Three-Dimensional Transmural Mechanical Interaction Between the Coronary Vasculature and Passive Myocardium in the Dog

Karen May-Newman, Jeffrey H. Omens, Richard S. Pavelec, Andrew D. McCulloch

Abstract The "garden hose" effect of coronary perfusion on diastolic left ventricular (LV) mechanics has been proposed to cause changes in systolic function by altering diastolic sarcomere length. We measured transmural distributions of three-dimensional shape change using radiopaque markers implanted in the LV free wall of eight isolated arrested canine hearts as functions of coronary arterial perfusion pressure (Pp) and LV pressure (P_LV) and related these deformations to the local muscle fiber architecture. Increased Pp from 0 to 110 mm Hg produced a 10% reduction in LV chamber volume (P<.01) and 25% to 40% decreases in local three-dimensional wall strain at matched P_LV, indicating myocardial stiffening. Significant decreases in the magnitudes of local deformation occurred preferentially in the cross-fiber and radial directions (P<.02), with no change in fiber strain. This suggests that changing coronary Pp does not alter diastolic fiber length; hence, the Frank-Starling law may not mediate the Gregg effect. Since the myocardial microvessels are primarily oriented parallel to the muscle fibers, the observed myocardial stiffening occurs in the directions transverse to the microvessels rather than along their length. Local myocardial wall volume in the unloaded LV demonstrated a uniform 5% increase from the unperfused state to Pp of 50 mm Hg. With further increases in Pp up to 110 mm Hg, the change in regional wall volume from the unperfused state developed a substantial transmural gradient increasing by 7% at the epicardium and 15% at the subendocardium. This reflects a significant increase (P<.02) in intramyocardial coronary capacitance from epicardium to endocardium, which may be related to a transmural gradient in coronary distensibility or vascularity. (Circ Res. 1994;74:1166-1178.)

Key Words • heart • mechanics • perfusion • coronary capacitance

Many experimental studies have demonstrated an increase in left ventricular (LV) diastolic stiffness due to increased coronary perfusion pressure (Pp) or flow. However, the magnitude of this "garden hose" or "erectile" effect of coronary perfusion appears to vary significantly with different experimental preparations and methods. In several previous studies, a 20% to 50% steepening of the diastolic pressure-volume relation with an increase in Pp has been measured.1-4 However, other investigators have observed no change in global ventricular compliance.5-7 Therefore, the significance of this phenomenon and its relation to normal physiological function has been questioned.8

If increased Pp can significantly impair LV filling, then it may also reduce end-diastolic sarcomere length and, hence, by the Frank-Starling mechanism, decrease systolic work. In an alternative hypothesis,9 an increase in sarcomere length due to increased Pp has been suggested to explain the mechanical effect of Gregg's phenomenon,10 ie, the observation that myocardial oxygen consumption and systolic contraction increase with increased arterial pressure. To test these hypotheses, measurements of local fiber lengths or regional deformation alter alterations in coronary perfusion are needed. Most previous studies on the effects of coronary pressure and flow on regional myocardial deformation have measured uniaxial segment lengths or wall thickness.1-7 More recently, two-dimensional measurements in isolated arrested canine hearts4 have demonstrated a decrease in epicardial principal strains accompanying the loss of ventricular compliance with increased Pp. However, there have been no studies of the effects of coronary perfusion on three-dimensional strain or its variation through the ventricular wall. Three-dimensional transmural strain in the passive dog heart without perfusion has been measured previously in our laboratory,11 providing an established method that was readily extended to study the effect of changing coronary pressure. The first objective of the present study was to measure changes in the regional mechanics of ventricular filling during perfusion at different coronary arterial Pps.

Since there is thought to be a close structural coupling between the coronary microvasculature and the surrounding myocytes,12 perfusion alone may also affect the regional shape and tissue volume of the myocardium. Recently, Judd et al13 showed that diastolic sarcomere length at the epicardium is not significantly affected by large decreases in coronary Pp in isolated working hearts, thus indicating no significant Frank-Starling effect on systolic function. However, since coronary blood flow and volume are not distributed homogeneously across the wall,14-16 there may be mechanical alterations in deeper layers. Regional strain associated with perfusion in directions other than those of the fibers may also reveal the nature of the interaction between vessels and myocytes. Therefore, the sec-
ond objective of the present study was to measure transmural distributions of three-dimensional deformation and volume change due to perfusion alone. The results from the present study demonstrate that perfusion significantly alters transverse but not fiber deformation and that there is a significant transmural gradient of intramyocardial capacitance.

Materials and Methods

Experiments on 11 mongrel dogs weighing 22 to 41 kg were performed. All animal studies were performed according to American Association for Accreditation of Laboratory Animal Care guidelines for the use of animals in research; protocols were approved by the University of California, San Diego, Animal Subjects Committee. On the day before the study, each dog was pretreated with 10 mg oral nifedipine. The methods for preparing the isolated passive heart for mechanical testing are similar to those we have described previously.11 The animal was anesthetized with pentobarbital sodium (25 to 30 mg/kg), intubated, and ventilated with positive pressure. The heart was exposed by median sternotomy and bilateral thoracotomy and supported in a pericardial cradle. Three columns of four to six 1-mm-diameter radiopaque beads were inserted in a triangular pattern into the anterior LV free wall. The columns, spaced 1 cm apart, were located adjacent to the second diagonal branch of the left anterior descending coronary artery. Larger (2-mm-diameter) beads were sutured on the epicardium over each column, and an epicardial reference bead was sewn on at the apex.

After a heparin injection (10 000 U/mL), the great vessels were ligated, and 60 to 120 mL of hypothermic hyperkalemic cardioplegic solution containing 2,3-butanedione monoxide (BDM) was injected into the aortic root to arrest the heart. The arrest solution had the following composition (g/L): dextran 60.0, NaCl 9.0, KCl 4.48, BDM 3.0, and nifedipine 0.0002. BDM was added to all perfusates to maintain the passive arrested state of the tissue by inhibiting crossbridge interaction.11 The heart was excised and rinsed. A specially designed plastic plug was secured in the aorta to allow perfusion of the coronary circulation. The plug consists of an 8-cm-long hollow acrylic central tube (3-mm inner diameter) attached to a 2.2-cm-diameter solid plug. Perfusate flowed through four 0.32-cm holes at the base of the plug. The plug was sutured in the aortic valve annulus, and the holes were positioned at the level of the coronary ostia. The plug contained a lead bead in the center to be used as a basal radiographic reference marker. Insertion of the aortic plug was accomplished within 5 minutes to allow initial perfusion. The isolated heart was intermittently perfused with a total of 250 to 500 mL of a cold oxygenated cardioplegic buffer composed of (g/L) dextran 60.0, NaCl 9.0, KCl 2.24, BDM 3.0, and nifedipine 0.0002, adjusted to a pH of 7.4. In the last 8 of the 11 hearts, 0.5 mg/L adenosine was added to the perfusate for coronary vasodilation, although bolus injection did not demonstrate any noticeable flow increase. The heart remained in a passive arrested state throughout the course of the experiment.

The chordae tendineae were cut, and a purse-string suture was placed in the mitral annulus to secure an oversized latex balloon attached to a mitral plug inside the LV. The balloon was connected to a volume infusion pump (Harvard Apparatus) and a pressure transducer (Statham P23XL). A small silastic suction line inserted into the ventricle through the apex was used to evacuate residual fluid and thebesian drainage between the balloon and the endocardium. The isolated heart was then oriented horizontally in a plastic tank and submerged in room-temperature cardioplegic solution, as illustrated in Fig 1. The aortic cannula was connected to a large adjustable reservoir containing room-temperature perfusate of the same composition as the cold perfusate described previously, bubbled with 95% O2/5% CO2. Total flow was measured with an in-line extracorporeal electromagnetic flowmeter (Biotronex Lab, Inc), and coronary arterial Pp was monitored with a transducer at the level of the heart. Coronary venous drainage and excess fluid that accumulated in the tank were periodically drained into a collection vessel and recirculated with a roller pump (Travenol Laboratories, Inc). Pressure, volume, and timing signals were acquired at 5 Hz during each inflation run and stored on computer. The heart was positioned so that the radiopaque beads were all visible in both views of a biplane x-ray imaging system with adjustable lateral and anterior-posterior image planes. X-ray videography was simultaneously recorded from both views for later image processing. Preparation of the heart and positioning of the x-ray system took 45 to 60 minutes; thus, the first experimental data were collected within 1 hour after arrest. In each experiment, small (1-g) tissue samples were taken from the right ventricle before and after the experiment for determination of tissue water content. These samples were weighed and completely dehydrated in an oven for 48 hours at 40°C.

Experimental Protocol

LV volume-loading cycles were performed at room temperature, and a typical recording is shown in Fig 2. Each cycle consisted of inflation at 75 mL/min to a cavity pressure of 20 to 30 mm Hg, immediately followed by deflation to zero pressure at the same rate. The myocardium was first mechanically preconditioned to squeeze out excess fluid from the tissue by repeated LV loading without coronary perfusion until the ventricular pressure-volume curve was unchanged for at least two consecutive cycles. Data were then obtained for this repeatable unperfused state. The next load cycle was applied during continuous coronary perfusion from the reservoir. Coronary perfusion was allowed only for the duration of one run, ±60 to 90 seconds, to limit fluid accumulation. Perfusion was stopped, and the unperfused preconditioned state was reestablished, usually within two to three cycles, ±5 minutes. This protocol of ventricular loading with and without coronary perfusion was repeated for three different levels of Pp in
random order: \( \approx 110 \) mm Hg (high), 80 mm Hg (medium), and 50 mm Hg (low), respectively. At the end of the study, the hearts were fixed in the unloaded state with 10% Formalin in phosphate buffer either by perfusion (three hearts) or by immersion of a tissue block containing the beads (eight hearts). The fixed tissue was used to measure the wall thickness and muscle fiber orientations in the region of the bead set. Fiber angles were measured in the fixed tissue at 10 to 12 points across the wall thickness. Tissue blocks were embedded in paraffin, and 20-\( \mu \)m sections were taken every 1 mm from epicardium to endocardium. The sections were stained with hematoxylin and viewed under low-power (\( \times 20 \)) light microscopy. An image at the center of the section was acquired onto a Macintosh computer using NIH IMAGE software, version 1.47. At least five measurements were made in each view and averaged. The transmural fiber angles were then computed relative to the cardiac circumferential coordinate axis as defined by the three surface beads on the block.

**Bead-Position Reconstruction**

At the end of the experiment, a three-dimensional geometric phantom was recorded on videotape with the positions of both x-ray tubes and image intensifiers unchanged. Based on the design of Daughters et al., the phantom consisted of an acrylic cylinder that was 6 cm in diameter with 28 gold beads (1 mm) arranged regularly in a helical pattern along its 15-cm length. A larger reference marker served to orient the helix. The phantom was positioned so that the reference marker and a minimum of 10 beads were visible in both views and recorded on VHS tape. Dewarpping grids in each plane were recorded to compute corrections for pincushion distortion in each view. The grids were composed of regular arrays of 1-mm stainless-steel beads press-fit into a rectangular pattern with 10-mm spacing holes, accurately machined in 0.32-cm thickness polycarbonate plate by a numerically controlled mill (Bridgeport Series I Interact with Heidenhain controller).

Biplane video images of the phantom and rectangular grids were acquired by use of a 480\( \times \)512-pixel eight-bit frame grabber (Data Translation DT2651) on the Q-bus of a VAXstation 3200. Two-dimensional pixel coordinates of the marker centroids on the images were located interactively by use of custom software. For each image plane, bicubic polynomial functions were fitted by a least-squares method to the \( x \) and \( y \) grid coordinates as functions of the image coordinates (rectification transformations). Inverse functions of image coordinates as bicubic polynomials of grid coordinates were also fitted by a least-squares method (distortion transformation). The rectification transformation was used to correct for magnification and spherical distortion of the image views. A minimum of 56 markers was used, and the root-mean-square error of the fit was 0.30 mm. Marker coordinates on the helical phantom were similarly measured in both views, and the camera matrices that transform the two-dimensional rectified coordinates to three-dimensional world coordinates were calculated by a least-squares method, as described by Potel et al. The average absolute error of this transformation was 0.29 mm.

Myocardial markers were located on three consecutive video frames from both views at each pressure, and their three-dimensional coordinates for each marker were computed from the camera transformations. These coordinates were averaged for the three frames and transformed to a system of local cardiac coordinates, defined by use of the basal and apical reference markers and epicardial column beads. The cartesian cardiac coordinate axes define the circumferential \( (x_1) \), longitudinal \( (x_2) \), and radial \( (x_3) \) directions of the individual heart, as defined previously.

**Data Analysis**

A least-squares finite-element method was used to calculate nonhomogeneous distributions of three-dimensional finite strain components in the region contained within the bead set. In this method, a single three-dimensional bilinear-quadratic finite element with six vertex nodes was fitted by the least-squares method to the coordinates of all the beads at the zero-pressure reference state. The corresponding deformed state of the element was then fit to the coordinates of the beads under load. The six independent components of the symmetric lagrangian Green's strain tensor referred to the cardiac coordinate system were then computed as a continuous function within the element. Transmural strain profiles were obtained along the centerline of the element. This method is described in more detail in previous studies. For each heart, bead positions were analyzed at two different LV pressures (\( P_{LV} \)), 0 and 10 mm Hg during each inflation cycle, at the different coronary Pps: 0, 50, 80, and 110 mm Hg.

When the strain referred to the cardiac coordinate system is transformed into the coordinate system of the myocardial fibers, the fiber and cross-fiber stretch and shear can be readily observed. A local coordinate system referred to the muscle fibers was obtained by rotating the local reference coordinates \( (x_1, x_2, x_3) \) in the epicardial tangent plane through the local fiber angle. The fiber angles measured in the fixed heart were used to transform the strain components to the fiber coordinate system for each individual animal.

Repeated-measures ANOVA was performed by using both perfusion and transmural depth as nominal factors for each strain component or volume change. Comparisons between individual means using the multivariate approach were performed to determine the significance of contrasts within one factor. Statistical significance was accepted at the 95% confidence level (\( P \leq .05 \)), with Bonferroni correction for multiple comparisons.

**Results**

Experimental results are reported for 8 of the 11 dogs studied. Three dogs were excluded from the analysis, two because of inaccurate calibration of the x-ray camera position and the other because of evidence of contracture (premature steepening of the pressure-volume relation). Geometric and anatomic parameters for the eight hearts are shown in Table 1. The average wall thickness in the hearts was 13 mm, and the bead sets were located 60±5% of the longitudinal distance from base to apex. All of the bead sets spanned at least 70% of the ventricular wall thickness, and four of eight exceeded 80%. Data were averaged at matched relative depths through the total wall thickness. In some animals, data at all three nonzero Pps were not available;
thus, the averages for certain Pps were computed with fewer than 8 animals. Comparisons of strain and volume changes between different Pps were performed only for the 6 animals for which data were obtained at all three pressures.

Four configurations of the ventricular myocardium were used to compute the transmural strain distributions: (1) the unloaded unfused state \( (P_{LV}=0 \text{ mm Hg}; \) \( Pp, 0 \text{ mm Hg}) \); (2) the loaded unfused state \( (P_{LV}, 10 \text{ mm Hg}; Pp, 0 \text{ mm Hg}) \); (3) the unloaded fused state \( (P_{LV}, 0 \text{ mm Hg}; Pp, >0 \text{ mm Hg}) \); and (4) the loaded perfused state \( (P_{LV}, 10 \text{ mm Hg}; Pp, >0 \text{ mm Hg}) \). Regional deformations associated with altered coronary Pp were quantified in two different ways. The “loading strain” at constant Pp was computed in the loaded state \( (P_{LV}, 10 \text{ mm Hg}) \) referred to the zero \( P_{LV} \) state. Thus, the effects of perfusion on the mechanics of filling were examined by comparing the loading strain in the unperfused LV (state 2 referred to state 1) with the loading strain at the highest Pp (state 4 referred to state 3). The effects of perfusion alone on regional LV wall shape were characterized by computing the “perfusion strain” in the perfused state \( (Pp>0 \text{ mm Hg}) \) with respect to the unperfused reference state \( (Pp=0 \text{ mm Hg}) \) at constant \( P_{LV} \). For example, the perfusion strain at zero \( P_{LV} \) was found by referring the configuration of state 3 to that of state 1. The total deformation in the loaded perfused state with respect to the unloaded unfused state is, therefore, a combination of the loading deformation and the perfusion deformation. However, this combination is not simply additive, since the nonlinear finite strains are not small.

### Pressure-Volume Relations

The mean LV volume change from zero pressure was computed at the different Pps \( (0, 50, 80, \text{ and } 110 \text{ mm Hg}) \) in \( P_{LV} \) increments of 5 mm Hg from 0 to 20 mm Hg (Fig 3). For 6 of the 29 load cycles that did not have a maximum pressure of at least 20 mm Hg, a cubic polynomial was used to extrapolate volumes for pressures outside the experimental range. LV volume change decreased slightly at all \( P_{LV} \)s with increased Pp. At \( P_{LV} \) of 10 mm Hg, this decrease was \( \approx 3 \text{ mL} \) at Pp=50 mm Hg and \( \approx 4 \text{ mL} \) at Pp=80 and 110 mm Hg. Repeate-

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**TABLE 1. Geometric and Weight Parameters**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Body Weight, kg</th>
<th>Heart Weight, g</th>
<th>Wall Thickness, mm</th>
<th>Bead Set Thickness, mm</th>
<th>Base-to-Apex Distance, %</th>
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<td>178</td>
<td>13</td>
<td>11</td>
<td>46</td>
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</table>

Mean±SD 27.2±6.6 216±45 13±2 11±2 60±9

*Heart weights were estimated for dogs 6 and 7 on the basis of the average heart weight-to-body weight ratio of 7.07±0.96 g/kg for normal dogs (n=38) from our laboratory.

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**Coronary Flow**

Coronary perfusate flow rates measured in the perfusion line are shown for each heart in Table 2. Total flow, normalized by the heart weight, yielded tissue perfusate flow rates of \( =2 \text{ mL} \cdot \text{min}^{-1} \cdot \text{g}^{-1} \) at a mean coronary Pp of 107 mm Hg for the isolated, nonworking, maximally vasodilated preparation. From linear fits to the measured coronary pressure-flow relations, mean±SD resistance was estimated at 41.9±14.2 mm Hg·min·g·mL\(^{-1}\), and the mean zero-flow pressure extrapolated from the fit was 14.9±11.4 mm Hg. During ventricular inflation, coronary flow decreased with increasing \( P_{LV} \) in a fairly linear manner, at a rate of 0.012 mL·min\(^{-1}·g^{-1}\) per mm Hg for all three Pps. The mean cavity volume at zero \( P_{LV} \) decreased up to 30% with perfusion, although this change was not statistically significant.

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**Fig 3.** Graph showing mean±SD pressure-volume curves for eight hearts at the highest perfusion pressure \( (Pp=110 \text{ mm Hg}) \) and zero Pp. Pressure is plotted vs left ventricular (LV) volume change averaged at four LV pressures. The mean curve showed a decrease (10%) in compliance at all ventricular pressures with coronary perfusion.
significant (P=.160). The ventricular volume occupied by the empty balloon and the mitral plug was 6 mL.

The change in tissue volume associated with fluid accumulation over the course of the entire experiment was assessed by computing the total element volume between the markers (in the unperfused unloaded state) at the beginning and end of each study (Table 2). This reference volume increased by a mean of 14±8% over the study duration. Short-term volume changes between successive perfused and unperfused runs were also studied by comparing the unperfused run immediately preceding or following the perfused run at each Pp. These volume changes between individual runs used for computing perfusion strains were small (≤3%) compared with the reversible changes associated with increased Pp (5% to 17%). These reversible changes were assumed to reflect predominantly vascular volume changes. Tissue water content assessed from measurements of wet and dry weights of tissue samples collected before and after the experiment showed an overall increase of 13±19%, which agrees closely with the finite-element calculation of volume changes; the greater variability in these measurements probably reflects their inherently lower accuracy.

**Loading Strain**

Strain components were calculated at 10 mm Hg P<sub>LV</sub> referred to zero pressure for both unperfused and perfused runs. Averaged data for all eight hearts showed similar patterns with and without perfusion at the highest Pp (110 mm Hg), as seen in Fig 4. Circumferential strain (E<sub>22</sub>) and longitudinal strain (E<sub>33</sub>) were positive because of the stretch of the wall under load and increased from epicardium to endocardium. Radial strain (E<sub>11</sub>) was negative, consistent with wall thinning, and was also greatest in magnitude nearest the endocardium. Shear strain also tended to increase toward the endocardium for all three components.

The difference between perfused and unperfused nonhomogeneous strain distributions was tested by two-way ANOVA with transmural depth and Pp as nominal category variables. All strain components, except the transverse shears (E<sub>13</sub> and E<sub>23</sub>), showed a significant effect of transmural depth (P<.0002). The longitudinal and radial strain components (E<sub>22</sub> and E<sub>33</sub>) both showed significant decreases with perfusion (P=.016 and P=.013, respectively) of approximately equal magnitude across the ventricular wall (Fig 4), indicating a loss of compliance in these directions with perfusion. However,

**TABLE 2. Perfusion Parameters**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Perfusion Pressure, mm Hg</th>
<th>Flow, mL/min</th>
<th>Flow/HW, mL·min&lt;sup&gt;-1&lt;/sup&gt;·g&lt;sup&gt;-1&lt;/sup&gt;</th>
<th>Unperfused Unloaded LV Cavity Volume, mL</th>
<th>Perfused Unloaded LV Cavity Volume, mL</th>
<th>Bead Set, % volume change</th>
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</table>

Mean±SD 107±10 505±151 2.30±0.96 12.7±8.1 9.8±5.0 14±8

HW indicates heart weight; LV, left ventricular.
distribution across the ventricular wall. Alternately, cross-fiber strain shows a large gradient increasing from epicardium to endocardium. The fiber–cross-fiber shear strain is negative and does not demonstrate a consistent transmural gradient. The effect of coronary perfusion on the in-plane strain components with respect to the fiber coordinate system shows that after an increase in Pp, strain in the cross-fiber direction decreases substantially, while fiber strain remains essentially unchanged. Statistical analysis of the fiber strain components by two-way repeated-measures ANOVA showed no effect of either depth or perfusion on fiber strain and fiber–cross-fiber shear. However, cross-fiber strain showed a significant effect both of depth (P=0.0001) and perfusion (P=0.194).

**Perfusion Strain**

The transmural deformations of the unloaded ventricular wall due to perfusion alone were found by computing the "perfusion" strain in the perfused state referred to the unperfused (Pp=0 mm Hg) state at matched ventricular pressures. At P1,0=0 mm Hg and the highest Pp (110 mm Hg), the circumferential, longitudinal, and radial perfusion strain components were all greater than zero, consistent with an increase in tissue volume with perfusion in the region of the beads (Fig 6). Mean circumferential and longitudinal perfusion strains were small and approximately equal across the ventricular wall. However, E3 was large and increased significantly from epicardium to endocardium (P=0.008). The mean perfusion shear strain was small, except for the circumferential-radial shear, E13, which was positive and increased slightly with depth through the wall. The perfusion strain computed at P1,0=10 mm Hg (Fig 7) was similar to that computed in the zero-pressure state, with two notable differences: the magnitude of the radial component was increased at the epicardium (and thus the gradient across the ventricular wall was smaller), and the magnitude of the transverse shear strain, E13, was increased. In fiber coordinates, the perfusion strain corresponds to a slight equibiaxial in-plane stretch and small shear strain components, with the exception of a substantial (0.02 to 0.04) fiber–radial shear.

**Wall Volume**

Fractional changes in local myocardial wall volume during increases in Pp were evaluated from the determinant of the deformation gradient tensor for the perfusion strain. Local tissue volume increased from the unperfused zero-pressure reference state to the perfused zero pressure (Pp=110 mm Hg) state by 7% at the epicardium to >15% near the endocardium (Fig 8). This substantial increase in wall volume with perfusion is also reflected in the three-dimensional perfusion strain, of which all three normal components (circumferential, longitudinal, and radial) were positive. The wall volume changes due to perfusion were similar at P1,0=10 mm Hg.

Complete data for wall volume change at all three Pps were available in six of eight hearts. In these hearts at the lowest Pp, the local wall volume increased by ~5% uniformly across the ventricular wall (Fig 9). As Pp increased, the overall wall volume increased, and the transmural distribution changed, increasing more at the
endocardium than the epicardium. Repeated-measures ANOVA indicated a significant effect of Pp on regional volume ($P = .0127$). Comparisons of individual means showed greatest differences between the lowest (50 mm Hg) and the highest (110 mm Hg) Pp ($P = .005$) in relation to the unperfused state (0 mm Hg). The differences between wall volumes at 80 mm Hg compared with 50 and 110 mm Hg were not statistically significant after Bonferroni correction ($P = .021$ and $P = .36$, respectively).

**Capacitance**

Fractional wall volumes were used to compute myocardial capacitance defined as the change of local myocardial wall volume divided by the change in coronary Pp at three different locations through the ventricular wall thickness: 10% (subepicardium), 40% (midwall), and 70% (subendocardium). Regional capacitance, shown in Table 3, was significantly higher at the inner layers of the ventricular wall for $P_{LV}$s of 0 and 10 mm Hg. Paired comparisons showed a significant effect of transmural depth on capacitance ($P = .0417$). Individual contrasts revealed the greatest difference between epicardial and endocardial values ($P = .0138$), but differences at the midwall site did not reach statistical significance (epicardial versus midwall, $P = .161$; midwall versus endocardial, $P = .174$).

**Discussion**

The main results of the present study can be summarized by two major points: (1) The decrease in global LV compliance with increased coronary Pp is associated with a decrease in passive strain in the longitudinal and radial directions, corresponding to a decrease in the cross-fiber strain but no change in the fiber direction. (2) Perfusion produces a significant (7% to 15%) increase in myocardial tissue volume that is greatest at the...
endocardium in the unloaded ventricle. This volume increase is associated with significant radial thickening and transverse shears and increases slightly further with ventricular load.

The reversible local shape changes in the ventricular wall due to perfusion presumably reflect the capacitance of the intact coronary vasculature,11,23 Examination of the changes in deformation with loading at a constant Pp and with perfusion at a constant ventricular load each provide unique information on the mechanical interaction between vasculature and myocardium. These findings can give insight into the mechanisms relating passive mechanical behavior to coronary vascular architecture as well as having implications for systolic function. Since changes were observed only in the cross-fiber and radial directions, this suggests that the deformations are strongly related to the anisotropic fiber architecture and may be associated with coronary microvessels aligned with the muscle fibers rather than larger transverse or transmural vessels. The significant transverse shears probably reflect the transmural variation in muscle fiber axis but may also be related to the connective tissue matrix connections between capillaries and myocytes.

The present study is a direct extension of our previous experiments in the unperfused isolated arrested dog heart.11 The present strain distributions with no perfusion agree closely in magnitude and transmural gradients with our earlier work, with the exception of the transverse shear strains, E13 and E23. Previous mean values of these measurements were small and not significantly different from zero at any depth in the wall. In the present experiments, both components were small but not zero. Neither was affected by perfusion. This discrepancy probably reflects improved spatial resolution in the biplane imaging system, since it has been shown that the transverse shear strains (especially E13) are particularly sensitive to measurement error in the bead coordinates.21 Unlike our previous study, the x-ray system in the present experiments permitted nonorthogonal biplane views, allowing for better imaging of the markers and improved resolution and noise levels of the video cameras. The calibration was performed with a three-dimensional phantom that spanned the image field rather than a local calibration bar and provided more accurate reconstruction of points over the entire image.

Limitations

The isolated arrested dog heart is a classic preparation for studying the mechanics of passive filling as a model of end diastole. As in our previous study,11 the strain was initially obtained after preconditioning without perfusion and computed only for the loading (ascending) portion of the cycle. The repeatability of the pressure-volume relation was used as an indicator of the extent of irreversible changes in the preparation during the experiment caused by edema or contracture, both of which produce a stiffening effect. Several interventions were used to delay the onset of contracture, including hypothermic hyperkalemic arrest, the calcium channel blocker nifedipine, and BDM, which protects isolated tissue from contracture by direct inhibition of crossbridge interaction.17 The results indicated a negligible effect of ischemia, as evidenced by the repeatable nonperfused pressure-volume curves. The room-temperature perfusate contained dextran to minimize edematous water accumulation during the study. In this preparation, irreversible changes in tissue volume assessed radiographically suggest that some edema occurred during perfusion, particularly at higher coronary pressures. The volume within the bead set at various time points in the study revealed a mean increase of

Table 3. Transmural Capacitance

<table>
<thead>
<tr>
<th>Dog</th>
<th>Subepicardium</th>
<th>Midwall</th>
<th>Subendocardium</th>
<th>Subepicardium</th>
<th>Midwall</th>
<th>Subendocardium</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>0.74×10⁻³</td>
<td>0.80×10⁻³</td>
<td>8.98×10⁻⁴</td>
<td>1.57×10⁻³</td>
<td>1.04×10⁻³</td>
<td>0.63×10⁻³</td>
</tr>
<tr>
<td>7</td>
<td>1.01×10⁻³</td>
<td>1.89×10⁻³</td>
<td>2.26×10⁻³</td>
<td>1.70×10⁻³</td>
<td>1.69×10⁻³</td>
<td>1.27×10⁻³</td>
</tr>
<tr>
<td>9</td>
<td>0.69×10⁻³</td>
<td>0.77×10⁻³</td>
<td>1.31×10⁻³</td>
<td>0.86×10⁻³</td>
<td>0.69×10⁻³</td>
<td>1.44×10⁻³</td>
</tr>
<tr>
<td>10</td>
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<td>1.07×10⁻³</td>
<td>1.86×10⁻³</td>
<td>0.05×10⁻³</td>
<td>1.05×10⁻³</td>
<td>1.60×10⁻³</td>
</tr>
<tr>
<td>14</td>
<td>1.59×10⁻³</td>
<td>1.90×10⁻³</td>
<td>1.72×10⁻³</td>
<td>1.19×10⁻³</td>
<td>1.65×10⁻³</td>
<td>3.62×10⁻³</td>
</tr>
<tr>
<td>18</td>
<td>0.99×10⁻³</td>
<td>1.47×10⁻³</td>
<td>1.72×10⁻³</td>
<td>1.23×10⁻³</td>
<td>1.34×10⁻³</td>
<td>1.37×10⁻³</td>
</tr>
<tr>
<td>Mean</td>
<td>0.84×10⁻³</td>
<td>1.32×10⁻³</td>
<td>1.63×10⁻³</td>
<td>1.10×10⁻³</td>
<td>1.31×10⁻³</td>
<td>1.65×10⁻³</td>
</tr>
<tr>
<td>SD</td>
<td>0.51×10⁻³</td>
<td>0.51×10⁻³</td>
<td>0.47×10⁻³</td>
<td>0.59×10⁻³</td>
<td>0.39×10⁻³</td>
<td>1.02×10⁻³</td>
</tr>
</tbody>
</table>

P_{LV} indicates left ventricular pressure.
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14% in local wall volume over the course of the entire experiment, which was consistent with the mean increase of 13% in measured water content. However, volume changes due to edema over the duration of a single perfusion run (=2 minutes) were very small (1% to 3%). Hence, it is unlikely that edema significantly affected the results of the strain analysis. In addition, each perfused run was paired with the unperfused run immediately preceding it to minimize any differences due to edema. Nevertheless, it is known that edema produces a stiffening behavior in the passive ventricle, so this factor may confound our results slightly.

A study by Van Dijk et al²⁴ on the effects of changing perfusate from blood to Tyrode’s solution in isolated cat hearts revealed alterations in coronary resistance and myocardial wall volume within 35 seconds after the onset of crystalloid perfusion. Resistance increased substantially after 30 to 60 seconds of perfusion with Tyrode’s, reaching a significant difference after 10 minutes or longer. Wall volume increased within the first 90 seconds by 1.7% and continued to increase until it reached a maximum value after 5 minutes. The authors concluded that a small increase in volume due to edematous interstitial volume increase was accompanied by large changes in coronary resistance and that the increase in interstitial volume occurred at the expense of intravascular volume. It should be pointed out that Tyrode’s solution does not contain any high molecular weight components, which would aid in the prevention of edema formation. In the present study, the heart was perfused intermittently with a crystalloid solution containing dextran. The coronary vasculature was perfused for periods of 2 minutes, followed by cyclic inflation loading to squeeze out any excess fluid. The heart was perfused for a total of 20 to 30 minutes during the entire study. Although the measurements of wall volume include tissue, intravascular, and interstitial volume in a lumped measurement, the tissue volume changes during a single run were almost completely reversible.

The isolated arrested heart is a useful model for studying diastolic ventricular mechanics. Measurements of strain during diastasis for the same hearts used in the isolated experiments demonstrated that the pattern of strain observed during loading of the isolated heart can be seen in the filling period of the beating heart. The advantage of the isolated preparation over the intact heart is in the degree of control over the arterial and venous coronary pressures and also in the mechanical loading conditions of the ventricle. However, although the vascular pressures at the two end points of the coronary circuit are known, the distribution of the pressure drop across the system is not, which may have some effect on our calculations of myocardial capacitance. Although transmural differences in intravascular pressure are ignored in the interpretation of these results, they are likely to be quite small.

Although the perfusate used in this preparation contained a maximal vasodilating concentration of adenosine, the extent of vasodilation in each experiment was not certain. This may account for the lower flow values observed in some animals (dogs 9 and 11). In addition, the approximate manner in which average tissue flow was calculated makes the measurement of flow and therefore resistance and zero-flow pressure subject to significant errors.

The digitizing and reconstruction of the three-dimensional marker coordinates was the largest source of error in the strain measurement. To minimize error, digital image processing was used to enhance and, where possible, automatically detect the markers on the video images. The least-squares finite-element method also filters spatial noise in the measured coordinates, and the continuous strain distributions allow results in different hearts to be averaged at matched positions through the wall thickness, without having to group discrete results from different depths. The measurement of fiber angles may contribute an additional error to the fiber and cross-fiber strain components. The standard deviation in the regression curves fitted to individual transmural fiber angle profiles ranged from 3° to 10°. This would give rise to a maximum additional error in the transformed strain of 0.009 for unperfused fiber strain and 0.008 for cross-fiber strain at midwall, for example. This error is significantly smaller than the error due to the measurement accuracy, which has been estimated to be ±0.02 for this method.²¹ Therefore, we have equal confidence in the transformed strains as the original strain components. The choice of an appropriate reference state for strain is important in the interpretation of the deformations of a body in which the stress is not known. It has been shown by Omens and Fung²⁰ that the unloaded state of the passive LV is not the zero-stress state, because of the presence of residual stress in the intact myocardium. Thus, it may be more appropriate to choose the stress-free state rather than the unloaded state as a reference for strain. However, three-dimensional residual strains are not currently known and were not measured in the present study. The stress-free state of the LV is found by cutting the tissue; hence, the myocardium could not be perfused in the zero-stress state since the wall and circulation would not be intact.

Loading Strain

The effect of coronary perfusion on passive ventricular mechanics was originally studied by measuring changes in the global compliance. Salisbury et al²³ measured an increase in ventricular pressure when the Pp of an isovolumic canine heart was raised. This observation led others such as Arnold et al²⁷ to postulate a “garden hose” effect, a stiffening of the myocardium due to engorgement of the coronary vessels as well as an increase in end-diastolic fiber length, which would explain changes in systolic function accompanying changes in perfusion as observed by Gregg.²⁰ Olsen et al²¹ showed a leftward shift of the LV pressure-diameter relation in arrested canine hearts with increased coronary Pp, independent of coronary flow. In another study, Vogel et al²³ found a decrease in diastolic global and regional compliance in isolated blood-perfused rabbit hearts with increased flow, independent of Pp. Some investigators have suggested that the passive stiffening effect of coronary perfusion is related to an increase in myocardial wall volume, irrespective of coronary Pp or flow. Using in situ canine hearts, Morgenstern et al²⁸ measured changes in intracoronary volume with a dye dilution technique; adenosine was used to alter flow independent of pressure. Their results
showed that both coronary blood flow and Pp can influence vascular volume independently. However, a model described by Glantz and Parmley demonstrated that a change in wall thickness or volume alone without a change in material properties is insufficient to account for the magnitude of the observed change in stiffness. The varied results of these studies indicate that more detailed information is required to understand the mechanism of this behavior and relate it to the structure of the myocardium and coronary vasculature.

To relate the mechanical effects of perfusion more closely to the structure of the wall, regional deformations have been studied by other investigators. In a study by McCulloch et al., two-dimensional epicardial strain was measured during passive inflation of isolated arrested canine hearts with and without coronary perfusion. Three markers on the epicardial surface defined the region for homogeneous strain measurement, and bipline video cameras were used to record the positions of the markers during testing. Their findings showed that LV volume change and epicardial strains both decreased significantly with increased coronary perfusion, although the pattern of deformation was not altered. Although many investigators have demonstrated similar findings, the stiffening effects of perfusion on wall mechanics have not been seen in all studies. Abel and Reis reported no change in end-diastolic PLV in isotamically contracting canine hearts with a change in Pp. However, these results were obtained at a single LV volume. Another study found no significant change in the viscoelastic properties of the intact bypass-perfused canine LV with alterations in coronary flow.

Resar et al. showed that changes in myocardial stiffness due to coronary perfusion in an isolated passive septum preparation are primarily related to perfusion of small postarteriolar vessels by testing before and after embolization with 15-μm microspheres. Moreover, a large component of the blood volume in the coronary system is contained in the capillaries. Therefore, their contribution may be of primary importance. It is also evident from the present study that the effect of perfusion is not isotropic, contrary to the suggestion of McCulloch et al. The anisotropic effect of perfusion observed in the present study suggests that the mechanics of the diastolic heart are strongly related to the ultrastructure of the myocardial muscle fibers and neighboring coronary microvessels. Since most coronary microvessels are closely aligned with the fibers, the decreased cross-fiber and radial strain translates to stiffening in the directions transverse to the microvessels rather than along the length. In addition, a slight increase in volume was observed with increased ventricular loading, independent of alterations in coronary perfusion. This unexpected finding suggests to us that as the ventricle is passively inflated, the vessels are elongated, thus slightly increasing the volume of the coronary vasculature.

The results of our present study show that altered Pp produced a significant change in myocardial longitudinal and radial strain. When the strain was transformed by rotation to the coordinate system of the muscle fibers, this change in deformation under load occurred mainly along the cross-fiber and radial axes, while fiber stretch remained unaltered. This suggests that diastolic sarcomere length is also unaltered by changes in Pp. There are indirect implications of this finding in relation to systolic function. If end-diastolic sarcomere length in the filling ventricle is unchanged by coronary perfusion, then the Frank-Starling mechanism is unlikely to be responsible for the increased function observed in the Gregg effect. Gregg and others have shown experimentally that an increase in Pp results in a concomitant increase in coronary flow, leading to an increase in both oxygen consumption and contractility. Arnold et al. demonstrated that increased Pp, independent of flow, causes a positive inotropic effect, thereby increasing metabolism. They postulated that the engagement of the coronary vessels leads to an increase in diastolic fiber length, resulting in stronger contraction. Our results suggest that this effect is not accomplished by simple mechanical fiber stretch. Judd et al. showed that complete loss of Pp in isolated blood-perfused hearts does not significantly affect diastolic sarcomere length. It is not surprising that the stiffening effect of coronary perfusion on myocardium does not increase diastolic fiber strain, as it is known that other circumstances in which a stiffening effect occurs, such as edema, lead to a decrease in function due to the mechanical effect. Thus, the mechanism responsible for the increase in cardiac contractility and oxygen consumption secondary to an increased coronary perfusion remains unclear. Alternative explanations for the Gregg effect have been proposed, including the possibility of experimental artifact.

Perfusion Strain

In addition to changes in passive mechanical behavior with loading, we also examined the myocardial wall deformations associated with changes in coronary Pp and flow. Previous studies of myocardial blood volume across the ventricular wall have shown conflicting results. Several investigators have measured blood vessel volume using labeled red blood cell or plasma tracers, generally in the range of 6 to 10 mL blood per 100 g myocardium and found ratios of endocardial-to-epicardial flow of 1.1 to 1.4. Liu et al. used radiopaque markers and indicator dilution to measure myocardial wall volume change through the cardiac cycle and found that both methods gave similar results. It is generally accepted that diastolic coronary blood flow is greater at the subendocardium than the subepicardium. Although the overall observations of a transmural gradient of coronary blood volume in the arrested heart are consistent with the hypothesis that the blood flow to the subendocardium is greater than that to the subepicardium, they do not verify it. However, several investigators have demonstrated higher flows in the subendocardium relative to the subepicardium in arrested maximally vasodilated hearts, yielding endocardial-to-epicardial ratios of 1.5 to 1.6.

Change in myocardial wall volume as a function of Pp is evaluated as the coronary capacitance. In an individual vessel, capacitance is related to vessel distensibility if volume is proportional to cross-sectional area. Previous measurements of vessel capacitance have been made by using either pressure-volume relations on isolated vessels or overall changes in myocardial volume. In the heart, studies performed on isolated segments of coronary artery have measured capacitance values of 0.002 to 0.005
mm Hg⁻¹. However, studies on isolated vessels are probably different from the behavior of vessels embedded in a dense muscle network. Coronary capacitance measured from changes in total wall volume is in the range of 0.075 to 0.10 g/mm Hg per 100 g tissue. In a distributed model of the coronary circulation, Spaan estimated the total compliance of the coronary system in the LV to be 0.138 mL/mm Hg per 100 g and total coronary blood volume at 19.2 mL/100 g, on the basis of a review of the literature. Our results of total wall volume increase with perfusion are consistent with these previous measurements and, in addition, indicate a twofold variation through the depth of the ventricular wall, which has not been previously described.

In the present study, perfusion strain is associated with the change in volume of the LV wall due solely to coronary perfusion at a given ventricular load. As expected, perfusion caused a repeatable increase in regional wall volume. This wall volume change increases myocardial volume by 7% at the epicardium to >15% near the endocardium. In the vasodilated state, the transmural gradient of vascular volume change implies a transmural variation in the number or diameter of coronary vessels. Several studies have demonstrated a transmural gradient in coronary blood volume that favors the endocardium. Wusten et al proposed that greater endocardial vascularity may account for their observation of a transmural gradient in small arteriole blood volume. However, most experiments have been unable to show whether this gradient occurs in arterial, capillary, or venous vessels. Moreover, studies have not distinguished between a transmural variation in vessel size (diameter) or number (density). Studies of capillary vessels have shown a transmural variation in number density that favors the epicardium but no gradient in diameter, suggesting that other vessels such as arteries or veins also contribute to overall intramyocardial capacitance. In the canine heart, Gerdes and Kasten found no significant difference in vessel diameter across the ventricular wall and a slight transmural gradient in vessel number density that increased from endocardium to epicardium. These findings indicate that the mechanism for transmural gradients in myocardial blood flow and volume remain unclear and that more information on changes in vessel morphology as a function of arterial pressure is needed.

Perfusion also produced a significant transverse shear strain, E₁₂, in the circumferential-radial plane. In fiber coordinates, this corresponds to fiber-radial shear at midwall and could be related to interconnections between microvessels and fibers. Caulfield and Borg described transverse capillary-myocyte collagen fibril interconnections. If perfusion caused an increase in vessel diameter, this may have resulted in unloading of transverse vessel-fiber interconnections and may thus allow more shear to occur in response to residual stress in the unloaded ventricle. At higher P₁, higher stresses would explain the greater shearing when the fibrils were unloaded by perfusion. This microvessel mechanical behavior is influenced by changes in both Pp and P₁. For instance, the observation that the change in perfusion strain with ventricular loading occurs as a relative increase in wall thickness indicates a change in the transmural distribution of myocardial stress, capacitance, or coronary resistance.

**Global Versus Local Properties**

Many investigators have used only global measures of passive mechanical behavior to characterize the effects of coronary perfusion. These measures, however, provide no details involving local mechanical behavior and are less sensitive to the changes in Pp, as local measurements of mechanics have revealed. For instance, a slight but significant decrease in the pressure-volume relation and hence diastolic mechanical properties was observed with increased Pp, although this difference was not evident at low ventricular pressures. These results may indicate why some previous studies have been unable to measure a change in diastolic behavior with perfusion. In other studies in which local properties were characterized with segment length measurements, the orientation and placement of the segment measurement is very important, and alignment with the circumferential or fiber directions is likely to be the least sensitive direction of measurement for detecting mechanical changes with perfusion, especially at the epicardium. The present study showed that the three-dimensional local strain during loading with and without coronary perfusion revealed significant stiffening behavior but only in the longitudinal and radial directions.

There have been many studies of coronary pressure-flow relations in the heart, as detailed in review articles by Klocke et al and Hoffman and Spaan. Most studies have found that this relation is linear for the diastolic or arrested heart and that the extrapolated y intercept, the zero-flow pressure, falls in the range of 18 to 25 mm Hg, although there are some problems with this extrapolation. Resistance is estimated as the slope of the linear relation. In the present study, the mean coronary vascular resistance was 41.9 mm Hg·mL⁻¹·min⁻¹·g⁻¹ and zero-flow pressure was 15 mm Hg (Table 2). On ventricular loading, the total coronary flow decreased slightly at a constant Pp by 1.3% per mm Hg P₁. Accurate measurement of this increase is difficult. The process increases in intramyocardial tissue pressure, especially near the endocardium. Recently, Watanabe et al measured pressure-flow relations in isolated supported dog hearts to determine lumped intramyocardial coronary capacitance during long diastoles. Consistent with our conclusions, their results suggested that the capacitance is located mainly within vessels <170 mm diameter and is reduced significantly by increases in diastolic wall stress or stiffness. Mechanisms proposed to explain changes in coronary resistance and zero-flow pressure include both local and global vessel behavior. Downey and Kirk have proposed that the coronary vessels respond to changes in local tissue pressure and collapse if tissue pressure is high enough, like a Starling resistor. According to Spaan, coronary flow limitation is due to the compliance of intramyocardial vessels and is a function of blood volume and vascular capacitance, which determine time constants for flow changes during step changes in pressure. Both of these theories rely on the role of intramyocardial pressure, which is defined as the pressure exerted by the tissue on the outside of the myocardial vessels. However, experiments have shown that neither if P₁ which determines radial wall stress or in-plane stresses are the primary determinants of the systolic flow decrease. These findings cast doubt on the role of intra-
myocardial pressure as a primary determinant of coronary blood flow. The nature of the interaction between ventricular mechanics and vascular flow determinants such as resistance, perfusion pressure, and vascular volume is apparently more complex. The results of the present study primarily suggest that the normal stress and strain components transverse to the muscle fiber axis may be involved.

Changes in coronary perfusion (pressure or flow) can alter the mechanics of the passive LV in two ways: by changing the reference state for strain and by changing the state of stress in the body. In terms of mechanics, the increase in volume of the myocardium may increase the strain energy and hence the wall stress. Since myocardial elasticity is nonlinear, this would be manifested as a stiffening effect. The transmural gradient of myocardial capacitance and the significant transverse shear stresses observed with perfusion show that the behavior of myocardial coronary microvessels is complex and that their structure, orientation, and surrounding collagen network are important in determining transmural differences in coronary flow that could lead to a functional gradient. A detailed study of coronary vessel morphology, with special consideration of transmural gradients and changes with Pp and PLV, could help in the development of a realistic model of the vasculature and the effects of stress in the surrounding tissue.

In summary, coronary perfusion produced slight global but larger local changes in the mechanical behavior of the myocardium during loading. Despite significantly altered myocardial compliance, fiber strain across the ventricular wall was not changed. This suggests that altered perfusion does not change diastolic fiber or sarcomere length; thus, the Frank-Starling mechanism may not mediate the Gregg effect. Three-dimensional deformations associated with perfusion demonstrated a significant transmural gradient of intramyocardial capacitance dominated by radial thickening.

Acknowledgments

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Three-dimensional transmural mechanical interaction between the coronary vasculature and passive myocardium in the dog.

K May-Newman, J H Omens, R S Pavelec and A D McCulloch

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