Regional Myocardial Function during Acute Coronary Artery Occlusion and Its Modification by Pharmacologic Agents in the Dog

By Pierre Theroux, Dean Franklin, John Ross, Jr., and William S. Kemper

ABSTRACT

Myocardial regional function during acute coronary artery occlusion was studied using ultrasonic dimension gauges in open-chest dogs. Three pairs of 2-mm ultrasonic crystals were implanted 1 cm apart near the endocardium in an ischemic segment, a control segment, and a segment at the margin of the ischemic zone. In the ischemic segment, coronary artery occlusion resulted in prompt dyskinesis which progressed to holosystolic expansion; length at end-diastole (diastolic length) increased by 11%, segment stroke work decreased by 91%, and the diastolic pressure-length relationship was displaced and steepened. In the marginal segment, active shortening and stroke work decreased by 37% and diastolic length increased by 4%. In the control segment, an initial increase in active shortening was observed, followed by compensatory operation of the Frank-Starling mechanism. Nitroglycerin administered during coronary artery occlusion decreased diastolic length and increased shortening in all three segments. An early beneficial effect of isoproterenol on all segments was later replaced by deterioration in marginal and ischemic segments. After propranolol administration, the decrease in shortening of the marginal segment was reduced to half of that observed during a control coronary artery occlusion, suggesting a protective effect of this drug. These results indicate the power of this approach, which provides continuous quantification of regional wall function in myocardial ischemia and during therapeutic interventions.

KEY WORDS myocardial infarct size, myocardial ischemia, Frank-Starling mechanism, diastolic length, dyskinesis, myocardial segment function, nitroglycerin, propranolol, isoproterenol, ultrasonic segment gauge

An important cause of impaired cardiac function in ischemic heart disease, in addition to myocardial tissue loss, is mechanical dysfunction of different regions of the left ventricle (1–3). Description and quantification of such local changes in myocardial function appear essential to an understanding of the effects of various experimental and clinical therapeutic approaches designed to improve myocardial performance and reduce tissue damage during myocardial ischemia (4–6). The goal of the present study was to apply a newly developed ultrasonic technique for the simultaneous characterization of the motion of small segments of the myocardium in ischemic, marginally ischemic, and normal zones and thus to study the effects of a brief coronary artery occlusion together with the modifications caused by nitroglycerin, isoproterenol, and propranolol.

Methods

Seventeen mongrel dogs weighing 24–32 kg (average 28 kg) were anesthetized with sodium pentobarbital (25 mg/kg, iv), and small supplemental doses were administered as required. Respiration was controlled by a Harvard pump delivering room air via an endotracheal tube. A thoracotomy was performed in the fifth left intercostal space, and the pericardium was opened. A high-fidelity Königsberg P-22 pressure micromanometer was inserted into the left ventricular chamber through the cardiac apex. The left anterior descending coronary artery was dissected free distal to its site of origin, and epicardial electrocardiographic (ECG) mapping was carried out using previously described techniques (4). After a con-
The ultrasonic technique used to obtain continuous measurement of the dimensions of these small segments of the myocardium simultaneously in vivo was recently developed (7) and is an extension of ultrasonic transit time measurement techniques developed earlier (8, 9). Hemispherical polystyrene divergent lenses were molded onto small (1-2 mm), 6-MHz piezoelectric disks. One crystal was excited by a 0.2-μsec, 200-V pulse. The resultant sound pulse traveled through the myocardium to the opposing crystal in a time proportional to the distance separating the crystals. A voltage proportional to the sonic transit time was developed. This pulse was repeated at a 1-kHz repetition rate to provide effectively a continuous (100-Hz frequency response) measure of dimensions of segments of the myocardium in the line separating the two crystals. Multiple myocardial segment dimensions were derived simultaneously from several pairs of transducers by separating the pulses to the projecting crystal of each of the pairs by 200 μsec. The measured transit time was calibrated against an accurate standard by substituting for the sonically derived signals a signal of precisely known duration derived from a stable, crystal-controlled oscillator. The resolution capability of the instrument was a small fraction of the wavelength of the sonic signal (less than 0.05 mm). The measured electronic drift was less than 0.05 mm for the time of the study. The overall functional stability was limited by the extent to which the transducers faithfully followed the movement of the myocardium in which they were embedded. Although an independent measuring technique of sufficient accuracy to precisely evaluate this possible source of instability in vivo is not available, the repeatability of the measurements during repeated brief occlusions (Table 1), the stability of the measurements over hours after acute implantation, and subsequent gross and histologic evaluation of the tissue indicated that movement of the crystals within the myocardium was not a significant source of error and that overall system stability approached the measured electronic stability. Moreover, the wave forms obtained before and during coronary artery occlusion in these experiments were closely similar to those obtained after coronary artery occlusion in animals with long-term implantations in which the crystals are held in place by a fibrous rim of tissue. In the present study the position of the crystals in the myocardium was examined at the end of each experiment; the crystals were within the inner one-third of the myocardium. Histologic studies were also done; they revealed an approximately 1-mm rim of focal injury surrounding the site of crystal implantation. Along the sides of the wire track, focal cell injury and interstitial hemorrhage extended out less than 1 mm. There was no evidence of other tissue damage in the muscle between the crystals.

Variables studied were heart rate, left ventricular peak systolic pressure, left ventricular end-diastolic pressure, the first derivative of left ventricular pressure (dP/dt), segment dimensions, segment shortening velocity, and indexes of segment power and stroke work. The micromanometer was calibrated against a mercury manometer attached to a Statham P23Db strain-gauge manometer. Zero pressure was determined at the end of the study with the gauge at the midpoint of the ventricle. dP/dt was derived from the output of the micromanometer using an active resistance-capacitance differentiating circuit with high-frequency cutoff set for 700 Hz. A triangular wave signal with a known slope was substituted for the pressure signal to directly calibrate dP/dt. Heart rate was measured using a cardiotachometer (Beckman type 9857B). End-diastolic and end-systolic segment lengths were identified on the recordings (Fig. 2); the calculated values were normalized by dividing the observed length by the control end-diastolic segment length and multiplying by ten. The absolute control values for end-diastolic segment length ranged from 8 to 20 mm.
Changes in Hemodynamics and Segment Length Induced by a 5-Minute Coronary Artery Occlusion

<table>
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<th>Control segment</th>
<th>Peak HR N (beats/min) (mm Hg)</th>
<th>+dP/dt (mm Hg/sec)</th>
<th>-dP/dt (mm Hg/sec)</th>
<th>EDL (mm)</th>
<th>ΔL (mm)</th>
<th>dL/dt* (cm/sec)</th>
<th>SW* (dyne/cm)</th>
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<td>Control</td>
<td>17 128 ± 4 111 ± 5 5.1 ± 0.4</td>
<td>1830 ± 160 2369 ± 171 10</td>
<td>0.94 ± 0.1</td>
<td>0.984 ± 0.06</td>
<td>2.2 ± 0.5 (10^4)</td>
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<td>CO</td>
<td>17 131 ± 4 112 ± 5 7.4 ± 0.7</td>
<td>1750 ± 170 2269 ± 157 10 12.2 ± 0.1 1.042 ± 0.06 2.7 ± 0.5 (10^4)</td>
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<tr>
<td>P*</td>
<td>&lt; 0.001 NS</td>
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<td>&lt; 0.001 &lt; 0.001 NS &lt; 0.001</td>
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<td>+0.2 ± 0.05 +0.2 ± 0.07</td>
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<td>ΔCCO</td>
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<tr>
<td>P**</td>
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</table>

N = number of dogs studied; HR = heart rate; peak LVSP = peak left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; + dP/dt = peak positive dP/dt; - dP/dt = peak negative dP/dt; EDL = end-diastolic segment length; ΔL = extent of shortening, dL/dt = maximal velocity of segmental fiber shortening during ejection; SW = stroke work; control = before occlusion; CO = after 5 minutes of coronary artery occlusion; ACO = changes induced by a first coronary artery occlusion; ACCO = changes induced by a second control coronary artery occlusion; P* = control vs. coronary artery occlusion (CO) vs. changes during a second coronary artery occlusion (ACCO). Values are means ± SE. A paired Student's t-test was used to determine P values; NS = not significant.

*Values for dL/dt and SW were calculated for 16 dogs.

(average 13 mm) and for end-systolic segment length from 7.4 to 18 mm (average 11.6 mm). The systolic change in segment length was calculated as the difference between the corrected end-diastolic length and the corrected end-systolic length. The length derivatives (dL/dt) of the three segments were obtained using a resistance-capacitance differentiating circuit and calibrated against a triangular wave signal with a known slope. Three Philbrick analog multipliers (model 4450) were used to obtain the product of left ventricular pressure and velocity of shortening (dL/dt) for each of the segments. For this purpose, zero pressure was taken at the end of slow left ventricular filling and shortening was considered positive and lengthening negative. The products were integrated (Philbrick integrators, model 4850), resetting to zero at the beginning of positive dP/dt. Thus, indexes of the developed instantaneous power and the developed work per stroke of different segments of myocardium were obtained simultaneously (Fig. 3A–C). These products and their integrations were calibrated against electronic outputs corresponding to known inputs of pressure (dynes/cm²) and velocity of shortening (cm/sec).

Data were recorded during the experiment on a Brush forced-ink oscillograph and, for 16 dogs, on a Hewlett-Packard magnetic tape recorder (model HP 3955 D). The taped data were later played back, and the recorded and derived variables were inscribed on two eight-channel Brush chart recorders driven simultaneously. Calculations were made from recorded variables taken at the end of expiration at a paper speed of 100 mm/sec. The effects of a 5-minute coronary artery occlusion were recorded for every dog. The severity of myocardial ischemia was assessed during that
occlusion by calculating the sum of ST-segment elevations (Σ ST) in millivolts (4). The reproducibility of the changes observed during a coronary artery occlusion was assessed by a second control coronary artery occlusion in ten dogs.

Diastolic pressure-length relationships before and during coronary artery occlusion were examined. End-diastolic lengths before and during the first coronary artery occlusion were compared at matched pressures corresponding to the end-diastolic pressure prior to the occlusion. Pressure also was plotted as a function of corresponding end-diastole; all values were obtained at end-expiration. Also included are data during compensatory pauses after premature beats induced by manipulations such as manual aortic constriction in some dogs and phenylephrine injection in other dogs. These interventions were used during control periods to increase diastolic pressures to levels comparable to and above those occurring during coronary artery occlusion. It was found that the relationship between diastolic pressure and length fit an exponential function above 3 mm Hg (10); accordingly, slopes and intercepts derived from diastolic periods were calculated before and after coronary artery occlusion in each of the 17 dogs at pressures higher than 3 mm Hg.

Nitroglycerin (0.4 mg) was administered intravenously by bolus injection, first in the control state and again after 3 minutes of coronary artery occlusion (eight dogs). The effects of a 10-minute isoproterenol perfusion (0.05-0.10 μg/kg min−1) were also studied before and after coronary artery occlusion in seven dogs. In four dogs, the effects of a coronary artery occlusion induced 5 minutes after propranolol administration (1 mg/kg, iv) were examined and compared with those of a control occlusion prior to propranolol administration. A 45-60-minute recovery period was allowed between each of these interventions (4).

All values were analyzed by the paired Student’s t-test and expressed as the mean ± SE.

### Results

Following coronary artery occlusion, rapid changes occurred in pressures and segment lengths (Fig. 2). These changes could be divided into initial changes that were unstable but directionally consistent and later changes that occurred when a steady state had been achieved after a few minutes. Table 1 summarizes the late changes calculated 5 minutes after coronary artery occlusion.

### EFFECTS OF CORONARY ARTERY OCCLUSION

#### Hemodynamic Changes

Shortly after the onset of coronary artery occlusion peak left ventricular systolic pressure decreased slightly (111 ± 4.5 to 102 ± 4.5 mm Hg, P < 0.001) as did peak positive dP/dt (1830 ± 160 to 1710 ± 150 mm Hg/sec, P < 0.001); there was also a marked decrease in peak negative dP/dt (2369 ± 171 to 1700 ± 128 mm Hg/sec, P < 0.001). Left ventricular end-diastolic pressure increased slightly from 5.1 ± 0.4 to 5.5 ± 0.05 mm Hg (P < 0.05), but heart rate remained constant (Fig. 2). A stable pattern was established between 2 and 5 minutes of occlusion (Table 1). By that time, positive dP/dt had improved but was still slightly and significantly lower than control, negative dP/dt was increased but not quite back to control, heart rate was faster, and end-diastolic pressure was significantly higher; peak left ventricular systolic pressure was unchanged from control (Table 1). The late response of left ventricular systolic pressure to coronary artery occlusion was unrelated to the size of the ischemic zone as determined by Σ ST: the average systolic pressure in the group with large infarcts (Σ ST > 16 mv was 112 ± 6 mm Hg before and 114 ± 7 mm Hg after coronary artery occlusion, and the values in the group with small infarcts (Σ ST < 16 mv) were 116 ± 9 mm Hg before and 115 ± 8 mm Hg after coronary artery occlusion. The increase in left ventricular end-diastolic pressure associated with coronary artery occlusion was significant
Analysis of three segments before and during the same coronary artery occlusion (Fig. 2). In each section from top to bottom are shown left ventricular (LV) pressure, excursions of the segment, the velocity of shortening of the segment (dL/dt), an index of instantaneous power, an index of work per beat, and an index of average power. Power was derived from analog computation of left ventricular pressure \( \times \) velocity of shortening; stroke work was obtained by integration of this product over each cardiac cycle. The numbers are positive values. Top: In the control segment (CS) following coronary artery occlusion, an initial decrease in end-systolic length was observed. This decrease was followed by an increase in end-diatolic length, extent of shortening, work per stroke, and average power. Peak velocity of segmental fiber shortening during ejection was unchanged. Middle: In the ischemic segment (IS) following coronary artery occlusion, end-diastolic length increased, and systolic shortening was rapidly replaced by lengthening. During the transient response illustrated in this figure, stroke work was negative; it will progressively return to approximately zero (± 9%) at equilibrium (see Table 1). Bottom: In the marginal segment (MS) following coronary artery occlusion, end-diastolic length increased, and the extent and velocity of shortening, power, and work decreased, showing depressed function of this segment.

\( P < 0.01 \) in both large and small infarct groups; it rose from 5.2 ± 0.6 to 6.4 ± 0.7 mm Hg in the latter group and from 4.8 ± 0.5 to 8.3 ± 1 mm Hg in the former group. \( \Delta P/dt \) fell by an average of 6% with small infarcts and by an average of 2.8% with large infarcts; heart rate increased slightly more with large infarcts.

**Segment Length Changes.**—Coronary artery occlusion resulted in significant changes in segment lengths at end-diastole (diastolic lengths), extent of systolic segment shortening, and segment work per beat in all three segments (Table 1). At 5 minutes of occlusion, the increase in diastolic length was 2.6% in the control segment, 4.1% in the marginal segment, and 11.5% in the ischemic segment. Shortening increased by a mean of 30% in the control segment; it decreased by 37% in the marginal segment and by 100% in the ischemic segment. Maximum velocity of segmental fiber shortening during the ejection phase was unchanged in the control segment, decreased by 32% in the marginal segment, and decreased by 65% in the ischemic segment. Segment work increased by 23% in the control segment, decreased by 36% in the marginal segment, and decreased by 91% in the ischemic segment (Table 1).

Within eight to ten beats following coronary artery occlusion, concomitant with the initial hemodynamic changes, shortening increased in the control segment by an average of 0.2 mm (21%), but diastolic length remained constant. This initial increase in shortening in the control segment from a constant end-diastolic length lasted 6–15 seconds after coronary artery occlusion (Figs. 2 and 3). Subsequently, diastolic length, shortening.
Increases in end-diastolic length (ΔEDL) of the control segments following coronary artery occlusion plotted against the sum of ST-segment elevations (∑ST) for each of the 17 dogs studied (A). A positive correlation between the size of the ischemic injury and the increase in length of the control segment is demonstrated. Changes in the extent of active shortening (ΔL) (B) and in stroke work (SW) (C) of the control segment observed after 5 minutes of coronary artery occlusion plotted against the corresponding increase in end-diastolic length of this segment for all the dogs studied. Significant relationships are shown indicating operation of the Frank-Starling mechanism in the nonischemic myocardium during coronary artery occlusion.

The time sequence of changes in the ischemic segment following coronary artery occlusion are shown in Figures 2 and 3 and illustrated in detail in Figure 5. Within 5 seconds of coronary artery occlusion, a decrease in active shortening was apparent in the ischemic segment. This change was rapidly followed by the appearance of a late systolic bulge (5–10 seconds). By 10–20 seconds, shortening during the ejection phase began to disappear in this segment; it was replaced by a systolic bulge at approximately 30 seconds. Within a few minutes, the paradoxical expansion progressively involved also the isovolumic phase of systole, resulting in a holosystolic bulge (shown at 3 minutes in Fig. 5). Diastolic length was increased by an average of 1.1 mm in the ischemic segment, and the height of the systolic expansion averaged an additional 1 mm above diastolic length so that the average ischemic segment length was increased throughout systole. The end of ejection, occurring slightly before peak negative dP/dt and also identified on the control segment recording, was marked by rapid shortening; diastolic lengthening waves then ensued. After a few minutes of occlusion, power in the ischemic segment was negative during isovolumic systole and slightly positive or negative during the ejection phase, i.e., energy was consumed by the ischemic segment, whereas during isovolumic relaxation power became positive so that the net segment work per stroke became approximately zero (Table 1).

The quantitative changes induced in the marginal segment by coronary artery occlusion consisted of a significant increase in diastolic length, more than in the control
Typical sequential changes in an ischemic segment following coronary artery occlusion. The excursion (distance between crystals in millimeters) is shown. A decrease in the extent of shortening and a late systolic bulge were observed almost immediately following coronary artery occlusion (CO) (5 and 10 seconds). These changes were followed by an aneurysmal expansion in the ejection phase first (1 minute) and then in all of systole (3 minutes). The vertical broken lines indicate end-diastole and end-systole.

Reproducibility of Changes During Coronary Artery Occlusion.—The reproducibility of the effects of the initial occlusion were assessed in ten dogs by comparison with a second coronary artery occlusion. The hemodynamic effects and the segment length changes were not significantly different during the two occlusions (Table 1).

Diastolic Pressure-Length Characteristics.—The diastolic lengths were calculated during the first coronary artery occlusion at a pressure matched to that at end-diastole prior to the occlusion. At a matched pressure of 5.1 mm Hg, the absolute end-diastolic length of the control segment was 14.3 ± 0.6 mm both during the control period and the coronary artery occlusion. In the ischemic segment, end-diastolic length averaged 12.4 ± 0.5 mm in the control state compared with a length of 13.2 ± 0.6 mm during coronary artery occlusion (P < 0.001). Figure 6 (top) shows representative pressure-length curves for a single dog in the control and ischemic segments before and during coronary artery occlusion. The curve is exponential at pressures higher than 3 mm Hg. The average slope of log pressure vs. length for all 17 dogs is also shown in Figure 6 (bottom). The slopes and intercepts of the curves in the control segments are the same before and during coronary artery occlusion. However, in the ischemic segment, during coronary artery occlusion the relationship is displaced to the right, the intercept is significantly lower, and the slope of the curve is significantly steeper than it was prior to the occlusion.

EFFECTS OF PHARMACOLOGIC AGENTS

Nitroglycerin.—Nitroglycerin given in the control state prior to coronary artery occlusion increased heart rate from 123 ± 4 to 128 ± 6 beats/min (NS), decreased peak left ventricular systolic pressure from 124 ± 14 to 100 ± 8 mm Hg (P < 0.05) and reduced left ventricular end-diastolic pressure from 3.6 ± 0.9 to 2.4 ± 0.8 mm Hg (P < 0.05); dP/dt was unchanged. Diastolic length was reduced in all three segments (average 10 mm to 9.5 ± 0.1 mm, P < 0.001), and shortening was in-
**TABLE 2**

**Effects of Pharmacologic Agents**

<table>
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<tr>
<th></th>
<th>Control segment</th>
<th>Marginal segment</th>
<th>Ischemic segment</th>
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<td>N</td>
<td>Control</td>
<td>CO</td>
<td>Nitroglycerin</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>129 ± 4</td>
<td>130 ± 5</td>
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<td>Peak LVSP (mm Hg)</td>
<td>114 ± 8</td>
<td>113 ± 7</td>
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<tr>
<td>LVEDP (mm Hg)</td>
<td>5.4 ± 0.5</td>
<td>6.4 ± 0.7</td>
<td>4.3 ± 0.8</td>
</tr>
<tr>
<td>+ dP/dt (mm Hg/sec)</td>
<td>2128 ± 336</td>
<td>2000 ± 240</td>
<td>2193 ± 230</td>
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<td>EDL (mm)</td>
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<td>10.16 ± 0.05</td>
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N = number of dogs studied, HR = heart rate, peak LVSP = peak left ventricular systolic pressure, LVEDP = left ventricular end-diastolic pressure, dP/dt = peak positive dP/dt, EDL = end-diastolic segment length, ΔL = extent of shortening, Control = before coronary artery occlusion, and CO = coronary artery occlusion. Nitroglycerin during coronary artery occlusion; the P* value compares Nitroglycerin to CO. Early Iso = early responses to an isoproterenol infusion during coronary artery occlusion. Late Iso = late responses to an isoproterenol infusion during occlusion. P* compares Early Iso to CO, and P* compares Late Iso to Early Iso. C* = control after recovery from the first coronary artery occlusion and before propranolol administration. Prop = values after propranolol administration, Prop CO = coronary artery occlusion after propranolol administration, and the P* values here compare the percent changes induced by the first coronary artery occlusion (CO) to the percent changes induced by the coronary artery occlusion after propranolol administration (Prop CO). Values are means ± SE. A paired Student's t-test was used to determine P* values; NS = not significant.
When nitroglycerin was given during occlusion, the hemodynamic responses to the drug were similar (Table 2). Diastolic length was reduced by 4.5 ± 1% in the control segment, by 5.4 ± 2% in the marginal segment, and by 4.2 ± 2% in the ischemic segment. Shortening increased by 21 ± 18% in the control segment and by 66 ± 25% in the marginal segment. In the ischemic segment, shortening was restored to 45 ± 12% of its preocclusion value; however, the early systolic bulge was still present in this segment (Fig. 7). The effects of nitroglycerin on left ventricular systolic and diastolic pressure lasted an average of 6 minutes. The observed improvement in shortening was concurrent with these hemodynamic changes, and when the hemodynamic parameters returned to the levels existing prior to nitroglycerin administration significant improvement in shortening of the marginal segment and the ischemic segment was no longer evident.

Isoproterenol.—Isoproterenol infused in the control state prior to coronary artery occlusion increased heart rate from 122 ± 4 to 152 ± 8 beats/min (P < 0.001); left ventricular end-diastolic pressure fell from 4.5 ± 0.5 to 2.5 ± 0.4 mm Hg (P < 0.01). Left ventricular systolic pressure increased from 121 ± 9 to 130 ± 17 mm Hg (P < 0.05), and dP/dt increased from 2450 ± 200 to 5700 ± 600 mm Hg/sec (P < 0.001). Diastolic length decreased from 10 to 9.6 ± 0.1 mm (P < 0.001), and shortening increased from 1.4 ± 0.2 to 2 ± 0.2 mm (P < 0.001) in all three segments studied.

The response to isoproterenol infusion during coronary artery occlusion was time dependent. The early responses were calculated after approximately 2 minutes when a steady hemodynamic state had been achieved; the late responses were calculated 3–7 minutes later. Table 2 shows that the early and the late values for heart rate, end-diastolic pressure, and dP/dt were significantly different from the preinfusion values but were not significantly different from each other except for end-diastolic pressure, which was significantly higher (P < 0.05) late in the infusion. Isoproterenol first decreased
diastolic length by 5 ± 1% in the control and marginal segments and by 9 ± 3% in the ischemic segment. Shortening increased by 24 ± 20% in the control segment and by 54 ± 30% in the marginal segment, and a significant amount of shortening was restored in the ischemic segment (77 ± 26% of the preocclusion shortening). These effects of isoproterenol on the control segment were sustained (4 ± 1% decrease in diastolic length and 33 ± 23% increase in shortening). However, diastolic length in both the marginal and the ischemic segment after the initial reduction then increased progressively toward preisoproterenol levels. The increases in shortening, although sustained in the control and marginal segments, fell to insignificant levels in the ischemic segment (Table 2).

Propranolol.—Propranolol (1 mg/kg) given in the control state prior to coronary artery occlusion decreased heart rate significantly from 126 ± 4 to 113 ± 7 beats/min and dP/dt from 1850 ± 240 to 1570 ± 180 mm Hg/sec (P < 0.05). Left ventricular end-diastolic pressure increased from 4 to 5.4 mm Hg (NS), diastolic length increased by an average of 2.2 ± 0.6%, and shortening decreased by 2.7 ± 1.7% (NS) (Table 2). With coronary artery occlusion, both before and after propranolol administration, the percent changes in heart rate, peak systolic pressure, end-diastolic pressure, and dP/dt were not significantly different. The percent changes in shortening and diastolic length were also the same in the control and ischemic segments. However, the percent decrease in shortening in the marginal segment was 46% during the control coronary artery occlusion prior to propranolol administration but only 23% during the occlusion after propranolol administration (P < 0.05).

Discussion

Since the original description by Tennant and Wiggers of systolic bulging following coronary artery occlusion (1), many workers using a variety of techniques have examined function in the ischemic zone of the myocardium following occlusion (5, 11–17). In this study, the availability of accurate and stable measurements of regional intramyocardial dimensions has provided, for the first time, the opportunity to quantify simultaneously and compare changes in normal, marginally ischemic, and ischemic muscle induced by a coronary artery occlusion. The ultrasonic approach has several advantages over previous techniques for measurement of segmental motion. The implantation of crystals is relatively atraumatic, involving only small punctures in the muscle, and there are no sutures to interfere with coronary blood supply; it approximates a true “forceless strain gauge,” providing a measure of dynamic length of multiple segments within the myocardium and near the endocardium.

Previous descriptions of functional changes in the myocardium during coronary artery occlusions have focused largely on the development of the bulge within the ischemic area during systole, its pattern, and its timing. Prinzmetal et al. (11), using high-speed cinemato graphy, described early systolic contraction with ballooning late in systole and sometimes throughout systole; they also described waxing and waning of this phenomenon. Hood et al. (13), using a mercury-in-Silastic gauge sutured to the epicardium, showed that the segment lengthening normally observed during isovolumic systole greatly increases during ischemia and that shortening during the ejection phase disappears. Heikkila et al. (15), using cineradiography of metal clips, described local akinesia rather than an extensive paradoxical systolic pulsation. Kerber and Abboud (16), using a fixed external ultrasound transducer, described an outward motion during isovolumic contraction and a decreased inward motion during ejection. In the present study, the ischemic zone exhibited decreased amplitude and duration of active shortening in the ischemic segment within ten beats following occlusion. A late systolic bulge then appeared which first involved the late ejection period and then all of systole; a slight degree of shortening usually occurred during ejection, and the end of ejection was always accompanied by a rapid shortening. When the systolic outward motion was fully developed during the steady state, the net work of the ischemic segments was approximately zero. This finding suggests passive elongation and elastic recoil of the ischemic muscle. Recently, Tyberg et al. (17) used the epicardial mercury-in-rubber gauge to generate pressure-length loops and described a negative net work in the ischemic zone, suggest-
ing incomplete elastic recoil properties of this segment. The discrepancy between their findings and ours could be explained by the basic differences in recordings obtained with the epicardial gauge and the ultrasonic crystals (18) and by the differences between epicardial and endocardial segment motion.

Few measurements have been made in the nonischemic myocardium outside the involved zone during the acute phase of coronary artery occlusion. Heikkila et al. (15) suspected that the Frank-Starling mechanism was effective immediately after infarction because of a longer end-diastolic length, although no increase in the extent or the velocity of active contraction was observed. In the present study, there was an early decrease in end-systolic length (increased shortening) from a constant end-diastolic length in the normal segment at the same time that the initial dyskinetic motion (decreased active shortening and late systolic bulge) was occurring in the ischemic segment. This increased shortening was also present in each of the occlusions carried out after beta-receptor blockade, suggesting that this response was not due to a local norepinephrine release or to reflex adenergic activation. This finding probably can be explained by a redistribution of local forces in the myocardium. Thus, the loss of shortening and the appearance of outward systolic motion in the ischemic zone indicate that active tension in this tissue was diminished and could not sustain the intracavitary pressure developed by the remaining myocardium. The ischemic region of tissue therefore bulged during systole, reducing the net afterload on the normal segment and leading to enhanced active shortening. Such a regional unloading has not been described previously in the uninvolved myocardium.

In the present study, operation of the Frank-Starling mechanism in the normal myocardium was clearly apparent, and there was evidence that this operation was proportional to the size of the ischemic zone. As the size of the ischemic zone increased, diastolic segment length in the control segment increased and was accompanied by a directly proportional augmentation of shortening and work (Fig. 4). Changes in systemic arterial blood pressure or contractility also could have affected active shortening, but calculations were made at a time when the values of peak systolic pressure were not significantly different from preocclusion levels; it is unlikely that slight changes in heart rate alone (128 to 131 beats/min) affected shortening substantially (19); left ventricular dP/dt was slightly decreased and velocity of shortening (dL/dt) in the control segment was not significantly changed (Table 1), suggesting that the inotropic state of this segment was not enhanced. Moreover, the relationship between the increase in end-diastolic length and the extent of shortening following coronary artery occlusion was not affected by propranolol (Table 2). Thus, there is direct evidence that a regional Frank-Starling effect in normal myocardium was present, accounting in part for the maintenance of overall ventricular function despite significant loss of regional tissue function.

In marginally ischemic tissue, the increase in end-diastolic length during coronary artery occlusion was intermediate between that of the control and ischemic segments. However, despite this increased resting fiber length, shortening and work decreased by an average of 40%, indicating that the marginal segment was working on a depressed function curve. Puri (20), by exploring the external surface of the dog left ventricle with a strain-gauge catheter during a period of coronary artery occlusion, described a segment with reduced shortening, which may have represented a marginal zone, although the marginal segment described in the present study was defined by ECG technique and clearly exhibited normal function prior to coronary artery occlusion. Since this segment showed persistent but reduced function during occlusion, it should represent a zone susceptible to effects of factors that can influence viable but partially ischemic tissue, in which modification of the size of the ischemic zone can be assessed.

End-diastolic length increased more in the ischemic segment than it did in the control segment during coronary artery occlusion, an observation recently made by others (17), suggesting that either a loss of active diastolic tone occurred or viscoelastic properties were altered by repeated systolic stretch of the ischemic tissue. To gain further insight into the diastolic properties of the ischemic segment, pressure-length curves were ana-
lyzed throughout diastole. There was a shift to the right of the curve, and the slope was steeper than that prior to coronary artery occlusion, suggesting reduced compliance. However, local radius of curvature and wall stress could not be assessed. It is possible that passive tension in the ischemic segment was actually higher than it was during the control state and that the segment was simply operating higher on its passive stress-strain relationship. Therefore, the mechanism of the observed changes in the diastolic pressure-length relationship remains to be elucidated by determining the stress-strain relationship, taking into account chamber geometry and local wall thickness. Our observation of an increased slope of the pressure-length relationship contrasts with the results of others (17, 21) early after coronary artery occlusion.

Previous observations have demonstrated that the acutely ischemic myocardium can respond to both positive and negative inotropic agents (13, 14). In the present study, nitroglycerin resulted in more shortening in the marginal segment with restoration of some shortening in the ischemic zone. However, it is difficult to assess the extent to which increased shortening in the ischemic segment represented recovery of active function, since decreased mechanical load on the ischemic segment would tend to decrease passive outward motion and increase inward motion. The observed association in our study of improved shortening in the marginal segment concomitantly with the hemodynamic effect of nitroglycerin to lower arterial blood pressure suggests that the improvement in function may be related primarily to this peripheral effect rather than to the regional redistribution of myocardial blood flow to the endocardium that has been described recently following nitroglycerin administration (22).

Isoproterenol improved contractility initially in both the marginal and the ischemic segment. However, these effects were not sustained, and after 5 minutes end-diastolic length and shortening returned to the pre-isoproterenol level in the ischemic segment. These results are consistent with those reported previously from this laboratory (14) and by Puri (20), and they support observations of deleterious effects of isoproterenol on myocardial metabolism (23) and infarct size (4).

The key difference observed during two occlusions before and after propranolol administration occurred in the marginal segment; the reduction in the extent of shortening was substantially less after propranolol administration than it was during the control occlusion. This improvement in the performance of the marginal segment extends previous observations that propranolol can decrease infarct size as estimated by the epicardial ECG mapping technique (4) and by histologic study (4, 24). We suggest that this effect may be due to reduced oxygen requirements in this region related to slower heart rate and reduced contractility.

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References

10. Gaasch WH, Battle WE, Oboler AA, Banas JS Jr, Levine HJ: Left ventricular stress and com


17. TATOOLES CJ, FORRESTER JS, WYATT HL, GOLDNER SJ, PARMLEY WW, SWAN HJC: Analysis of segmental ischemic dysfunction utilizing the pressure-length loop. Circulation 44:748-754, 1974


20. PURI PS: Studies on contractility in the zone or partial ischemia as a means of evaluating effects of cardiotonic drugs on the size of myocardial infarction (abstr). Clin Res 19:646, 1971


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