Relation Between Reversal of Diastolic Creep and Recovery of Systolic Function After Ischemic Myocardial Injury in Conscious Dogs

Donald D. Glower, Jutta Schaper, J. Scott Kabas, H. Martin Hoffmeister, Wolfgang Schaper, John A. Spratt, James W. Davis, and J. Scott Rankin

Although prolonged functional abnormalities after transient myocardial ischemia have been well described, the interrelationship between postischemic systolic and diastolic alterations remains controversial. Therefore, 24 chronically instrumented conscious dogs were studied with left ventricular and pleural micromanometers, ultrasonic dimension transducers in the left anterior descending (LAD) coronary distribution, and vena caval and coronary artery occluders. The LAD was occluded for 15 minutes and reperfused for 24 hours while vena caval occlusions were performed at intervals to measure myocardial segment length at 0 mm Hg transmural diastolic left ventricular pressure (Ld). Coronary occlusion produced an immediate fall in systolic function as assessed by ejection shortening and stroke work and also induced a 16 ± 4% increase in Ld, which was termed diastolic creep. Throughout reperfusion, reversal of diastolic abnormalities correlated strongly with recovery of segmental shortening and stroke work (p < 0.001). Correlation between systolic dysfunction and diastolic creep was also observed during alteration of inotropic state by dopamine, during initial reperfusion hyperfunction, and during pharmacologic manipulation of afterload. In 5 additional dog hearts fixed in diastole by rapid glutaraldehyde infusion after coronary occlusion, myocardial creep measured by the segment length transducers paralleled sarcomere elongation measured by electron microscopy. Thus, the direct correlation between diastolic creep and systolic dysfunction throughout reperfusion and during hemodynamic alterations suggests that diastolic properties of postischemic myocardium may not be entirely passive and that systolic and diastolic dysfunction induced by ischemia may have a common basis at the cellular level.

Regional myocardial ischemia is known to produce both systolic and diastolic dysfunction, each of which may be reversible and yet may persist as long as 72 hours after reperfusion. Several mechanisms of prolonged postischemic dysfunction have been proposed, including high energy phosphate depletion, mitochondrial injury, sarcoplasmic reticulum dysfunction, cytosolic calcium influx, contractile protein damage, and myocardial edema. Yet another explanation for postischemic dysfunction may relate to direct interaction between systolic and diastolic abnormalities. Edwards et al showed that ischemia produced a time-dependent stretch of myocardial segments, which was termed "creep." In studies of ventricular overstiffness, overstretch of myofilaments has been shown to cause prolonged myocardial dysfunction. Currently, few data exist regarding interaction between systolic and diastolic dysfunction after ischemic injury. Interdependence of systolic and diastolic abnormalities, if present, would imply that postischemic diastolic properties are not entirely passive, i.e., not independent of inotropic state as is the case in nonischemic settings. Such interdependence of postischemic systolic and diastolic properties would significantly alter current understanding of the subcellular mechanisms of ischemic myocardial injury. A study was therefore designed to examine and define the interrelation, if any, between systolic dysfunction and diastolic alterations after reversible ischemic injury.

Materials and Methods

Preparation

After premedication with cephazolin (250 mg) and iron dextran (100 mg), 24 dogs (18-30 kg) were anesthetized with thiamylal sodium (20 mg/kg), intubated, and ventilated with a Bennett MA-1 respirator (Puritan-Bennett, Los Angeles, Calif.). Through a left fifth interspace thoracotomy, pneumatic occluders were placed on the superior and inferior venae cavae and on the left anterior descending coronary artery just distal to the first diagonal branch (Figure 1). A bipolar pacing electrode was sutured to the surface of the left atrium. A silicone rubber tube (2.6 mm i.d., 4.9 mm o.d., Dow Corning, Midland, Mich.) was implanted in the base of the left atrial appendage for later passage of a micromanometer into the left ventricle. A similar tube with multiple side holes was positioned in the
FIGURE 1. Closed-chest experimental preparation with pneumatic coronary occluder, subendocardially placed ultrasonic dimension transducers, and pleural and left ventricular micromanometers (see text).

pleural space adjacent to the left ventricle for measurement of pleural pressure.

Pairs of cylindrical piezoelectric crystals (1.5 mm o.d., Vernitron no. 1-1015-5A, Bedford, Ohio) were implanted in the left ventricular subendocardium to assess regional segment length. One pair was embedded in the distribution of the circumflex coronary artery, and a second pair was placed in the distribution of the left anterior descending coronary artery, distal to the pneumatic occluder (Figure 1). Each pair was aligned 10–15 mm apart in the minor axis circumference midway between the base and apex. Cables and tubes were passed through the chest wall into a dorsal subcutaneous pouch, the pericardium was left open, and the thoracotomy was repaired in layers. Each dog was allowed to recover for 7–10 days before the cable connectors were exteriorized through a small skin incision using 1% lidocaine local anesthesia.

Data Acquisition

One day after exteriorization, each dog was sedated with intramuscular morphine (0.7 mg/kg) and studied in the conscious state, while lying quietly on its right side. Piezoelectric transducer connectors were attached directly to a sonomicrometer constructed in our laboratory. The sonomicrometer had a sampling rate of 1,000 Hz with a practical frequency response of 0 to 50 Hz. Minimal resolution was 0.08 mm, and maximal electronic drift was 0.05 mm/hr. Micromanometers (Millar Instruments, PC-350, Houston, Tex.) were passed through the implanted silicone rubber tubes into the left ventricle and into the pleural space adjacent to the left ventricle. The manometers were prewarmed in a water bath at 38°C under constant electrical excitation by a pressure amplifier (Hewlett-Packard, model 8805-2, Waltham, Mass.) and were simultaneously balanced and calibrated immediately prior to each study. The resultant manometer drift was less than 0.5 mm Hg/hr, and the useful frequency response of the micromanometers was in excess of 10 kHz.

In 8 studies, control data were recorded, and lidocaine (50 mg) and heparin (300 U/kg) were given intravenously. Ten minutes later, the left anterior descending coronary artery was occluded for 15 minutes and then reperfused. A 15-minute ischemic period was chosen to provide maximal ischemic insult short of actual infarction, which generally occurs after 20 minutes of ischemia in this model (D.D. Glower, unpublished observation). Data were recorded just prior to coronary reperfusion and 15 minutes, 1 hour, 4 hours, 12 hours, and 24 hours after reperfusion. At each time point, data were obtained both during rapid vena caval occlusion and during atrial pacing at 120 beats per minute. Rapid vena caval occlusion, performed by sudden full inflation of the inferior and superior vena caval occluders, consistently emptied the left ventricle within 10–15 seconds. Morphine (0.7 mg/kg) was given intramuscularly 20 minutes prior to data acquisition at 4, 12, and 24 hours of reperfusion.

In another 8 chronically instrumented dogs, a similar protocol was followed. Data recorded after 3 minutes of reperfusion were compared with data obtained after 15 minutes of reperfusion to examine the hyperfunction period of initial reperfusion. Inotropic state was then altered by intravenous infusion of dopamine (15 μg/kg/min) from 60 to 90 minutes of reperfusion. Measurements obtained during dopamine infusion at 90 minutes of reperfusion were compared with data recorded prior to dopamine at 60 minutes of reperfusion.

In 8 additional dogs, autonomic blockade was accomplished with propranolol (0.5 mg/kg) and atropine (0.1 mg/kg), and left ventricular afterload was varied pharmaceutically after 15 minutes of coronary occlusion followed by 15 minutes of coronary reperfusion. Adequacy of autonomic blockade was assessed by abolition of the normal tachycardic response to vena caval occlusion and release. Data were recorded during infusion of phenylephrine (0–1 μg/kg/min) or nitroprusside (10–20 μg/kg/min) administered in random order to produce mean left ventricular ejection pressures of approximately 180 and 80 mm Hg, respectively. All data were collected within 5 to 7 minutes after onset of drug infusion.

Four to seven days after coronary artery reperfusion, each dog was killed and autopsied to confirm the position of all hardware. The hearts were excised, sectioned transversely at 1-cm intervals, and stained with triphenyltetrazolium chloride to inspect for infarction.
Electron Microscopic Studies

Five additional dogs were studied in the open-chest state. Each dog was anesthetized with triamylal sodium (20 mg/kg), intubated, and ventilated. The heart was instrumented through a left fifth interspace thoracotomy in a fashion identical to the chronically implanted dogs. After administering heparin (200 U/kg) intravenously, a small cannula (4 mm o.d.) was inserted into the aortic root and connected to perfusion reservoirs via a roller pump (Figure 2). A number 20 French catheter (initially clamped) was inserted into the left ventricular apex and connected to a saline-filled reservoir at a height of 12 cm H₂O above the heart.

After instrumentation, control recordings of left ventricular pressure and regional segment length were obtained during vena caval occlusion. Following intravenous administration of lidocaine (50 mg) and additional heparin (200 U/kg), the left anterior descending coronary artery was occluded. After 15 minutes of coronary occlusion, the aorta distal to the aortic cannula was cross-clamped. Simultaneously, the apical left ventricular vent was opened to maintain left ventricular pressure at 12 cm H₂O, and the right ventricle was vented into the pericardium through a right ventriculotomy. With the coronary occluder deflated, 2 liters of 0.9% NaCl with 25 mM KCl and 5 mM disodium EDTA were infused into the aortic root at a perfusion pressure of 70 mm Hg to produce diastolic arrest at a ventricular pressure of 12 cm H₂O. Immediately thereafter, 2 liters of 2% glutaraldehyde in sodium cacodylate buffer were infused into the aortic root. Physiologic measurements were recorded after 12 minutes of coronary occlusion, during diastolic arrest, and after glutaraldehyde infusion. All hearts were excised and stored in 0.1 M sodium cacodylate and 7.5% sucrose buffer.

In each open-chest study, tissue blocks were obtained from the ischemic left anterior descending coronary zone and from the nonischemic circumflex coronary region. Blocks were postfixed in OsO₄ in veronal acetate buffer and dehydrated in ethanol. After treatment with propylene oxide, the samples were embedded in Epon. Ultrathin sections were then prepared, carefully maintaining tissue block orientation so that sections were tangential to the in situ myocardium and parallel to the myofilaments. Sections were stained with uranyl acetate and lead citrate prior to taking photomicrographs on a Philips EM 300 electron microscope. From the control and ischemic zones of each dog, sarcomere length was measured as Z band separation for approximately 500 individual sarcomeres in each zone.

Data Analysis

Physiologic data were filtered with a 50 Hz low-pass analog filter and digitized at an 8-channel sweep speed of 200 Hz by an A/D converter (ADAC, model 1012, Woburn, Mass.). The A/D conversion time per channel was 30 microseconds, creating a phase delay between channels of less than 4.5 degrees. After data collection and storage on digital magnetic tape, data analysis was performed on a microprocessor (DEC, model PDP 11/23, Maynard, Mass.) using interactive programs developed in our laboratory.

Left ventricular transmural pressure was calculated as the difference between left ventricular and pleural pressures. The first time derivative of left ventricular transmural pressure (dP/dt) was determined from a running 5-point polyorthogonal transformation of the digital left ventricular pressure waveform. The cardiac cycle was defined using dP/dt, with diastole beginning at the first zero crossing of dP/dt after peak negative dP/dt and ending 40 msec prior to peak positive dP/dt. Beginning ejection was placed 20 msec after peak positive dP/dt, and end ejection was set 40 msec prior to peak negative dP/dt. This narrow definition of ejec-
tion was chosen to minimize effects of isovolumic segment length changes on ejection phase indexes during ischemia and has been shown not to differ significantly from systolic shortening in time course of recovery from reversible regional ischemia.

Ejection shortening was calculated as the change in myocardial segment length over the ejection period, and segmental stroke work was calculated for each cardiac cycle as the area enclosed by the segment length vs. left ventricular transmural pressure loop. The unstressed myocardial segment length ($L_0$) was determined from vena caval occlusion data (Figure 3) as the myocardial segment length at a diastolic left ventricular transmural pressure of 0 mm Hg. $L_0$ was defined at beginning diastole where $dP/dt$ was zero. Diastolic pressure-length curves were constructed using data from diastasis where ventricular filling rate was low and the effects of ventricular filling rate should be small. Diastasis was defined as late diastole where segment length plateaued and varied by less than 2%.

For raw hemodynamic data, statistical comparison of repeated means was performed using one-way analysis of covariance with preischemic control data as covariates. Comparison of repeated measurements expressed as percent of preischemic control was performed with one-way analysis of variance. Variability in $L_0$ was expressed as the variance not attributable to variance between dogs or between times. Linear regressions were compared by the method of Snedecor and Cochran. Unless otherwise stated, data are represented as means ± SEM.

**Results**

Typical analog recordings of ischemic and nonischemic segment lengths and pleural and left ventricular pressures are shown in Figure 4. In all studies, 15 minutes of coronary occlusion produced holosystolic bulging in the ischemic zone. Coronary reperfusion was accompanied by an initial period of transient hyperfunction of segment shortening in the ischemic zone followed by a deterioration of function and then a more gradual recovery of normal shortening over 24 hours of reperfusion. No dog displayed any gross or histochemical evidence of myocardial infarction at autopsy.

Mean hemodynamic variables from the 8 conscious dog studies are shown in Figure 5. No significant changes in heart rate occurred during ischemia or reperfusion ($p < 0.25$). Although all dogs were paced continuously at 120 beats per minute, some dogs displayed second-degree AV heart block with pacing during early reperfusion. Fifteen minutes of coronary occlusion significantly increased left ventricular end-diastolic pressure from 11 ± 1 to 16 ± 1 mm Hg while end-diastolic segment length in the ischemic zone rose from 13.5 ± 1.0 to 15.0 ± 1.1 mm. End-diastolic pressure subsequently returned to control values over the first hour of reperfusion. No significant change in mean peak systolic pressure or peak positive $dP/dt$ was observed ($p > 0.25$).

Coronary occlusion decreased ejection shortening and stroke work in the ischemic zone to 10 ± 8% and 15 ± 6% of control values, respectively (Figure 6), and increased unstressed diastolic segment length, $L_0$, by 16 ± 4% (termed diastolic creep). All parameters recovered at least 50% of the ischemia-induced deficit by 15 minutes of reperfusion. By 12 hours of reperfusion, ejection shortening and $L_0$ were not significantly different from control values. Stroke work improved during reperfusion with significant depression remaining at 24 hours but resolving by 4 days of reperfusion when stroke work returned to 103 ± 7% of control values. No significant changes in stroke work, ejection shortening, or $L_0$ were observed in the nonischemic zone throughout the study ($p > 0.25$). The variability...
in $L_0$ in the nonischemic zone assessed over the 24 hours of study was 5.6%, compared with the 16% change in $L_0$ produced by regional ischemia.

Examination of data from all studies during control conditions, ischemia, and throughout reperfusion (Figure 7) revealed significant inverse linear correlations between recovery of systolic function and reversal of diastolic creep. The correlation was significantly greater using ejection shortening instead of stroke work to assess systolic function ($p < 0.05$) with correlation coefficients of -0.810 and -0.679, respectively. The right panels of Figure 7 suggest that the weaker correlation using stroke work resulted partially from a disproportionate recovery of stroke work during the period of initial hyperfunction at 15 minutes of reperfusion.

The inverse correlation between diastolic creep (percent increase in $L_0$) and systolic function (stroke work at a constant end-diastolic length) during altered inotropic state or loading conditions is illustrated in Figure 8 ($r = -0.847$, $p < 0.05$). Both initial reperfusion hyperfunction and dopamine increased stroke work in the reperfused ischemic zone by 32 ± 12% and 178 ± 38%, respectively, while decreasing diastolic creep or $L_0$ by 2.3 ± 1.0 and 6.8 ± 1.1% of control values, respectively. Nitroprusside infusion increased stroke work at a constant end-diastolic length in the postischemic zone by 42 ± 17% while decreasing $L_0$ by 4 ± 1%. Conversely, phenylephrine decreased stroke work by 29 ± 14% and increased $L_0$ by 5 ± 2%. Mean left ventricular ejection pressures during control conditions and with infusion of nitroprusside and phenylephrine were 122 ± 6, 83 ± 8, and 168 ± 8 mm Hg, respectively. Mean heart rate with autonomic blockade did not vary significantly ($p > 0.2$) and was 156 ± 11, 173 ± 7, and 168 ± 12 beats per minute under control, nitroprusside, and phenylephrine conditions, respectively. During either nitroprusside or phenylephrine infusion, changes in myocardial creep occurred rapidly within 3–5 minutes and were easily reversible. Infusion of nitroprusside and phenylephrine did not affect the slope of the stroke work vs. end-diastolic length relation ($p > 0.05$, Table 1). The $x$ intercept, however, was decreased by nitroprusside and increased by phenylephrine, reflecting a leftward or rightward shift of the entire curve (Figure 9).

The effect of altered inotropic state on diastolic properties is illustrated in Figure 10, which displays diastolic pressure-dimension relations during vena ca-
val occlusions. In Panel A, 30 minutes of dopamine infusion after 60 minutes of reperfusion shifted the regional compliance curve leftward. Thirty minutes after stopping dopamine, the diastolic compliance curve had shifted back to the predopamine position. Panel B similarly shows that initial reperfusion hyperfunction shifted the regional diastolic compliance curve leftward within 3 minutes of reperfusion and that the curve again moved rightward by 15 minutes of reperfusion. Thus, both diastolic pressure-length curves (Figure 10) and unstressed segment length, L₀ (Figure 8), demonstrated sensitivity of regional myocardial diastolic properties to alterations in inotropic state after ischemic injury.

**Electron Microscopic Data**

Representative electron micrographs of ischemic and nonischemic myocardium from the same dog are shown in Figure 11. Ischemic tissue tended to display relaxation of the sarcomeres with widening of the I bands (Panel B). Occasional disruption of structures surrounding the myofilaments was observed, but in no case were there any findings of infarction or irreversible ischemic injury. Electron micrographs of tissue from the nonischemic zone were entirely normal (Panel A).

As shown by electron microscopy, mean epicardial sarcomere length was significantly greater in the ischemic region than in the nonischemic zone (2.45 ± 0.12 μm vs. 2.34 ± 0.08 μm, p < 0.05). Endocardial length also tended to be greater in the ischemic zone (2.36 ± 0.13 μm vs. 2.28 ± 0.06 μm), although this difference was not statistically significant (p = 0.5). Finally, mean sarcomere length was greater in the epicardium than in the endocardium (p < 0.05 ischemic zone, p = 0.5 nonischemic zone).

Sonomicrometry showed that diastolic segment length in tissue examined microscopically increased by 10 ± 2% in the ischemic zone relative to the nonischemic zone (p < 0.05). As Table 2 demonstrates, potassium arrest and glutaraldehyde fixation had no significant effect on relative segment lengthening in the ischemic zone. The 10% increase in segment length measured by sonomicrometry corresponded to a 5 ± 2% increase in the ischemic to nonischemic sarcomere length ratio seen on electron microscopy.

### Table 1. Effects of Nitroprusside and Phenylephrine on X Intercept and Slope of Stroke Work vs. End-Diastolic Length Relation

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All data taken after 15 minutes of coronary occlusion and 15 minutes of reperfusion. *p < 0.05 vs. control.
Discussion

In engineering terms, a material that demonstrates plastic deformation or stretch under constant load over time is said to display creep. Creep has been demonstrated in myocardium under both ischemic and nonischemic conditions. Pinto and Patitucci measured creep rates in nonischemic isolated cardiac muscle of 2%/100 sec at loads of $3-7 \times 10^4$ dyne/cm², which approximates mean diastolic wall stress in the intact heart. In volume-overloaded intact hearts, Dodge et al., Ross et al., and Crozatier et al. found creep in the form of rightward shift of diastolic and end-systolic pressure-volume curves. Myocardial ischemia has been shown to produce creep or rightward shift of regional diastolic pressure-length curves, global diastolic pressure-volume curves, and end-systolic pressure-volume relations. The term creep was first applied to ischemia-induced changes in the diastolic pressure-length relations by Edwards et al. and Arentzen et al.

As defined by Edwards et al., unstressed diastolic segment length ($L_0$) provided a practical measure of...
diastolic creep while eliminating the effects of ventricular filling on segment length. Moreover, $L_0$ had the additional physiologic basis of correlating well with the segment length at which no segmental stroke work is performed. Although $L_0$ occurred at a point where segment length was changing rapidly (Figure 3), determination of $L_0$ was simple and reproducible with a 5.6% variability, sufficiently small to detect the 16% change in $L_0$ occurring with ischemic injury. $L_0$ should be insensitive to dynamic changes in segment length or ventricular pressure since the viscoelastic contribution to the passive properties of cardiac muscle is small. While the technique of measuring creep and $L_0$ by vena caval occlusion could have biased creep measurements because of the afterload dependence of creep, the afterload changes produced by rapid vena caval occlusion were relatively minor. In short, the technique of assessing creep by measuring $L_0$ should be adequate for detecting directional changes in creep but might not yield absolute values totally comparable to those obtained from static, isolated tissue experiments.

Several studies have examined the nature of creep at the cellular level. Spiro et al showed that muscle length and thereby myocardial segment length directly reflect sarcomere length. Predictably, therefore, electron microscopy has demonstrated that myofilament relaxation with widened I bands can accompany transient ischemia and may represent the histologic correlate of creep. Ross et al also found that creep induced by volume overload correlated with both increased sarcomere length and disarray of the myofilaments. In nonischemic insect flight muscle and rabbit skeletal muscle, pyrophosphate, ADP, and B,G-imido-ATP produced creep representing 0.1–0.5% of muscle length, probably from reorientation of myosin filament heads without breaking actin-myosin bonds. On the other hand, the 16% change in muscle length observed during ischemia in this study would require sliding of actin on myosin filaments since electron microscopy has not revealed significant ischemia-induced elongation or malalignment of the actin and myosin filaments themselves. Available evidence suggests, therefore, that creep represents a degree of disengagement of the actin-myosin filaments manifested by rightward shift of the muscle force-length curve.

Figure 11. Typical electron micrographs of nonischemic (Panel A) and ischemic (Panel B) myocardium after 15 minutes of coronary occlusion. Note that ischemic tissue displays myofilament relaxation with increased Z band separation and widening of I bands.
Data presented herein indicated that creep measured by sonomicrometry and myofilament relaxation by electron microscopy did correlate and probably reflected the same phenomenon. The significantly greater creep occurring in muscle length compared with sarcomere length (10 ± 2% vs. 5 ± 2%, \( p < 0.05 \)) may have resulted from transmural sarcomere recruitment and nonhomogeneous recruitment of buckled fibers, each of which would minimize sarcomere lengthening as ventricular volume and segment length increased. Indeed, electron microscopic data from ischemic tissue in the present study were consistent with transmural sarcomere recruitment in that epicardial sarcomere lengths were greater than in the endocardium (Table 2).

Figures 7 and 8 established several basic determinants of postischemic myocardial creep. First, ischemia-induced creep was load dependent, as might have been expected, since creep itself was defined as a load-induced plastic deformation. Second, Figures 7 and 8 demonstrated a direct correlation between systolic dysfunction and diastolic creep throughout reperfusion and under conditions of altered load and inotropic state. The minor deviations from linear correlation observed for stroke work as opposed to ejection shortening (Figure 7) may have resulted from the many factors such as preload that influence stroke work or ejection shortening while having little effect on diastolic properties. Although a measure of systolic function independent of preload might more clearly demonstrate the relation between creep and systolic dysfunction, no such measure is available at present.

In contrast to the present study, other reports have contained data suggesting apparent dissociation between postschemic systolic and diastropic properties. Using a model of pacing-induced "demand ischemia," Momomura et al described the phenomenon of incomplete relaxation and impaired ventricular distensibility that occurred in the relative absence of systolic dysfunction. However, the impaired distensibility observed by Momomura et al could not be distinguished from abnormally prolonged relaxation or failure to achieve diastole, defined as that period of the cardiac cycle where force generation is absent. Therefore, this impaired distensibility may have been neither a diastolic phenomenon nor a demonstration of diastolic creep in the absence of systolic dysfunction. Momomura et al also observed an apparent absence of creep accompanying systolic dysfunction after 3 minutes of coronary occlusion. This observation may have resulted from collecting data over an inadequate and limited preload range. Figures 9 and 10 dramatize the fact that data collection over a wide range of preload can be essential to detect and quantify the subtle length changes that creep may induce. Thus, the dissociation between postschemic systolic and diastrophic properties described in previous studies may be more apparent than real.

The fact that systolic dysfunction and diastolic creep do correlate suggests that either a common underlying etiology was present or else interaction existed between creep and systolic dysfunction themselves. That systolic dysfunction contributed to diastolic creep was supported by the transient improvement in creep produced by inotropic interventions such as dopamine and reperfusion hyperfunction. That creep contributed to systolic dysfunction was supported by the marked afterload sensitivity of systolic function in postschemic myocardium (Figures 8 and 9), in contrast to the lesser afterload sensitivity of nonischemic myocardium. As Table 1 demonstrates, the postschemic effects of loading on systolic dysfunction in fact resulted from changes in the \( x \) intercept and not the slope of the stroke work vs. end-diastolic length relation. Because the \( x \) intercept has been shown to be equivalent to \( L_0 \), creep may be largely responsible for the afterload sensitivity of systolic function in ischemically injured myocardium. Other authors have found supportive evidence that even transient myocardial overstretch caused prolonged systolic dysfunction that could not be fully explained by myofilament disengagement or increased work.

If either creep or systolic dysfunction were not a primary cause of the other, each could have resulted from some third mechanism. Unlike other explanations, contractile protein malfunction is attractive as a possible common mechanism since the contractile elements are end-effectors for both systolic dysfunction and diastolic myofilament creep. Contractile protein malfunction could result from myosin ATPase inactivity, from deficiency of labile substrates such as ATP and ADP, or from increased cytosolic calcium levels. Because ischemia-induced creep was readily reversible in 3 to 30 minutes by change in inotropic

### Table 2. Ischemic/Nonischemic Myocardial Length Ratio by Ultrasonography and Electron Microscopy

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*\( p < 0.05 \) vs. 1.000.
state, labile substrate deficiency or excess is a more attractive explanation than protein disruption, which might require slower repair processes. Clearly, further work is needed to link postischemic dysfunction directly to ischemia-induced metabolic disturbances.

The existence of myocardial creep has significant physiologic implications beyond the cellular mechanisms of myocardial injury. From Laplace’s law, creep may contribute to aneurysm formation by augmenting wall stress in ischemic myocardium through increased radius of curvature and decreased wall thickness. The existence of creep may alter static myocardial compliance (\\(dP/dV)\\) while not affecting dynamic compliance (\\(dV/dP)\\), indicating a need to specify carefully whether the terms, compliance and stiffness, reflect static or dynamic values in the presence of regional creep.

Finally, the dynamic nature of postischemic \(L_g\\) suggests that diastolic properties such as creep may not be entirely passive after ischemic injury. Although it has been shown that physiologic changes in inotropic state and loading do not affect diastolic properties in nonischemic settings,\(^{11}\\) Figures 8, 9, and 10 demonstrate that after ischemic injury, both loading conditions and inotropic state can significantly alter diastolic properties. Although previous authors\(^{12}\\) found that both nitroprusside and isoproterenol may increase systolic shortening and decrease end-diastolic segment length in ischemic and border zones, the relative roles of creep and changing end-diastolic pressure were not identified. The coupling between systolic and diastolic behavior after ischemic injury, therefore, indicates that unlike nonischemic myocardium, postischemic myocardium possesses diastolic properties that are not strictly passive, i.e., not independent of inotropic state. This active component of postischemic diastolic properties has previously been unrecognized and again indicates significant interrelation between the cellular mechanisms of systolic and diastolic properties after ischemic myocardial injury.

In conclusion, myocardium undergoing regional ischemic injury displays load-dependent creep that correlates with myofilament relaxation on electron microscopy. Ischemia-induced diastolic creep is rapidly reversible by changes in inotropic state, demonstrating that postischemic diastolic properties are not entirely passive. Finally, a direct correlation exists between creep and systolic dysfunction throughout reperfusion and during changes in load and inotropic state, suggesting a close link between ischemia-induced diastolic myocardial creep and systolic dysfunction at the sarcomere level. Recognition of creep is essential, therefore, to understanding physiologic events during regional myocardial ischemia and may be useful in directing future research to bridge the gap between ischemic myocardial function and metabolism.

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**KEY WORDS** • creep • ischemia • regional ventricular function
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