Altered Load Dependence of Postischemic Myocardium

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Intermittent myocardial ischemia can produce areas of postischemic ("stunned") myocardium in the heart of the human with coronary artery disease. These areas are no longer ischemic, but have diminished contractile performance. Although the effects of loading conditions on systolic contraction of normal, ischemic, and failing myocardium have been investigated in great detail, the way in which load affects contraction of postischemic myocardium is not known. The aim of this study was to determine in anesthetized dogs how loading conditions affect the systolic function of a region of myocardium after 10 min of ischemia and 1 h of reperfusion. Sets of piezoelectric crystals were implanted in a test zone and in a remote zone of myocardium. Measurements of systolic wall thickening were made during nine combinations of left atrial pressure (5, 6, and 9 cmH₂O) and mean arterial pressure (70, 90, and 110 mmHg). One set of measurements was made under baseline conditions, and a second set was made after 10 min of coronary occlusion and 1 h of reperfusion. Ischemia and reperfusion reduced wall thickening in the test zone 36 ± 3% and diminished the response to increases in preload. In contrast, the response of the test zone to changes in afterload was unchanged. An interaction between the test zone (in which depressed contraction was observed) and the surrounding myocardium (in which enhanced function was observed) produced the appearance of a regional wall motion abnormality as afterload increased. These results emphasize that the load dependence of postischemic myocardium differs from that of normal myocardium and must be taken into account in clinical studies in which regional contraction is used to monitor the heart for ischemia. (Key words: Complications, misidentification; regional wall motion abnormality. Heart: afterload; blood pressure; contractility; preload; myocardial function; regional myocardial performance. Monitoring: echocardiography.)

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AN IMPROVED UNDERSTANDING of the mechanisms causing intraoperative myocardial ischemia requires a sensitive and specific diagnostic tool for detecting and quantifying myocardial ischemia. Abnormalities of myocardial contraction, especially when ischemia involves just one area of the left ventricle, can be detected by cardiokymography or echocardiography. These regional wall motion abnormalities (RWMA) occur soon after the onset of ischemia during procedures such as coronary angioplasty and provide a sensitive, graded measure of the degree of ischemia in conditions producing a primary decrease in myocardial blood flow.1–3 However, measures of contractile performance are affected also by the length of the fibers in the ventricular wall just before systole (preload) and by the wall stress encountered during the ejection phase of contraction (afterload). Although the load dependence of ventricular contraction has been recognized as a factor limiting the specificity of RWMA in the diagnosis of intraoperative ischemia,4 no previous study has systematically investigated the phenomenon.

The goal of this study was to determine how loading conditions affect contraction of a region of myocardium that is injured by 10 min of total coronary occlusion and then reperfused for 1 h. This model was designed to mimic the clinical situation in which coronary spasm or platelet aggregation at the site of an atherosclerotic stenosis produces transient flow reductions that lead to areas of viable but dysfunctional myocardium. The question was not "How does load affect ischemia?" but rather "How do loading conditions affect the contraction of postischemic myocardium?".

Materials and Methods

PREPARATION

The protocol was approved by the institutional Animal Care and Use Committee. Eight mongrel dogs were sedated with morphine sulfate (2.75 mg·kg⁻¹subcutaneously) and then anesthetized with α chloralose (100 mg·kg⁻¹iv). Anesthesia was maintained with α chloralose (10 mg·kg⁻¹·h⁻¹). The trachea was intubated, and the dogs' lungs were ventilated with oxygen-enriched room air (Harvard) to maintain arterial carbon dioxide tension (Paco₂) between 35 and 45 mmHg and arterial oxygen tension (Pao₂) above 100 mmHg. The dogs were kept warm (rectal temperature 38–39°C) with a heating pad and lamp. A dilute solution of sodium bicarbonate (150 mM) was infused at 5 ml·h⁻¹ to counteract the metabolic acidosis that accompanies chloralose anesthesia in this species.5
Arterial pressure was measured through a polyethylene tube (PE 260) introduced into the arch of the aorta via the left brachial artery using a saline-filled transducer (Gould). An analog-averaging circuit with a time constant of 2 s was used to determine mean arterial pressure (MAP). A catheter-tip transducer (Millar) was introduced into the left ventricle via the right carotid artery and used to measure left ventricular (LV) pressure. The LV pressure signal was differentiated to provide a timing signal for sonomicrometer measurements (see below). A three-lead surface electrocardiogram (ECG) was recorded.

Halothane (1%) was administered through a non-rebreathing circuit to ensure adequate anesthesia, and a thoracotomy was performed. The left chest was entered through the fifth intercostal space. Formalin (0.1 ml) was injected into the area of the atrioventricular node to cause a complete heart block. Occasionally, several injections were necessary to achieve a block, but no more than 0.5 ml formalin was used. Digoxin (50 μg, intravenously [iv]) was given to prevent arrhythmia. The heart was paced throughout the experiment at 100 beats per min with a lead sutured to the apex of the right ventricle. A ground electrode was connected to the chest wall.

In four dogs, a 0.5–0.75-cm section of the proximal left anterior descending coronary artery (LAD) was dissected free from the surrounding tissue, and a heavy suture was placed around the vessel for later use as a snare occluder. In the remaining four dogs, a similar procedure was carried out on the proximal circumflex artery (LCX). Experiments were done with both the LAD and the LCX perfusion zones as "test" zones because they differ in collateral flow, recovery from ischemia, and contraction pattern. Temporary (15–20-s) occlusion of these vessels caused the distal perfusion zone to become cyanotic and dyskinetic and allowed accurate placement of piezoelectric transducers in the center of the affected area. A flat 5-mHz piezoelectric crystal with an epoxy lens was tunneled tangentially down to the subendocardium, and a second crystal was sutured to the epicardium for measurement of LV wall thickness. The distance between the crystals was minimized to enhance the likelihood that the crystals would be oriented perpendicular to the ventricular wall. A second pair of crystals was implanted in an area of myocardium remote from the test area. This set of crystals was located in the center of the perfusion territory of the control artery to avoid the border zone of depressed function that surrounds an ischemic area. The location of the inner crystal and the perpendicular orientation of each pair of crystals relative to the epicardial surface of the heart was confirmed at autopsy.

A small Tygon tube with a side hole and an end hole was inserted 2 cm into the left atrium through a purse-string suture in the appendage for measurement of left atrial pressure (LAP). The pericardium was carefully reapproximated but not closed tightly. Bupivacaine (0.25%, 1–2 ml at each site) was injected at the fourth, fifth, and sixth intercostal spaces posterior to the incision to obtain intercostal blocks. These injections were done to minimize incisional pain. The lungs were reexpanded. The chest was closed in layers. The coronary snare was led to the exterior through a small intercostal incision. A pleural drain was attached to an underwater seal. Halothane was discontinued.

Heparin (750 U·kg⁻¹·h⁻¹, iv bolus, plus 250 U·kg⁻¹·h⁻¹, iv) was given, and a large-bore shunt installed between a femoral artery and femoral vein. Flow through the shunt was controlled by a screw clamp. A 1:1 pressurized blood reservoir was connected to the other femoral artery. Blood flowed from the animal into the reservoir if MAP exceeded reservoir pressure, and vice versa. Dextran (6%, 150 ml) was given to expand the blood volume.

**EXPERIMENTAL PROTOCOL**

Measurements of regional wall thickness were made during transient steady states lasting 20–30 s at each of nine hemodynamic conditions: combinations of "target" LAPs of 3, 6, and 9 cmH₂O and target MAPs of 70, 90, and 110 mmHg. These nine conditions were produced in random order. The MAP–LAP combinations of 3–70, 6–90, and 9–110 usually were easy to achieve with withdrawal or infusion of blood. To achieve low MAP and high LAP, the arterial-to-venous shunt was opened; blood was infused from the reservoir; and small bolus doses of sodium nitroprusside (50–200 μg) were administered. To achieve high MAP and low LAP, the shunt was closed; blood was withdrawn into the reservoir; and small bolus doses of angiotensin (0.5–4 μg) were administered. The amount of these drugs necessary to achieve the hemodynamic endpoints was similar before and after ischemia and reperfusion. Regional contraction changed rapidly with changes in loading conditions; a full response occurred within four to five heart beats after an abrupt change in loading conditions. Investigators using inferior vena caval occlusion to construct pressure–volume loops would argue that the response to changes in load should be practically instantaneous. The responses were maintained as long as hemodynamic conditions remained steady. This study differs from experiments in which regional contraction reflects ischemia, and a certain period of progressive changes in contractile performance is observed after the onset of ischemia.

After the initial nine measurements were obtained, MAP was set to 75–80 mmHg by use of the pressurized blood reservoir in an attempt to provide uniform myocardial oxygen demand and collateral blood flow, and then the artery supplying the test zone was totally occluded with the snare for exactly 10 min. After the ischemic pe-
rior, the snare was removed. Resumption of coronary flow was not measured directly but was inferred from the rapid improvement in segmental function that occurred in all dogs after release of the snare. An intramural ECG obtained using the subendocardial crystal as the exploring electrode demonstrated ST-segment elevation during occlusion but rapid return to baseline after release of the occluder in three dogs. Reperfusion continued for 1 h to allow contraction of the postischemic myocardium to stabilize before the second set of nine measurements was made.

As a partial check for deterioration with time during the second set of measurements, the 90–6 MAP–LAP combination was produced first and then again after the other eight combinations in all dogs. A paired comparison revealed no significant differences in systolic wall thickening between the two measurement periods ($t = 0.181$, degrees of freedom (df) = 7), and so the values were averaged. The other MAP–LAP combinations were obtained in random order.

After the second set of measurements, the dog was killed with injection of a saturated solution of potassium chloride (1 ml·kg$^{-1}$). The heart was removed, and thin, transmural sections of the test zone were incubated for 10 min in warm triphenyltetrazolium chloride (TTC) (1.5% solution in 20 mM potassium phosphate buffer). All tissue was stained brick-red by reaction of TTC with vital tissue. In no dog was there evidence of infarction in the test zone.

**DATA ANALYSIS**

Wall thickness in the test and in the remote zone was measured with a multichannel sonomicrometer (Triton). These measurements and the hemodynamic data were recorded on an oscillograph (Gould) at paper speeds of 100 mm·min$^{-1}$ except for short, eight-ten-beat segments at 100 mm·s$^{-1}$ at each MAP–LAP combination. End-diastolic wall thickness (EDT) was taken at the time of the ventricular pacemaker spike observed in the surface ECG. Thickness at the start of ventricular ejection (EST) was obtained by determining aortic end-diastolic pressure and then using this pressure in the LV pressure signal to time aortic-valve opening. End-systolic wall thickness (EST) was taken 20 ms before peak negative rate of change of LV pressure (dP/dt). These values were obtained for four to six heart beats during each measurement period and were averaged. Beats in which atrial contraction affected end-diastolic length at the time of the pacemaker spike were not used in the analysis. The effects of ventilation on wall thickening were small (fig. A, appendix), probably because small tidal volumes and fast respiratory rates (15–20 breaths per min) were used. Identical values were obtained from the crystal set located in the remote zone. The absolute change in thickness during systole was calculated as EST − EDT. The absolute change in thickness during LV ejection was calculated as EST − EJT. Percent wall thickening during systole was calculated as (EST − EDT)/EDT) × 100.

Hemodynamic and wall thickness data were analyzed by computer with a standard statistical package (Statistical Package for Social Sciences—Personal Computer Version 1.1). Analysis of variance was used to test the hypotheses that preload (LAP), afterload (MAP), the location of the test area, or ischemia and reperfusion affect regional systolic wall thickening. Regression analysis with a "dummy variable" was used to determine if regional compliance (EDT vs. LAP) was altered in the postischemic state. A significance level of $P < 0.05$ was used.

The hypothesis that ischemia and reperfusion affected the sensitivity of the test zone to afterload was examined by a paired comparison ($t$ statistic) of the slopes of the relations between systolic wall thickening and MAP obtained before and after ischemia and reperfusion in individual dogs.

**Results**

Independent control of MAP and LAP was a key aspect of this study. While hemodynamic control was reasonably accurate, a distribution of MAP and LAP values around the "target" values was unavoidable. These distributions are presented in figure 1. Visual inspection confirms that values very close to the target values were obtained in most cases, and the distribution of values around the target value were similar in the control and the postischemic states. Because of the accuracy of hemodynamic control, the continuous pressure data were recoded into categorical values for MAP (70 mmHg = 1; 90 mmHg = 2; etc.) and LAP (3 cmH$_2$O = 1, etc.). This procedure permitted use of analysis of variance (ANOVA), a powerful statistical approach.

Systolic wall thickening in the test area (averaged over all MAP–LAP combinations) was reduced from 34.5 ± 3.0% (standard error) to 22.0 ± 3.4% (a 36% decrease) after 10 min of total ischemia and 1 h of reperfusion ($P < 0.001$, table 1). The ANOVA model demonstrated that systolic wall thickening in the test area was inversely related to MAP both before ($P = 0.008$) and after ($P = 0.014$) ischemia and reperfusion. A paired comparison of the relation between systolic wall thickening and MAP in individual animals confirmed that the slope was not changed by ischemia and reperfusion ($t = 0.39$, df = 7), indicating unchanged sensitivity to afterload. In the ANOVA model, systolic wall thickening was related positively to LAP ($P = 0.003$) before ischemia and reperfusion, but the correlation was nonsignificant afterward (fig. 2).

The location of the test zone (LAD vs. LCX) was not
a significant factor in the ANOVA model; however, the two-way interaction term between location and treatment was significant ($P < 0.001$). This interaction occurred because ischemia and reperfusion produced a greater decrease in systolic wall thickening when the LAD was occluded (from a mean of 37 to 19%, averaged over all nine MAP–LAP combinations) compared to a smaller change when the LCX was occluded (from 32 to 25%). The second-order interaction terms of location with MAP and LAP were not significant, indicating that a similar response to preload and afterload occurred in the LAD and LCX regions.

Statistical results similar to those obtained with normalized systolic wall thickening were obtained when the absolute value of thickening during systole (in millimeters; table 2) was used as the dependent variable in ANOVA. Similar results also were obtained when the absolute value of thickening that occurred during ejection (in millimeters) was analyzed (table 3). A similar pattern of significance was found also in a multivariable regression analysis using raw (instead of categorical) MAP and LAP values.

### Table 1. Systolic Wall Thickening (Percent of End-diastolic Thickness)

<table>
<thead>
<tr>
<th>LAP (cm H$_2$O)</th>
<th>Control (MAP [mmHg])</th>
<th>Postischemic (MAP [mmHg])</th>
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<tbody>
<tr>
<td></td>
<td>70</td>
<td>90</td>
</tr>
<tr>
<td>Test zone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>30 ± 2</td>
<td>29 ± 3</td>
</tr>
<tr>
<td>6</td>
<td>38 ± 3</td>
<td>32 ± 2</td>
</tr>
<tr>
<td>9</td>
<td>44 ± 2</td>
<td>42 ± 3</td>
</tr>
<tr>
<td>Remote zone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>24 ± 2</td>
<td>22 ± 2</td>
</tr>
<tr>
<td>6</td>
<td>29 ± 3</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>9</td>
<td>35 ± 5</td>
<td>35 ± 5</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

MAP = mean arterial pressure; LAP = left atrial pressure.

ANOVA revealed a significant effect both of LAP and of MAP on systolic wall thickening before ischemia and reperfusion. The response to LAP was nonsignificant after ischemia and reperfusion, but the response to MAP was unchanged.
Another multivariable regression model using EDT instead of LAP as a measure of preload produced virtually identical results—retention of response to afterload and loss of response to preload.

The relationship between EDT and LAP, reflecting LV diastolic compliance, was not affected by ischemia and reperfusion (fig. 3). This conclusion was reached by two separate statistical analyses. First, it was determined that a semilogarithmic plot of LAP versus EDT was linear, had high correlation coefficients (0.8–0.96) in individual animals, and was better fit to the data than were a variety of exponential relationships. The slopes and intercepts of these semilogarithmic plots were determined in each animal before and after ischemia and reperfusion. A paired comparison demonstrated no change in slope (t = 0.18, df = 7) or intercept (t = 0.13, df = 7). Second, multivariable regression analysis with a dummy variable was unable to find an effect on the relation of EDT to lnLAP that could be attributed either to time or to ischemia and reperfusion. (The equation produced was: lnLAP = −1.15 EDT + 11.12; P < 0.0001. The dummy variable was not selected for the model and had a P value of 0.73.) Data from one dog are shown in figure 3 as an example of the lack of change in regional compliance. Complete data for the test and remote zones are given in table 4.

Contraction in the remote zone increased slightly after ischemia and reperfusion of the test zone (table 1). The grand mean (averaged over all values of MAP and LAP) for systolic wall thickening in this zone increased from 28 to 30% (P < 0.05). The combined effects of enhanced function in the remote zone and reduced function in the test area produced an heterogeneous global contraction pattern after ischemia and reperfusion. When the ratio of systolic wall thickening in the test zone to that in the remote zone was plotted against MAP, a linear relation with a slope not different from zero was obtained before ischemia and reperfusion. In contrast, after ischemia and reperfusion, the slope of the relation was significantly less than zero (P < 0.05; fig. 4). This result indicates that increases in MAP accentuated regional contractile differences.

Discussion

Regional myocardial contraction was reduced on average 36% by 10 min of total coronary occlusion followed by 1 h of reperfusion. The response of postischemic myocardium to increases in preload (as reflected by LAP) was reduced by ischemia and reperfusion, but the response to increases in afterload (as reflected by MAP) was unchanged. An heterogeneous contraction pattern developed when MAP increased because of an interaction of the postischemic area with surrounding myocardium.
**FIG. 3.** Regional myocardial compliance was unchanged by ischemia and reperfusion for all dogs, as illustrated by the data from one dog. The ventricular wall thinned as LAP increased. The lack of an effect on the relationship between EDT (assumed to be inversely proportional to fiber length) and distending pressure indicates that ischemia and reperfusion altered neither the stiffness of the tissue nor its tendency to deform under low loads (creep).

**ASSUMPTIONS**

The interpretation of these results depends in large measure on the correctness of the assumption inherent in the experimental design.

We assumed that ischemia was, in fact, limited to the period of coronary occlusion and did not continue into the postischemic period. Several lines of evidence support this assumption. Systolic contraction in the test area returned rapidly (over 10–30 s) to preocclusion values in all dogs after following snare release, and a unipolar ECG obtained from the subendocardial crystal in the ischemic area of three dogs showed rapid resolution of ST-segment elevation. Absence of necrosis with TTC staining provides further evidence that ischemia was of limited duration. Another study has shown that lactate production ceases rapidly and that little metabolic evidence of ischemia is present 30 min after reperfusion.\(^8\)

We also assumed that contraction of the postischemic zone was stable when the measurements were made. The natural history of contraction of postischemic myocardium as well as observations in the current study (data not shown) support this concept. Our experiment involved a 10-min coronary occlusion during which normal systolic

**FIG. 4.** Systolic wall thickness of the test zone was 130–140% of that observed in the remote zone under control conditions, probably reflecting the location of crystals or heterogeneity of regional contraction. During control conditions, contraction in both zones was affected equally by increases in afterload. In contrast, after ischemia and reperfusion, systolic wall thickening decreased in the test zone and increased in the remote zone. These changes reflected a series interaction between strong and weak myocardial regions and produced the appearance of a regional wall motion abnormality as MAP increased.

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**TABLE 4. End-diastolic Thickness (mm)**

<table>
<thead>
<tr>
<th>LAP (cm H₂O)</th>
<th>Control (MAP [mmHg])</th>
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<th></th>
<th>Postischemic (MAP [mmHg])</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Test zone</td>
<td>70</td>
<td>90</td>
<td>110</td>
<td>70</td>
<td>90</td>
<td>110</td>
</tr>
<tr>
<td>3</td>
<td>10.1 ± 0.5</td>
<td>9.8 ± 0.5</td>
<td>9.8 ± 0.5</td>
<td>9.9 ± 0.5</td>
<td>9.9 ± 0.5</td>
<td>9.7 ± 0.4</td>
</tr>
<tr>
<td>6</td>
<td>9.4 ± 0.4</td>
<td>9.1 ± 0.4</td>
<td>9.1 ± 0.4</td>
<td>9.2 ± 0.4</td>
<td>9.1 ± 0.4</td>
<td>8.9 ± 0.4</td>
</tr>
<tr>
<td>9</td>
<td>8.9 ± 0.4</td>
<td>8.6 ± 0.3</td>
<td>8.6 ± 0.4</td>
<td>8.7 ± 0.4</td>
<td>8.5 ± 0.4</td>
<td>8.5 ± 0.4</td>
</tr>
<tr>
<td>Remote zone</td>
<td>3</td>
<td>10.0 ± 0.6</td>
<td>9.8 ± 0.6</td>
<td>9.8 ± 0.5</td>
<td>9.9 ± 0.5</td>
<td>9.8 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>9.3 ± 0.4</td>
<td>9.1 ± 0.4</td>
<td>8.8 ± 0.4</td>
<td>9.2 ± 0.4</td>
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<tr>
<td></td>
<td>9</td>
<td>8.9 ± 0.4</td>
<td>8.7 ± 0.4</td>
<td>8.6 ± 0.4</td>
<td>8.8 ± 0.5</td>
<td>8.5 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SEM. MAP = mean arterial pressure; LAP = left atrial pressure.
thickening in the test zone was replaced by akinnesia or dyskinesia. After reperfusion, systolic wall thickening rapidly returned to normal but then gradually declined over 30–45 min. In part, these dynamic events probably result from coronary hyperemia during early reperfusion. The excessive coronary flow improves regional function through a “garden-hose” effect.2–11 Although we did not measure coronary flow directly, it is reasonable to assume that flow had returned to baseline by 1 h after reperfusion.12 Our measurements were made during a 20–30-min period that began 1 h after reperfusion. Other studies have shown that regional function of posts ischemic myocardium is stable between 1 and 4 h after reperfusion.13,14 The absence of significant deterioration in the contraction of the remote zone provides further evidence against a large time effect; however, no sham experiments were done to assess the stability of the preparation.

We assumed that the small intravenous doses of sodium nitroprusside and angiotensin used to alter arterial tone and adjust MAP had no direct effect on myocardial contractility. Phenylinephrine, used in several pilot studies and then abandoned, produced a positive inotropic effect consistent with stimulation of myocardial ß receptors.15 Changes in arterial pressure may have influenced myocardial contraction indirectly, however, via the baroreceptor mechanism. Increases in arterial pressure may have lessened sympathetic tone and reduced inotropic state, whereas decreases in arterial pressure may have had the opposite effect. These baroreceptor-mediated changes in contraction would increase the apparent afterload-sensitivity of regional contraction, an effect that should have been of similar magnitude during control and posts ischemia measurements. If we had used very rapid changes in MAP, reflex effects might have been avoided altogether. We chose to use slow alterations in load and steady-state measurements to avoid the Anrep effect16 and to mimic more closely the conditions in clinical anesthesia.

We made the assumption that ventricular pacing would not seriously affect the contraction pattern of the LV. Independent control of heart rate aided adjustment of MAP and LAP and avoided rate-related effects on regional contraction (the Treppe phenomenon) and on ventricular filling. The pacing lead was attached to the apex of the right ventricle in order to obtain a reasonably uniform depolarization of the left ventricle via the Purkinje system. Despite this effort, temporal heterogeneity of depolarization produced small effects on regional contraction manifest primarily during isovolumic contraction (fig. A, appendix). To minimize the effects of this phenomenon on the measurements, end-diastolic measurements were taken at the time of the pacemaker spike, well before contraction in any area of the heart had begun. Wall thickness was measured also at the time of aortic valve opening, and wall thickening during ejection was calculated with this value, because use of “ejection-phase” wall thickening has been recommended as means to avoid these problems.17 Calculated wall thickening during ejection (table 3) was 10–20% less than total wall thickening but was similarly affected by load.

A recurrent problem in studies of myocardial contraction is determining when systole ends. We made measurements 20 ms before peak negative LV dP/dt in order clearly to avoid events during diastole.18 The significance of wall thickening that occurs during early diastole while load is decreasing rapidly remains unknown.19 Other techniques for determining the end of systole have been used, but all techniques share the same problem in that all attempt to time regional contraction from global events, although even in normal hearts significant temporal heterogeneity of contraction exists.20

A major assumption of this study was that changes in wall thickness reflect alterations in the length and contractile activity of individual muscle fibers in the ventricular wall. When fibers shorten, the wall thickens, and during systole an inverse relationship exists between segment shortening and wall thickening. During diastole, fibers lengthen and the wall thins. The disadvantage of using wall thickness is that ischemia (and probably posts ischemic dysfunction) is most intense in the inner layers of the ventricular wall, so that measurements of wall thickening may underestimate events in the subendocardium. The conceptual advantage of thickness measurements is that they are less sensitive than are segment length measurements to the orientation of the fibers surrounding the crystal sets. One practical advantage is that wall thickening can be measured using conventional imaging techniques in humans. The leap from regional wall thickening to “regional wall motion” is a large one, and global contraction was not measured in the current study.

The conclusions of this study may have been different if we had used one of the more sophisticated measures of regional contraction, such as a midwall stress/strain analysis.21 The conceptual advantages of such an approach are clear, because the forces acting on individual sarcomeres during both diastole and systole depend not only on ventricular pressure but also on ventricular dimensions. Diastolic forces seem to have been well represented by LAP in the current study, since regional compliance during diastole was unchanged by ischemia and reperfusion. The phenomenon of diastolic creep,22,23 in which sarcomeres elongate as a result of ischemia and reperfusion and in which the material properties of ventricular muscle change, was not observed. The use of MAP as a measure of regional afterload is simplistic; however, there is not yet a satisfactory way to define regional afterload in an heterogeneous ventricle,24 in large part because the local radii of curvature are difficult to define.

This experiment controlled MAP as an easily measured
determinant of LV afterload. Some might argue that total peripheral resistance, aortic impedance, peak systolic pressure, or peak systolic wall stress are better indicators of afterload than is MAP. Fortunately, these factors usually covary, and the essence of the study was the comparison of postischemic values with control values. Afterload (however defined) was probably similar at each MAP-LAP combination before and after ischemia and reperfusion. Cardiac output was not determined in this study, and so no calculated resistance values are available.

Finally, digoxin (50 μg, iv) was given to each dog at the time of thoracotomy (about 2 h before any measurements were made) to decrease the incidence of arrhythmia. This small dose of digoxin is only about 20% of a loading dose for full stimulation but may have increased contraction. Such a positive inotropic effect should have been present throughout both measurement periods, however, since the elimination half-life of digoxin in dogs is over 20 h. 25 Well-maintained contraction in the remote zone supports this contention.

INTERPRETATION

When coronary artery lesions become unstable, episodic decreases in blood flow caused by coronary spasm, thrombosis, or platelet accumulation can occur, causing transient myocardial ischemia. In these patients, ambulatory ECG monitoring reveals numerous daily episodes of ST-segment depression. Between ischemic episodes, the myocardium is adequately perfused but may manifest prolonged dysfunction, 26,27 a situation that has been termed “stunned” or “postischemic” myocardial contraction. 28 The current study aimed to determine how changes in the loading conditions of the heart affect the contraction of postischemic areas of myocardium.

How does postischemic myocardium respond to changes in preload? Regional contraction, expressed as wall thickening during systole, increased about 40% with a 12% decrease in EDV (equivalent to a similar increase in preload) under control conditions. The response to a similar increase in preload was diminished to 23% after 10 min of ischemia and 1 h of reperfusion. This change is equivalent to a flattening of the Frank-Starling curve in a whole-heart preparation. The phenomenon cannot be explained by an alteration in diastolic compliance: neither a stiffening of the region due to edema 29 nor an increase in deformation due to creep 30,31 was observed. The relation between LA pressure and EDV was unchanged by ischemia and reperfusion (see Results section).

In one previous study of severely injured myocardium, there was less bulging during systole with increases in preload. 31 Although this finding may indicate increased “systolic function” with increased preload, it is more likely a passive effect. Higher preloads increase the stretch of elastic tissue in the postischemic zone and thus decrease bulging during the subsequent systole. Another study involving 1 h of normothermic global ischemia concluded that preload dependence was unchanged. 32 In that study, however, the data that were not normalized demonstrated a markedly diminished contractile response to increased preload after ischemia and reperfusion and therefore are consistent with the current findings.

The current results apply to clinical situations involving postischemic myocardium such as those encountered after coronary thrombosis with reperfusion, cardiac surgery with ischemic arrest, or cardiac transplantation. The findings suggest that augmenting preload is unlikely to improve contractile performance, and therefore that pharmacologic techniques should be used to increase intrinsic contractility and improve cardiac performance. In support of this hypothesis, other studies have demonstrated that postischemic myocardium has diminished contractile state but retained contractile reserve. 33,34 Although it might seem logical that increasing contractility would make the situation worse, administration of calcium or catecholamine drugs improves performance without evidence of worsening injury. 35,36

How does postischemic myocardium respond to increases in afterload? The diminished contractile response to increased preload of postischemic myocardium is similar to that seen in patients who have cardiac failure. A second attribute of cardiac failure is an enhanced sensitivity to increases in afterload. 37 This sensitivity is the basis for strategies to improve global cardiac function by reducing afterload. 38 Although the similarity between postischemic and failing myocardium suggests that contraction of postischemic myocardium might also be more sensitive to afterload than is normal myocardium, the current results do not support this idea. Afterload sensitivity was unchanged after ischemia and reperfusion (figs. 2 and 5). One might argue that the experimental protocol of the current study was not right to produce enhanced afterload sensitivity. Yet a moderate degree of ischemic injury, as produced in the current study, should have a high likelihood of enhanced sensitivity. Less-severely injured myocardium would have an afterload sensitivity similar to normal myocardium, and more severely injured myocardium would have reduced contractile function at all afterloads. Therefore, it seems unlikely that a short-term ischemic event can increase regional afterload sensitivity, although such a change might have been observed if a larger amount of myocardium had been involved.

Despite an unchanged regional sensitivity to changes in afterload, the altered global contraction pattern after ischemia and reperfusion produced the appearance of a RWMA as MAP increased (fig. 4). This phenomenon results from the interaction of strong and weak myocardium contracting in tandem. 39 Contraction of the remote zone
One puzzling aspect of the current results is that contractile performance of the postischemic area clearly was reduced, but that the slope of the EST–peak systolic pressure relationship—a standard measure of regional contractility—was not affected (fig. 5). Instead, the EST–PSP relationship was shifted in a parallel fashion. This result is similar to that observed in other studies and implies a change in the material properties of the heart with ischemia and reperfusion such that actin–myosin overlap is altered—a phenomenon termed “creep.” This lack of a decrease in slope reflects an unchanged sensitivity to afterload.

LIMITATIONS

Because we studied only a single ischemic period, our results may not apply to clinical or experimental circumstances in which multiple or chronic episodes of ischemia produce dysfunction. The load-dependence of myocardium subjected to a more serious insult is likely to differ if active contraction is abolished and only the passive properties of the myocardium determine movement during systole. The heart rate was carefully controlled at 100 beats per min in the current experiment. Interpretation of RWMA may be even more difficult if the heart rate in addition to the loading conditions changes, because of rate-related changes in the duration of diastole and contractility. MAP was controlled as a technique for varying LV afterload. The results may not apply to situations in which aortic impedance is altered without changes in arterial pressure. Although it is possible that the trends observed would continue outside the ranges of MAP (70–110 mmHg) and LAP (3–9 cmH2O) studied, there is no guarantee they do. The pericardium was closed after implantation of the crystal sets and the left atrial catheter. The pericardium probably provided a bit of restraint for the left ventricle and facilitated interactions between the left and right ventricles. Whether these effects influenced the results is unknown, but certainly preparations in which the pericardium is open may behave differently.

Compared to normal myocardium, postischemic myocardium has a diminished response to increases in preload and an unchanged response to increases in afterload. An interaction of the depressed contraction in the postischemic zone and the enhanced function of the surrounding areas gave the appearance of RWMA as afterload increased. These findings suggest that inotropic support, rather than augmentation of preload, is the logical method to enhance contraction of postischemic myocardium. The findings also suggest a basis for nonischemic RWMA that

occur when afterload is increased in patients who have coronary artery disease and regions of postischemic myocardium.

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Appendix

Ventricular pacing was used to control heart rate after injection of formalin into the atrioventricular node to create a permanent heart block. The negative lead from the pacemaker was sutured tightly to the apex of the right ventricle. While ventricular pacing can produce inhomogeneous contraction patterns that would seriously affect regional load dependence, this phenomenon seemed to be of minor significance in the current studies, as figure A demonstrates. Data are shown from one animal during ventricular pacing and during a short period when the pacemaker was turned off. Regional wall thickness shows the effect of atrial contraction, also apparent in the ECG tracing. The configuration of wall thickness trace during systole is similar with paced beats and with spontaneous beats. A slightly increased systolic thickening in the spontaneous beats probably results from increased preload, reflected in a thinner wall at end-diastole. Note that the QRS duration of the paced beats was not dramatically prolonged; this suggests that the depolarization was spread to the left ventricle by the Purkinje system.

![Graph showing relationship between Pao (mm Hg), WT (mm), and ECG waves](https://example.com/graph.png)