferential; E_{22}, longitudinal) as a function of time in cardiac cycle during control (continuous line) and 5 minutes of ischemia (dotted line). End diastole occurred at 0 msec and end systole at 320 msec with a left ventricular end-diastolic pressure of 6 mm Hg.

FIGURE 7. Average end-systolic circumferential (E_{11}) and longitudinal (E_{22}) two-dimensional strains for the midwall for the control period and at 30 seconds, 1 minute, and 5 minutes of ischemia. Data at 5 minutes of ischemia from the three-dimensional method are shown next to the two-dimensional points. Significant differences from control are denoted by an asterisk.
of the end-diastolic configuration in the circumferential than in the longitudinal direction. The radial strain ($E_{33}$) was negative (wall thinning) and increased significantly with increasing depth in the wall. The product of the stretch ratios computed from the mean values shown in Figure 8 were 1.06 for the epicardium, 1.02 for the midwall, and 1.04 for the endocardium.

End-diastolic shearing deformations during ischemia were negative and not different across the left ventricular wall. Finite shear angles (averaged for all three layers) at 10 minutes of ischemia were $93 \pm 3^\circ$ ($E_{12}$), $94 \pm 7^\circ$ ($E_{13}$), and $99 \pm 5^\circ$ ($E_{23}$). Only the change in the longitudinal–radial shear strain ($E_{23}$) was statistically different from control (or $90^\circ$). Three-dimensional end-diastolic strains for 5 minutes of ischemia (data not shown) were not significantly different from those during 10 minutes of ischemia. Figure 5C illustrates the diastolic deformation changes. The reference configuration is the control end-diastolic configuration, and the deformed configuration is end diastole of the ischemic beat. Note that a substantial portion of the deformation occurs in the transition from control to ischemic end-diastole. Figure 5D combines the effects of both systolic and diastolic deformations. In this case, in contrast to panel B where the ischemic end-diastolic reference frame was used as the reference for the end-systolic parallelepiped, the control end-diastolic configuration and the ischemic end-systolic configuration were used. The large thinning and the predominance of the circumferential lengthening shown in panel D put in perspective the relative magnitudes of diastolic and systolic deformations with ischemia. Thus, it is clear that a large proportion of the deformation in the left ventricular wall occurring in ischemia is present in the diastolic state before systolic contraction occurs.

**Discussion**

This study shows for the first time that local deformation of ischemic tissue involves major changes in the magnitudes of all three normal strains and significant changes in shearing deformations. Moreover, the normal systolic transmural gradients of circumferential ($E_{11}$) and radial deformation ($E_{33}$) were lost during ischemia, and a major diastolic reconfiguration of the involved region occurred.

**Systolic Deformations**

Tennent and Wiggers first described the changes in regional myocardial function after a total LAD occlusion. Normal muscle shortening in the anterior wall was replaced with segment lengthening (bulging) within a few beats. Subsequently, a variety of methods was developed and used to study acute ischemia, with comparable results. However, it was not until the development of the ultrasonic transit-time dimension technique (which provided excellent spatial and temporal resolution) that more insight into acute and chronic changes in local deformation of ischemic tissue was obtained. These and other similar studies have demonstrated that after the complete interruption of coronary blood flow, segment shortening in the ischemic area deteriorates within seconds and is replaced by holosystolic bulging (segment lengthening) with the corresponding appearance of local systolic wall thinning. In the present study, changes in strain patterns occurred rapidly and were essentially complete within a few minutes, similar to previous studies. Longitudinal strains tended to reflect dyskinetic wall motion earlier than circumferential strains, although the time course of loss of shortening was similar in both directions. Three-dimensional data during the control period indicate that in the midwall and endocardial layers, circumferential shortening ($E_{11}$, Table 1) exceeded longitudinal shortening ($E_{22}$). However, at 5 and 10 minutes of acute myocardial ischemia, segment lengthening (bulging) was present in similar magnitudes along both the circumferential and longitudinal directions. In contrast, in the epicardium, circumferential and longitudinal shortening were similar in control, giving way to similar degrees of lengthening at 5 and 10 minutes of ischemia. In the study performed by Gallagher et al, epicardial segment shortening of gauges oriented in line with the local fibers (nearer longitudinal) and in the circumferential direction showed approximately equal strains in control (in agreement with our data). However, there was nearly a twofold greater bulging in the circumferential than the longitudinal direction with a total coronary occlusion. Thus, our results differ from those of Gallagher et al in that segment lengthening in the epicardium was approximately equal in both circumferential and longitudinal directions during ischemia. Gallagher and coworkers did not measure shear strains, and it seems likely that the large changes in shears observed in the present study could have contributed to an underestimation of the epicardial fiber (approximately longitudinal) strain in the Gallagher study. Thus, the difference between these two studies emphasizes the necessity of exam-
ning the full three-dimensional data when comparing strains under ischemic conditions.

Prinzen et al\textsuperscript{25,26} directly measured epicardial deformation and estimated function in the endocardium using transmural pins in conjunction with a ventricular model. They found that during the control period, epicardial ejection shortening was small and similar to the present study, but there was a tendency for greater circumferential than longitudinal shortening. In the epicardium during 5 minutes of acute myocardial ischemia, in-plane strains were essentially akinetic—a finding that differs primarily in magnitude from the present study. However, the two studies are difficult to compare. In the Prinzen study,\textsuperscript{26} coronary blood flow was not reduced to a similar degree, so the differences could be explained by lesser degrees of ischemia. The reference configuration used by Prinzen and colleagues was the start of ejection, whereas we use end-diastole as the reference configuration. For example, in Figure 6 there is early shortening during ejection with ischemia (E1\textsubscript{10}), but because of the large isovolumic bulge, end-systolic strain still is positive. These results are similar to those of Lew et al,\textsuperscript{4} who demonstrated that most of the paradoxical lengthening in the ischemic area occurs during isovolumic systole, whereas it is virtually akinetic during ejection. In addition, the technique of Prinzen et al does not measure transverse shears, which might also account for the differences observed between the two studies.

This study also indicates that during control and ischemia, significant in-plane strains occur in directions perpendicular to the local myofibers during systole. These data imply that there must be either substantial rearrangement of myofibers or large shape changes in the cross sections of myocytes or the interstitium during the control period and that these changes during acute ischemia result in fiber and cross-fiber lengthening instead of shortening. This lengthening indicated by positive fiber and cross-fiber strains may well lead to the overextension of myocardial tissue and cell separation during ventricular contraction, thus further extending the damage caused by ischemia.

A potential mechanism for equalization of circumferential and longitudinal deformation in ischemia is the longitudinal distribution of the LAD bed. The shape of the ischemic area at risk is oblong, spanning a considerably greater distance in the longitudinal direction than in the circumferential direction. As ventricular contraction occurs, ischemic myocardium expands preferentially in the longitudinal direction because of the greater amount of compliant tissue present along the same orientation. Thus, the shape of the ischemic zone may partially influence the pattern of local deformation.

Several previous studies\textsuperscript{6,12,27,28} performed in the normal heart have demonstrated the presence of greater shortening and wall thickening in the deeper layers of the left ventricular wall. With acute ischemia, we found a loss of the normal transmural gradients of deformation during systole. Crozatier et al\textsuperscript{29} examined sarcomere lengths in ischemic hearts fixed at end diastole and showed increased sarcomere lengths near the endocardium. This finding agrees with our results as shown in Figure 8, where greater segment lengthening occurred in the endocardium. Crozatier et al, however, showed that sarcomere lengths in ischemic hearts fixed at systolic pressures were uniform across the wall. The data of Crozatier et al imply greater end-systolic strains (deformation from end diastole to end systole) at the epicardium. Results from the current study show no differences in systolic strains across the wall, implying that there is a transmural gradient in deformation in the extracellular matrix (or at least, not in line with myofibers) that is greater at the endocardium.\textsuperscript{14}

Another possible explanation for the lack of a systolic gradient in strain is that edge loads on the ischemic region in the marginally perfused areas (border zones) may be very complex. A transmural gradient of border function could exist consisting of greater edge loads imposed on the ischemic region by adjacent epicardium that is shortening more normally than the endocardial margin beneath it. This mechanism could explain why the expected gradient in lengthening due to geometry gives way to more transmurally uniform behavior.

Changes in the pattern of in-plane (both fiber and cross-fiber) strains were observed as early as 30 seconds after coronary occlusion. It is difficult to conceive that major damage to the extracellular matrix had occurred so early into ischemia to solely explain such changes. However, a variety of mechanisms is possible, including disruption of collagen struts by physical, not enzymatic, factors, cell shape change and realignment, and loss of tissue turgor.

We found that the normal positive shearing deformations observed during the control period became negative with ischemia. The most consistent changes were observed in the longitudinal–radial transverse shear strain (E\textsubscript{23} shear angle shifted from 85° during control to 97° after 10 minutes of ischemia). Only a limited number of studies have looked at shearing deformations with acute myocardial ischemia.\textsuperscript{30} Osakada et al\textsuperscript{30} examined the posterior wall of the left ventricle during circumflex coronary occlusion and found that during the control period, shearing motion was present between the epicardial and endocardial surfaces along the longitudinal–radial coordinate plane (E\textsubscript{23}) and circumferential–radial coordinate plane (E\textsubscript{13}). Their data showed a reduction in systolic shear with ischemia, whereas our data indicate a change\textsuperscript{10} in transverse shear strain of greater magnitude from positive values to substantial negative values. Their control shear strains were significantly smaller when compared with ours, most likely because their measurements of transverse shears represent an average value across the entire wall thickness. The presence of negative transverse shear strains in passive normal and ischemic diastolic data
could be due to the large wall thinning and longitudinal curvature of the deforming region.

Negative end-diastolic and end-systolic shearing deformation may influence transmural myocardial blood flow. Evidence indicates that myocardial shear strains may contribute to the normal systolic compression of coronary flow. In addition, other experiments suggest that most of the acute collateral flow is diastolic. Thus, shifts in diastolic and systolic shear strains may result in limiting systolic and collateral blood flow during acute ischemia, compromising the viability of the myocardium even further.

**Diastolic Deformations**

End-diastolic data from our study indicate that the ischemic area of the left ventricle has undergone substantial deformation relative to control. The end-diastolic configuration expands preferentially along the circumferential direction and is accompanied by substantial wall thinning, both of which increase significantly toward the inner half of the wall. This increase in diastolic length with ischemia has been reported in studies performed using uniaxial methods. In 1972, Forrester et al reported a moderate but not statistically significant rightward shift in the pressure–volume relation (creep or plastic deformation), a finding corroborated in a study performed by Theroux and coworkers. Results from our studies also indicate that segment lengthening along the minor axis of the heart at the midwall and endocardial layers is significantly greater than along the major axis. These data are in agreement with findings from Edwards et al, who show a greater increase in end-diastolic length along the circumferential rather than the longitudinal direction.

In computing the end-diastolic deformation, we used the control coordinate data at end diastole as the reference configuration. The average end-diastolic pressure for this configuration was 2.3 mm Hg. Therefore, the initial reference interbead spacings did not represent an unstrained configuration. After ischemia, the end-diastolic pressures increased to a mean of 4.3 mm Hg. Thus, part of the end-diastolic deformation observed during ischemia could be due to the increase in diastolic pressure. However, in two of the experiments, no change in LVEDP was observed from control to ischemia, and end-diastolic deformations were comparable to those in the other animals. In addition, using data obtained from a prior study in which end-diastolic deformations at the anterior midwall were computed for a wide range of LVEDP in normal dogs, we determined how much of the observed midwall deformations could be due to pressure load only. Strains were calculated using a 2 mm Hg reference pressure and a step increase to approximately 4 mm Hg (similar to our ischemia study). Results indicate that pressure load alone could account for only approximately 15% of the circumferential and 40% of the longitudinal strains that we observed during ischemia, thus accentuating the difference between the two strains due to ischemia alone. No previous attempts to measure end-diastolic shearing deformation with ischemia have been reported. Our results indicate that shear strains \((E_{12}, E_{13}, \text{and } E_{23})\) become negative during ischemia, and, in particular, a dramatic change in \(E_{23}\) occurs from positive to negative values.

Several studies have shown a rightward shift of the end-diastolic pressure dimension relation. However, this data has been the first to show that the diastolic reconfiguration occurs in both the fiber and cross-fiber directions and that thinning and shears are greater in the endocardium. Several factors may contribute to the diastolic reconfiguration and thus the end-systolic strain pattern. These include disruption of the extracellular matrix cell shape changes, changes in boundary conditions imposed by healthy adjacent tissue, and loss of tissue turgor. Presumably, loss of turgor would result in negative strains in all directions. However, although we observe negative strains in the radial direction, large lengthening strains were observed in the in-plane directions, resulting in no detectable decrease in the product of the stretch ratios. This finding argues against loss of tissue turgor being a major factor.

**Limitations**

Both the two- and three-dimensional techniques assume homogenous strains within a triangular area or tetrahedral volume. Clearly, there is a transmural gradient of normal shortening and wall thickening. However, these tetrahedra are small, and the errors in this technique in normal tissue are small (approximately 5%) and have been discussed in depth in a recent publication. It also is possible, of course, that during ischemia there was a sufficient transmural or in-plane gradient in blood flow, resulting in further functional inhomogeneities within individual tetrahedrons. However, end-systolic strain data from each animal indicated that after a total LAD occlusion, a uniform loss of function occurred transmurally. Moreover, the transmural gradient in blood flow was small; that is, average blood flow was 0.13 ml/min/g (0.06±0.04 ml/min/g endocardium, 0.19±0.20 ml/min/g epicardium). These values previously have been demonstrated to result in a total loss of transmural function.

The resolution of the radiographic technique also is a potentially limiting factor for some of the ischemic diastolic measurements that involve large wall thinning strains. The system can resolve bead separations of 0.2 mm. If the height of each tetrahedron was 2 mm in the normal tissue at end diastole, then radial thinning deformations with ischemia of 15% in diastole and an additional 10% in systole still would leave sufficient resolution in the radial direction. However, the 0.2-mm resolution of the system may have added to the scatter in both the diastolic and systolic data.

Because the anterior left ventricular wall became significantly thinner during acute ischemia, fewer tetrahedrons met the established geometric selection.
criteria. The homogeneity assumption may be compromised (and thus become a limiting factor) if tetrahedrons of 4 mm height were used for strain analysis. An ischemic left ventricular wall approximately 10 mm in thickness. The use of "tall" tetrahedrons in a thin wall for strain analysis can result in either underestimation or overestimation of radial strains, depending on the location of the base of the tetrahedron where the calculations for in-plane strains are made. The mean heights of the tetrahedrons in each layer averaged 3.5 mm for the epicardium, 3.0 mm for the midwall, and 2.8 mm for the endocardium. Thus, "tall" tetrahedrons occurred only in the epicardium, where in all cases the tetrahedron bases were taken from the three surface beads placed on the anterior wall of the left ventricle. Given the end-diastolic results observed in our study, correction of the overestimation of epicardial E33 during ischemia probably would result in an accentuation of the gradient observed for radial strain (epicardial E33, >0.06), thus not really changing the results obtained with our current tetrahedra height selection approach.

Summary and Implications

The two-dimensional results from the midwall indicate that after 30 seconds of a total occlusion of the LAD, dyskinesia appeared first in the cross-fiber (longitudinal) direction, and hypokinesia was present in the circumferential direction. However, the rate of loss of function in the two directions was similar, and by 1 minute of acute ischemia, segment lengthening was present in both directions. Both the two- and three-dimensional results also indicate that after 5 minutes of a total coronary occlusion, end-systolic in-plane lengthening across the left ventricular wall occurs in approximately equal amounts along the circumferential and longitudinal directions. One of the most startling findings of the present study was the effect of ischemia on transverse shear strains. These strains, which are significant in the normal myocardium, changed sign (from a closing to an opening angle) and were nearly equal in magnitude to the normal strains. These large shearing deformations in ischemia potentially could influence collateral blood flow and certainly indicate that uniaxial measurements of deformation in ischemic myocardium, which do not account for shearing deformation, must be interpreted with caution. Although there is clear evidence that changes in uniaxial dimensions are a sensitive indicator of changes in regional blood flow and thus ischemia, the mechanical interpretation of uniaxial results is difficult because they fail to reflect the complex three-dimensional deformations that occur in the myocardium. End-diastolic results also indicate that the left ventricular wall undergoes a significant passive reconfiguration that varies transmurally. These end-diastolic data imply that within 10 minutes of acute ischemia, structural rearrangements or changes in material properties (creep) occur in the myocardium, implying possibly structural rearrangements within both the myocyte and the extracellular matrix.

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KEY WORDS • regional function • ischemia • ventricular mechanics • diastole • systole
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