Impaired thickening of nonischemic myocardium during acute regional ischemia in the dog

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ABSTRACT To study the regional function of nonischemic myocardium after the onset of regional ischemia, graded circumflex coronary arterial stenosis was induced in 18 open-chest anesthetized dogs. Two-dimensional echocardiographic views were obtained at each degree of occlusion in a cross-sectional plane marked by two to three metal beads sewn to the left ventricular epicardium. Percent systolic thickening was measured at 16 equally spaced points around the left ventricle and correlated with microsphere-determined regional myocardial blood flow. Baseline thickening averaged 44.9 ± 6.4%. During transmural ischemia percent systolic thickening decreased to −16.1 ± 4.0% in the ischemic region and also decreased in adjacent nonischemic regions (to 2.4 ± 2.4% in segments closest to the ischemic region [adjacent 1] and to 15.5 ± 3.9 in segments further away [adjacent 2]), but was unchanged in segments directly opposite the ischemic region (remote region). During subendocardial ischemia, percent systolic thickening fell only in the ischemic and adjacent 1 regions (1.4 ± 5.2% and 24.9 ± 5.0%, respectively). Dipyridamole, 0.21 to 0.42 mg/min iv, given to seven dogs during transmural ischemia, caused a three- to fivefold increase in flow to the nonischemic and no change in flow to the ischemic region; function was not altered in any region. Propranolol, 0.1 mg/kg iv, was given to five dogs during transmural ischemia to depress contractility in the remote region. Percent systolic thickening fell in the remote (from 50.0 ± 7.7% to 34.6 ± 5.6%), but increased in adjacent 1 (from −0.25 ± 3.7% to 15.2 ± 3.9%) and in adjacent 2 (from 17.4 ± 2.8% to 33.4 ± 3.9%) regions, and remained unchanged in the ischemic region. We conclude the following: (1) During transmural ischemia percent systolic thickening is markedly impaired in nonischemic myocardium immediately adjacent to the ischemic region, and is impaired to a lesser degree in regions located relatively far from the ischemic border. Dysfunction therefore overestimates the extent of regional ischemia after total coronary occlusion. (2) During subendocardial ischemia function ceases in the ischemic region and functional impairment of nonischemic myocardium is restricted to immediately adjacent regions. (3) Dysfunction of adjacent regions is not caused by “relative ischemia” related to increased local oxygen demands or to a steal phenomenon. (4) Mechanical tethering of nonischemic myocardium adjacent to ischemic regions, secondary to changes in left ventricular shape during contraction, may contribute to the impairment of systolic thickening in adjacent regions during transmural ischemia.


AFTER total occlusion of a major coronary artery, systolic myocardial thickening is replaced by thinning in the center of the ischemic region, while contraction remains unchanged in the nonischemic myocardium located far from the ischemic border.1 In the ischemic border zone, the relationship between myocardial contraction and blood flow is less well understood. Depressed function has been found, but not to the same extent as in the center of the ischemic region.1-3 Intermediate function in the border zone has been attributed to the presence of “moderately” ischemic tissue, which could be related either to myocardium with intermediate levels of flow or to a mixture of ischemic and nonischemic myocardium between the two points at which length (function) is being measured. In addition, previous studies have found impaired myocardial function in normally perfused regions located adjacent to ischemic areas.1-3 However, because these studies

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used single-dimensional techniques, the topographic mapping of regional dysfunction and determination of its relationship to perfusion around the entire left ventricular circumference was not possible.

The purpose of this study was to investigate the topographic relationship between regional myocardial perfusion and function in a full cross section of the canine left ventricle during graded coronary arterial occlusion. We found marked changes in local function within the nonischemic portion of the left ventricle as ischemia progressed from the inner half to involve the entire thickness of the left ventricular wall.

Methods

Experimental preparation. We studied 27 mongrel dogs (17 to 28 kg) anesthetized with chloralose (50 to 100 mg/kg body weight mixed with saline and urethane given intramuscularly). Seven dogs developed ventricular fibrillation after coronary occlusion and were excluded from the study. Two experiments were used as sham studies, as detailed below. The results presented below come from the remaining 18 dogs that survived the entire experimental protocol. After median sternotomy, the pericardial sac was opened and the heart was cradled by the pericardium. A screw occluder, an electromagnetic flowmeter (Biotronex), and a silk thread passed through a short segment of polyethylene tubing were placed on the proximal left circumflex coronary artery of each dog, and catheters were placed in the left atrium and aorta.

The sinus node was crushed with a hemostat to avoid an excessive increase in heart rate. Two to four steel beads (3/16 inch in diameter with holes drilled to allow a suture to pass through) were sewn to the epicardium to establish a two-dimensional plane for echocardiographic measurements perpendicular to the long axis of the left ventricle at the level of the tip of the papillary muscles.8 The beads were used to ensure a reliable match between tissue samples for flow and echocardiographic measurements. Left atrial and aortic pressures (Statham P23Db transducers), lead II of the electrocardiogram, and circumflex coronary arterial blood flow were continuously recorded on a direct-writing recorder (Gould, Inc.). Myocardial blood flow measurements were made with use of 9 to 11 μm diameter radioactive microspheres, with Tween 80 added, labeled with 141Ce, 103Ru, 99Nb, 113Sn, or 46Sc (New England Nuclear). Microsphere vials were vibrated for 5 min on a Vortex mixer before use. Approximately two million microspheres were injected into the left atrium, followed by a 5 ml saline flush, for each measurement. Starting just before the injection and continuing for 2 min afterward, reference blood samples were withdrawn at a constant rate by a calibrated Harvard pump.

Two-dimensional echocardiograms were obtained with an ATL Mark 300 IC echocardiograph equipped with a 5 MHz transducer. A latex bag filled with mineral oil was held stretched and placed gently on the anterior surface of the left ventricle by one of the investigators. The echocardiographic transducer was applied lightly to the anterior surface of the bag to minimize transmission of pressure to the heart. The transducer was then angled until a cross-sectional view of the left ventricle was obtained that contained all metal beads sewn to the epicardium. To detect any changes in left ventricular shape due to external pressure applied to the heart from the echocardiographic transducer and/or the mineral oil sac, both the transducer and the sac were lifted slowly from the heart while the image was monitored, at the end of each recording, by one of the investigators. There was no change in left ventricular shape detected during this maneuver. The echocardiograms were stored on ½ inch videotape (Sony Betamax) for later analysis and quantification.

Experimental protocol. After control measurements (microsphere injection and echocardiograms) were obtained, the circumflex artery was progressively stenosed to a level at which reactive hyperemia was abolished. For this procedure, flow was measured with the electromagnetic flowmeter and 10 sec transient occlusions produced with the silk thread snare were superimposed to progressive levels of stenosis produced by the screw occluder until the total disappearance of reactive hyperemia followed the release of a transient occlusion.9 Fifteen minutes were allowed between transient occlusions with the silk thread snare, but the screw occluder was never loosened throughout the entire process of generating circumflex coronary arterial stenosis.

Measurements of flow (microspheres) and function (echocardiograms) were repeated at the level of abolished reactive hyperemia, at two greater levels of occlusion that were determined by further advancing the screw occluder, and after total ligation of the coronary artery by the silk thread. All measurements were made 15 to 20 min after the establishment of each level of occlusion. In 12 of the 18 experiments, the protocol was the same except that the first measurements were not made at the lowest level of stenosis but instead were obtained 30 to 40 min after total coronary occlusion, after the administration of either dipyridamole (0.21 to 0.42 mg/min iv in seven experiments) or propranolol (0.1 mg/kg iv bolus in five experiments). In two sham experiments, measurements were made 15 to 20 min after total occlusion and repeated 15 to 20 min later without drug administration. Propranolol was then given intravenously, and a third set of measurements was made 15 to 20 min afterward.

At the end of each experiment, the animal was killed by a left atrial infusion of monastral blue dye (1 ml/kg, Dupont) over 1 min.10 Immediately afterward, the heart was arrested by injection of a potassium chloride solution. It was then fixed in formalin, and 48 hr later dissected free of the atria, right ventricle, large epicardial vessels, and fat, and cut transversely into six to seven slices, each approximately 1 cm thick. For the specific slice marked by the metal beads, the outlines of the left ventricular wall, the topographic boundaries of the region that remained unstained by monastral blue, and the position of the metal beads were traced on a transparent plastic sheet. The metal beads were then removed, their position was marked on the epicardial surface, and the slice was weighed. The slice was then divided into 16 circumferential segments that were also marked on the plastic sheet described above (figure 1). These segments corresponded anatomically to the 16 segments analyzed echocardiographically (see above). The 16 segments were further subdivided into inner and outer halves for flow measurements. All tissue samples were weighed and counted for radioactivity along with reference blood samples in a well-type gamma scintillation counter (Packard Model No. 5986) at energy windows adjusted to the peak emission for each of the five nuclides. Regional myocardial blood flow (F) was calculated by the formula F = R × Cm/Cr (ml/min/g), where R = reference blood flow pump withdrawal rate; Cm = counts per gram in myocardial tissue sample; Cr = counts in reference blood sample.11

Topographic analysis of data. Ischemia was defined retrospectively in our protocol as a 50% or greater reduction in myocardial blood flow in relation to flow in the averaged segments of the remote region (the region farthest from the ischemic border inside the nonoccluded bed; see below) for each intervention. Subendocardial ischemia was defined as a 50% or greater reduction in flow in the subendocardial half only, while transmural ischemia was defined as a similar reduction in...
flow in both the subendocardial and subepicardial halves of a given segment. Monastral blue was used to guide the selection of the topographic regions to be described. The border between unstained and stained myocardium was irregular but sharp, and could be visualized easily. The segments that included this border on each side contained both unstained and stained sections of myocardium and were not included in the analysis. All other segments inside the unstained portion of the slice were totally free of monastral blue and were included in the analysis. Myocardial blood flow, and later function, were analyzed for topographic regions for each heart as follows: (1) Ischemic, the two to five segments (out of the full 16) inside the totally unstained portion of the myocardial slice. (2) Adjacent 1, the two segment pairs stained blue on all faces and containing no nonblue tissue inside (as determined by further subdivision) and located immediately adjacent to the segments that included the border on both sides. (3) Adjacent 2, the two segment pairs adjacent to each adjacent 1 region. (4) Remote, the one to four segments diametrically opposite to the center of the unstained portion of the myocardial slice.

Sampling selection based on monastral blue staining was tested against the microsphere standard. A flow map of the slice marked by the beads was obtained from microsphere blood flow measurements from each of the halves of the 16 circumferential segments for each specific intervention (figure 1). The standard for comparison from each intervention was obtained by averaging the subepicardial and subendocardial halves of the segments inside the remote region, which was previously selected by monastral blue staining. Ischemic segment halves were not found inside the adjacent 1, adjacent 2, or remote region at any time. Conversely, no segments with blood flow of 50% or more of the corresponding remote averages were found inside the ischemic region after coronary ligation. The segments that contained the ischemic border had ischemic and nonischemic halves and were thus excluded from the analysis of regional function. The sampling selection based on monastral blue staining was proven accurate when tested against the microsphere standard, and was used for the analysis of regional measurements obtained at control and during all interventions after total coronary occlusion. However, during subendocardial ischemia, the four topographic regions were selected from the circumferential microsphere flow map alone. In this situation, the ischemic region included all segments with subendocardial ischemia, and adjacent 1 comprised the two segment pairs immediately adjacent to each side of the ischemic region. The adjacent 2 and remote regions were selected in the same manner as was previously described for all other experiments.

To calculate the extent of subendocardial or transmural ischemia as the percentage of the circumference, the number of sectors comprising the ischemic region, plus the sectors containing the border of each side, were divided by 16 and multiplied by 100. (The entire circumference of the left ventricle comprised 16 equally spaced sectors for echocardiographic analysis; see Analysis of echocardiograms, below). The distances from the center of the adjacent 1, adjacent 2, and remote regions to the ischemic border were measured at midwall for each side of each slice containing the beads (figure 1). Averages were obtained from the two sides of the slice for each heart. During subendocardial ischemia, distances were measured from the center of the adjacent 1, adjacent 2, and remote regions to the border between the adjacent 1 and the ischemic region.

Transmural ischemia was always produced after total circumflex occlusion. However, in four dogs transmural ischemia was also generated at the highest level of stenosis preceding total occlusion. Nevertheless, data listed in this text as transmural ischemia or total occlusion values refer exclusively to values obtained after the circumflex coronary artery had been ligated. Although the same protocol was followed for every experiment, subendocardial ischemia was generated in only eight experiments. In two of the eight experiments, it was found at two consecutive levels of stenosis and for them, values of subendocardial ischemia represent the average for the two consecutive interventions in the same dog.

**Analysis of echocardiograms.** All echocardiographic measurements were made in the cross-sectional plane marked by the metal beads. We used the cross-sectional cavity area at end-diastole and the fractional change in cavity area (end-diastolic cavity area — end-systolic cavity area divided by end-diastolic
cavity area × 100) as indexes of overall left ventricular size and function, respectively. End-diastolic thickness and percent systolic thickening (%T = end-systolic thickness – end-diastolic thickness divided by end-diastolic thickness × 100) were measured at each of the 16 equally spaced circumferential points around the left ventricular cavity (figure 1). Cross-sectional cavity area and myocardial thickness were determined every 32 msec throughout an entire cardiac cycle for each intervention. End-diastolic and end-systolic cavity areas were taken as the largest and smallest areas of a complete cycle, respectively, while end-diastolic and end-systolic thickness were taken as left ventricular wall thickness when cavity areas were the largest and smallest, respectively, for a given cardiac cycle.

For quantitative analysis of the echocardiograms, we used a computer-aided contouring system described previously. Echocardiograms were transferred from videotapes to a videodisk (VAS) and after selection of a representative cardiac cycle (the metal beads could be visualized in every frame), individual frames were displayed on a high-resolution x,y,z oscilloscopic screen for computer-aided contouring. The computer superimposed two sets of 16 equally spaced in an angle around the image, and the operator placed the points to fit the endocardial and epicardial margins of the left ventricular wall. A least-fit contour for each set of points was selected by the computer, using a spline-fitting technique. The echocardiogram was then advanced two fields (32 msec) and the new position of epicardium and endocardium was contoured by the same process. This procedure was repeated for the entire cardiac cycle from the onset of the QRS to the onset of the next QRS, producing 10 to 25 fields of data for each intervention. The reproducibility of results with the use of this particular system to measure myocardial thickness has been reported. Intraobserver differences were not statistically significant, but interobserver differences were (p = .006), although the percentage differences between observers was small (5%).

Myocardial blood flow, measured by microspheres in each circumferential segment (circumferential flow map, figure 1), was matched to regional percent systolic thickening with the help of the plastic grid generated at the time of the anatomic examination (see above), and the echocardiographic still frames were displayed on the oscilloscopic screen. The metal markers were used not only as landmarks for the topographic match of flow and function, but also for the alignment of each echo frame throughout the cardiac cycle. End-diastolic thickness and percent systolic thickening for each of the four topographic regions during each intervention were obtained by averaging the values of all segments inside each region.

During transmural ischemia the cross-sectional end-systolic shape of the left ventricle was noted to flatten, and then return toward its normal circular configuration after propranolol (see Results). To quantify this abnormality in shape and its restoration by β-blockade, the ratio of maximum to minimum left ventricular end-systolic endocardial diameter was calculated in the five dogs given propranolol. Measurements were made during the control period, transmural ischemia, and transmural ischemia after propranolol. Diameters were obtained directly from the freeze-frame end-systolic echocardiographic cross-sectional images. This was done by constructing straight lines that always passed through the geometric center of area of the left ventricular cavity (see figure 7). Maximum and minimum diameters were measured regardless of their location around the endocardial surface. Papillary muscles were not included in these measurements. The relationships of these diameters to the ischemic, adjacent 1, adjacent 2, and remote regions were recorded. A ratio of 1 would, of course, imply a perfectly circular shape; the greater the ratio, the less circular the shape.

**Statistical analysis.** The significance of differences in flow, percent systolic thickening, and other variables for different locations or interventions was calculated by analysis of variance with repeated measures. The Student–Newman–Keuls test was used to test for the significance of differences between two individual locations or interventions isolated from the repeated-measures analysis of variance. Paired t tests were used when values from the control period were compared with values for transmural ischemia only. Values are given as mean ± SD.

### Results

#### Regional transmural ischemia

**Extent of ischemia and distances from the ischemic border to the centers of adjacent 1, adjacent 2, and remote regions (table 1).** After total coronary occlusion in the experiments, the extent of ischemia, expressed as the percentage of the left ventricular cross-sectional circumference, was 35.0 ± 5.3%. The mean distances from the ischemic border to the centers of the adjacent 1, adjacent 2, and

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Extent of ischemia as % circumference</th>
<th>Distance (mm) from the ischemic border to the center of region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjacent 1</td>
<td>Adjacent 2</td>
</tr>
<tr>
<td>1</td>
<td>TO 43.7</td>
<td>7.5</td>
</tr>
<tr>
<td>2</td>
<td>TO 43.7</td>
<td>8.0</td>
</tr>
<tr>
<td>3</td>
<td>TO 37.5</td>
<td>8.0</td>
</tr>
<tr>
<td>4</td>
<td>SBI 25.0</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>TO 37.5</td>
<td>9.0</td>
</tr>
<tr>
<td>6</td>
<td>TO 37.5</td>
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<td>8</td>
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<td>10.5</td>
</tr>
<tr>
<td>18</td>
<td>SBI 25.0</td>
<td>10.5</td>
</tr>
</tbody>
</table>

**TABLE 1**

Extent of ischemia and distance from ischemic border to center of various regions

Mean ± SD TO 35.0 ± 5.3 8.5 ± 1.0 24.9 ± 2.5 44.8 ± 8.1 SBI 27.3 ± 4.6 6.5 ± 1.0 25.2 ± 2.7 49.6 ± 10.0

**TO** = total occlusion; **SBI** = subendocardial ischemia.

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remote regions were 8.5 ± 1.0, 24.9 ± 2.5, and 44.8 ± 8.1 mm, respectively.

Heart rate, arterial pressure, and left atrial pressure. The mean heart rate did not change significantly after total coronary occlusion (from 134 ± 4.3 to 130 ± 7.0 beats/min; NS). Peak systolic arterial pressure fell from 119 ± 3.2 to 111 ± 4.2 mm Hg (p < .01), while diastolic and mean arterial pressures were unchanged (88 ± 3.4 to 85 ± 3.6 and 100 ± 3.7 to 95 ± 4.5 mm Hg, respectively; NS). Left atrial pressure increased from 6.3 ± 0.5 to 9.2 ± 0.7 mm Hg (p < .001).

Cross-sectional end-diastolic cavity area, end-diastolic wall thickness, fractional change in cavity area, and left ventricular shape. After total occlusion of the circumflex artery, left ventricular end-diastolic cavity area increased from 9.9 ± 0.6 to 15.8 ± 0.7 cm² (p < .001). End-diastolic wall thickness decreased from 10.1 ± 2.5, 10.5 ± 2.1, 10.8 ± 2.5, and 10.8 ± 2.5 mm to 6.7 ± 1.2, 7.6 ± 1.2, 8.7 ± 1.2, and 8.8 ± 1.6 mm in the ischemic (p < .001), adjacent 1 (p < .001), adjacent 2 (p < .002), and remote (p < .002) regions, respectively. Fractional change in cavity area decreased from 62.0 ± 2.8% to 25.0 ± 2.0% (p < .001). The cross-sectional left ventricular shape at end-systole after the onset of regional transmural ischemia became elongated and distorted (figure 2). The adjacent regions encompassed, but were not limited to, the segments with a more accentuated curvature, while the ischemic and remote regions typically occupied the flatter portions of the left ventricular cross section. Left ventricular end-systolic configuration after total coronary occlusion varied with the size and position of the ischemic region. At end-diastole, shape distortion was slight (figure 2).

Regional myocardial blood flow (figure 3). After total coronary occlusion, myocardial blood flow changed only in the ischemic region. Subendocardial and subepicardial flow in the ischemic region fell from 0.97 ± 0.1 and 0.99 ± 0.1 ml/min/g during control to 0.04 ± 0.02 and 0.19 ± 0.05 ml/min/g during ischemia, respectively (p < .001 for both). Most importantly, flow remained at control levels in both subendocardial and subepicardial layers of the adjacent 1, adjacent 2, and remote regions. Also, values of myocardial blood flow in the three individual nonischemic regions (adjacent 1, adjacent 2, and remote) at control and during transmural ischemia did not differ.

Regional myocardial systolic thickening (figure 4). After

FIGURE 2. Cross-sectional echocardiograms of dog No. 16 at control (top) and during transmural ischemia (bottom) at end-diastole (left) and end-systole (right). Left ventricular shape becomes elongated and distorted at end-systole (bottom right). The arrows mark the ischemic borders obtained from the microsphere flow map and monastral blue injection.
FIGURE 3. Myocardial blood flow in the four anatomic regions at control and during subendocardial (SE) ischemia and transmural (TM) ischemia in eight experiments. Flow changes were restricted to the ischemic region and involved only the subendocardium during critical stenosis (linear decline in flow from control to transmural ischemia) and the entire wall thickness after total coronary occlusion. Most importantly, there were no changes in flow (ANOVA) in the adjacent 1, adjacent 2, or remote region during either subendocardial (ENDO) or transmural ischemia.

After total coronary occlusion, systolic thickening (control percent systolic thickening = 42.5 ± 4.0%) was replaced by thinning (−16.1 ± 4.0%; p < .001) in the ischemic region. In the adjacent 1 region, percent systolic thickening was reduced markedly from 42.6 ± 8.0% to 2.4 ± 2.4% (p < .001); that in the adjacent 2 region was less drastically reduced, from 46.1 ± 6.7% to 15.5 ± 3.9% (p < .001). Thickening remained unchanged in the remote region (48.4 ± 7.2% to 50.1 ± 8.4%; NS). When compared with each other, values from the four anatomic regions were similar at control, but became markedly different after the onset of regional transmural ischemia. Thus, after total coronary occlusion, dysfunction far exceeded the boundaries of the ischemic myocardium (24.9 ± 2.5 mm), and only in the most distant nonischemic portions of the ventricle (remote, 44.8 ± 8.1 mm) did percent systolic thickening remain unchanged in relation to control.

Subendocardial ischemia (figures 3 and 4). In eight experiments, subendocardial ischemia was generated by graded coronary occlusion before complete obstruction of the left circumflex coronary artery was attained. The extent of subendocardial ischemia expressed as the percentage of the left ventricular cross-sectional circumference was 27.3 ± 4.6% for these eight experiments. The mean distances from the center of the adjacent 1, adjacent 2, and remote regions to the ischemic border were 8.5 ± 1.0, 25.2 ± 2.7, and 49.6 ± 10.0 mm, respectively (table 1). During subendocardial ischemia, heart rate, arterial pressure, left atrial pressure, end-diastolic cavity area, and end-diastolic wall thickness did not differ from control. Fractional change in cavity area decreased from 60 ± 5.0% to 43 ± 6.3% (p < .005).

During subendocardial ischemia, changes in myocardial blood flow (figure 3) were restricted to the subendocardial layer of myocardium in the ischemic area. Subendocardial flow fell from 0.97 ± 0.1 to 0.31 ± 0.04 ml/min/g (p < .001), while flow in the subepicardium remained unchanged (from 0.99 ± 0.1 to 0.91 ± 0.07 ml/min/g; NS). Blood flow in the adjacent 1, adjacent 2, and remote regions remained at control levels.

The extent of transmural ischemia was assessed by left ventricular wall thickness. The percentage of the wall thickness that was ischemic (figure 3) was significantly greater in the ischemic region (7.2%) than in the remote region (50.1%). The thickness of the ischemic border was abolished during subendocardial ischemia, and was replaced by thinning during transmural ischemia. In adjacent 1, function was further depressed during subendocardial ischemia and progressively abolished during transmural ischemia, while in adjacent 2, only during transmural ischemia was function impaired (Student-Newman-Keuls test, p < .001). In the remote region, there were no changes in regional myocardial function at any time (multiple measures ANOVA).
Thus, thickening in the ischemic region was abolished when ischemia involved the inner half of the left ventricular wall, and the extent of dysfunction beyond the ischemic border was restricted to the adjacent 1 region (8.5 ± 1.0 mm; table 1).

Coronary reserve in nonischemic myocardium during regional transmural ischemia (figure 5). To assess coronary reserve in nonischemic myocardium after total coronary occlusion, we gave dipyridamole (0.21 to 0.42 mg/min iv) to seven dogs. The circumferential extent of ischemia, heart rate, left atrial pressure, end-diastolic cavity area, end-diastolic thickness, and fractional change in cavity area did not change during administration of dipyridamole. Mean arterial pressure fell (91 ± 7.1 to 73 ± 7.5 mm Hg; p < .03), but regional percent systolic thickening remained unchanged. The cross-sectional configuration of the left ventricle also remained unaltered during dipyridamole.

Changes in myocardial blood flow were not statistically significant in the ischemic region during dipyridamole (0.17 ± 0.04 to 0.09 ± 0.02 ml/min/g in the subepicardium and 0.03 ± 0.02 to 0.01 ± 0.01 ml/min/g in the subendocardium), but were marked in the nonischemic myocardium (figure 5). Flow increased three- to fivefold during infusion of dipyridamole in the adjacent regions, suggesting that increased local oxygen demands in the face of normal blood flow ("relative ischemia") are not responsible for dysfunction there. Furthermore, the magnitude of flow augmentation was not the same throughout the nonischemic portion of the left ventricular cross section, but gradually increased from adjacent 1 to remote.

Effect of propranolol on thickening and shape during transmural ischemia (figures 6 and 7; table 2). After propranolol, heart rate decreased from 128 ± 7.2 to 95 ± 14.4 beats/min (p < .03). The circumferential extent of ischemia, arterial pressure, left atrial pressure, end-diastolic area, end-diastolic thickness, and fractional change in area as well as regional myocardial blood flow remained unchanged when compared with values during total occlusion before propranolol.

Systolic thinning in the ischemic region was also unchanged before and after propranolol (from −22.6 ± 9.0% to −20.8 ± 7.2%; NS), but noteworthy changes occurred in the nonischemic region of the left ventricle. While percent systolic thickening declined in the remote region (from 50.0 ± 7.7% to 34.6 ± 5.6%; p = .02), thickening of adjacent nonischemic myocardium actually increased (from −0.25 ± 3.7% to 15.2 ± 3.9% [p = .02] in adjacent 1, and from 17.4...
FIGURE 7. Cross-sectional end-systolic view at the level of the papillary muscles in one of the five dogs given propranolol after the onset of transmural ischemia. Top, Control period; middle, transmural ischemia; bottom, transmural ischemia plus propranolol.0 1 mg/kg). Note distortion in left ventricular shape during transmural ischemia, largely restored after propranolol (see text). Ischemic region is located between the arrows. White lines in middle panel illustrate maximum and minimum left ventricular endocardial diameters used for calculation of ratios (see table 2). These lines are eliminated from the other two panels for clarity of illustration. In this illustration, minimum diameter intersects centers of ischemic and remote regions; maximum diameter intersects adjacent 1 on one end, and the border of ischemia and adjacent 1 on the other.

TABLE 2
Ratios of maximum to minimum left ventricular end-systolic endocardial diameter

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Control</th>
<th>Transmural ischemia</th>
<th>Transmural ischemia plus propranolol</th>
</tr>
</thead>
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<td>1</td>
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<tr>
<td>Mean ± SD</td>
<td>1.20 ± 0.11</td>
<td>1.57 ± 0.10</td>
<td>1.27 ± 0.18</td>
</tr>
</tbody>
</table>

F = 16.6; df = 2, 12; p < .001 (one-way ANOVA).

± 2.8% to 33.4 ± 3.9% [p < .001] in adjacent 2; figure 6).

During transmural ischemia, the cross-sectional shape of the left ventricle changed from its normal circular configuration to a flattened configuration, as illustrated in figure 2. This shape change was confined largely to end-systole. After administration of propranolol, the cross-sectional shape of the left ventricle was restored toward normal (figure 7; table 2). In the five dogs given propranolol after the onset of transmural ischemia, control period ratio of maximum to minimum left ventricular end-systolic endocardial diameter averaged 1.20 ± 0.11, increased to 1.57 ± 0.10 during transmural ischemia, and fell to 1.27 ± 0.18 during transmural ischemia plus propranolol (table 2; p < .002 by ANOVA). During transmural ischemia, the minimum diameter intersected both the ischemic and the nonischemic remote regions in all five animals. The maximum diameter intersected the adjacent 1 or 2 regions at both its ends.

Discussion

Our results indicate that during regional transmural ischemia the function of normally perfused myocardium immediately adjacent to the ischemic border is markedly impaired. These results are consonant with previous findings from other laboratories, but the single-dimensional techniques employed in these studies limited their ability to relate perfusion and function topographically. With the use of two-dimensional imaging techniques we were able to match perfusion and function around the entire left ventricular circumference. We found that dysfunction during transmural ischemia extends to regions located relatively distant (24.9 ± 2.5 mm) from the ischemic border, although impairment of thickening is less severe there than in the immediately adjacent regions (8.5 ± 1.0 mm).
After total circumflex coronary arterial occlusion, global left ventricular function was depressed in all of our experiments. The left ventricular cavity size was increased and wall thickness reduced, possibly in response to the Frank-Starling mechanism. Furthermore, our data indicate that the circular shape of the normal left ventricular cross section becomes ellipsoid during systole (figure 7). The possible relationship between this pattern of shape change and adjacent nonischemic myocardial dysfunction is discussed in detail below.

Our results also show that systolic thickening ceases when ischemia involves the inner half of a segment of the left ventricular wall. Gallagher et al. reported a 75% reduction in systolic thickening during subendocardial ischemia, and systolic thinning only when transmural ischemia was present. Since the ability of the myocardium to shorten and thicken during systole depends not only on its state of contractility, but also on its local load or stress, the abolition of systolic thickening in wall segments subjected to endocardial ischemia could result from the exposure of a functionally thinner left ventricular wall to the normal intracavitary left ventricular pressure. Such relative overload could impair local shortening and thickening and yet allow the subepicardial layers to develop sufficient tension to prevent stretching and bulging of the entire wall during systole. Alternatively, radial tethering of subepicardial to subendocardial layers during subendocardial ischemia has also been postulated as a possible mechanism of impaired thickening. During subendocardial ischemia, dysfunction also exceeded the ischemic border to encompass nonischemic regions. However, when compared with transmural ischemia, dysfunction in nonischemic adjacent myocardium was much less profound, being restricted to adjacent 1 regions.

Method. One potential explanation for dysfunction of adjacent nonischemic myocardium would be “contamination” of adjacent 1 regions by ischemic tissue. This is unlikely because of the rigid criteria employed in the selection of adjacent 1 regions, based on a combination of two currently used methods to assess myocardial perfusion. When injected into the left atrium after total circumflex coronary ligation, both 9 to 11 μm microspheres and monastral blue reach the entire heart, with the exception of those regions normally perfused by the vessel (the occluded bed) and unreachable through collaterals (the ischemic region). In our laboratory, in the assessment of the size of the ischemic region the results obtained with these two methods have been shown to correlate well. Nevertheless, we considered the radioactive microsphere method as the standard, and used the monastral dye results exclusively as a guide for sampling selection. Therefore, adjacent 1 tissue samples were blue on all faces and contained no nonblue tissue inside them. Most importantly, however, microsphere-determined blood flow in adjacent 1 regions remained at the same level as in adjacent 2 and remote regions during both subendocardial and transmural ischemia. The possibility that adjacent 2 samples could have been contaminated by ischemic tissue is even smaller, owing to the greater distance between these regions and the ischemic border.

The intermediate zone that connects ischemic to normally perfused myocardium (ischemic border) has been described as being 8 to 15 mm wide and irregular, owing to the complex interdigitation of capillaries between adjacent vascular beds and, to a lesser extent, to a gradient of collateral flow that exists from the lateral to the central portions of the ischemic region. In our experiments, the ischemic border encompassed one, or less frequently two, of the circumferential segments on each side of the ischemic region after total occlusion. These segments did not enter the topographic analysis of myocardial function because they were neither transmurally ischemic nor transmurally nonischemic, but they were added to the ischemic region in the estimation of the circumferential “extent of ischemia.” Thus, although the ischemic border was relatively sharp in our experiments, the transition from systolic thinning of transmurally ischemic tissue to normal thickening of remote, nonischemic myocardium was much less abrupt, and occurred over a much larger segment of the left ventricular wall.

Myocardial function was assessed by two-dimensional echocardiography and metal beads were sewn to the epicardium to account for changes in the angle of cross-sectional imaging. These markers defined a cross-sectional plane before any measurement was made and could be seen on each frame throughout the cardiac cycle. In addition, changes in end-diastolic thickness were uniform for the four topographic regions during different interventions, and were consistent with changes in parameters of global left ventricular size, function, and shape. Systolic thickening was chosen as the regional parameter of function on the basis of previous work done in our laboratory that showed its advantages over wall motion analysis.

The analysis of myocardial functional changes was done by averaging values from circumferential segments located inside selected topographic regions. Although this approach represents a powerful way of
comparing different experiments, it may also dilute myocardial dysfunction of a given segment or impair the spatial resolution inside a given region. However, analysis of individual (one-sixteenth circumference) segments would have introduced an unacceptably high “noise” level into the data.

**Mechanism.** The possibility of local ischemia due to exceptionally high oxygen demands in the adjacent regions could not be ruled out solely by the maintenance of local blood flow at control levels during coronary occlusion. Adjacent regions, owing to their peculiar location between remote and ischemic myocardium, may be under increased local wall stress with consequent high metabolic demands. Recently, evidence of local metabolic changes in nonischemic adjacent myocardium has been reported. Furthermore, increased stress or load could also generate local compression of intramyocardial vessels with increased local impedance to coronary blood flow. The interaction of these factors could result in “relative” regional ischemia and consequent hypokontractility. Nevertheless, the very absence of improvement in regional function in the face of a three- to fivefold increase in blood flow after dipyridamole suggests that adjacent regions are, in fact, nonischemic and still retain the potential to autoregulate their own blood supply to a great extent.

The experiments with dipyridamole do indicate a reduction in the maximal coronary vasodilating capacity of adjacent regions when compared with remote regions. This difference may be a consequence of local extravascular compression of intramyocardial vessels associated with locally increased wall stress or overload. This was not seen before dipyridamole because of autoregulation; however, it became evident during maximal vasodilatation.

Another potential mechanism of dysfunction in nonischemic adjacent regions is increased local wall stress, which could result in a reduction in percent systolic thickening in the absence of ischemia or other mechanisms of impaired contractility. Although regional stress has been measured directly, the existing techniques have been criticized. Stress has also been estimated from measurements of left ventricular pressure, wall thickness, and cavity dimensions, and has been related to a variety of theoretical models of the left ventricle. A thorough recent review of the advantages and limitations of such models emphasizes the potential use of the finite element method in the estimation of regional myocardial stress. The author of the review also points out the need for validation of mathematical models by reliable direct measurements.

Bogen et al. used the finite element theory to model the human left ventricular cross section damaged by regional transmural infarction. They estimated circumferential myocardial stress to be greater in the adjacent regions than in the remote ones, where it coincided with stress estimates for the noninfarcted heart. Moreover, for large infarcts (41.3% of the cross-sectional circumference), stress estimates were markedly increased in the immediately adjacent regions and values for regions only 70 to 80 degrees away from the ischemic border (well inside what would be the adjacent 2 regions in our study) coincided with those in noninfarcted hearts.

From their model, Bogen et al. also predicted an inverse relationship between adjacent myocardial dysfunction and infarct stiffness. Although we did not measure or estimate local wall stress in our study, the fact that dysfunction progressed laterally into nonischemic myocardium as ischemia was extended from the inner half to involve the entire thickness of the left ventricular wall suggests that wall stress may have increased in adjacent regions, as the ischemic zone became less stiff and bulged or stretched during systole. In addition, the presence of high extravascular restraints to blood flow in adjacent regions could also result from increased wall stress in these regions. Most importantly, the improvement of systolic thickening in adjacent regions, coincident with the decline in function of remotely located nonischemic myocardium after propranolol, strongly supports the concept that increased wall stress contributes to impairment in these regions during regional ischemia.

While the concept of adjacent dysfunction caused by increased wall stress is attractive, it still requires insight into the mechanisms of such a selective topographic increase in wall stress. The potential contribution of ischemic zone dysfunction to impaired adjacent zone performance has previously been recognized, but the mechanisms have not been detailed. Wyatt et al. postulated that ischemic tissue may function as a parallel resistance, transmitting to adjacent nonischemic myocardium some of its own contractile characteristics. In our studies, total coronary occlusion resulted in transmurally ischemic tissue that possessed no contractile properties. In addition, acute severe ischemia, as was generated in our experiments, results in increased myocardial compliance in the first half hour after total coronary obstruction. Thus, the possibility of adjacent myocardial tethering by stiff or noncontractile ischemic tissue in our studies seems unlikely. On the other hand, the possibility of adjacent tethering caused by ischemic wall bulging or overstretching
should be considered, particularly in the face of the marked left ventricular deformation seen during systole. Such deformation could conceivably alter the balance of forces inside adjacent wall segments by changing the angles of myocardial fibers connecting remote, adjacent, and ischemic regions. Local wall stress may increase, and systolic shortening be reduced, by this mechanism. In our study, marked changes in the systolic left ventricular cross-sectional configuration occurred after the onset of transmural ischemia. Moreover, the association of partial restoration of normal shape with improvement in the function of adjacent regions after propranolol supports the concept that mechanical tethering of adjacent nonischemic myocardium, secondary to left ventricular deformation during systole, could have caused locally increased wall stress with consequent impairment of systolic thickening.

Propranolol and practolol have been shown previously to depress function of remote nonischemic myocardium during regional ischemia and decrease systolic thinning of ischemic areas. We did not detect any changes in systolic thinning of the ischemic region after propranolol. Myocardial function in the border zone during regional ischemia has also been previously shown to improve after propranolol. These results were attributed to improved local balance of oxygen supply/demand in moderately ischemic segments. By contrast, Vatner et al. reported further depression of myocardial function in the ischemic border zone, which was attributed to the negative inotropic effects of propranolol in these areas. Although in Vatner’s study mean percent systolic shortening decreased after propranolol, this depression was less in the border zone than in remote regions when absolute values were compared.

In our experiments, the cross-sectional shape of the left ventricle became distorted during systole after total coronary occlusion. By contrast, at end-diastole this shape distortion was only slight. Thus, the possibility that shape changes could alter loading conditions on adjacent nonischemic myocardium during diastole and place these areas in an unfavorable position on the Frank-Starling curve is unlikely. Such a mechanism has been postulated to explain dysfunction of myocardium adjacent to fibrous or fibromuscular aneurysms. Alternatively, the changes in the normal systolic shape of the left ventricle may have overloaded or overstressed particular segments of the left ventricular wall. The impaired thickening seen in adjacent nonischemic regions in our study may be attributable to this mechanism. We hypothesize that interventions that reduce shape deformation during systole may improve adjacent myocardial dysfunction. Such a salutary effect could result from increased stiffness of ischemic or infarcted regions, or from external restraint to left ventricular systolic deformation. The presence of an intact pericardial sac may theoretically work in the latter manner, if its size becomes limiting during systole.

In conclusion, our results indicate that during subendocardial ischemia dysfunction exceeds the ischemic border to impair thickening of immediately adjacent nonischemic regions, and reaches even further during transmural ischemia. Therefore, dysfunction overestimates ischemia during progressive occlusion of the left circumflex coronary artery. Ischemia owing to high oxygen demand is not the mechanism responsible for dysfunction in adjacent regions since thickening there does not improve even in the face of intense local vasodilation and increase in flow. Maximal vasodilating capacity is only slightly limited in these areas, possibly by increased extravascular restraints to blood flow.

Finally, our data support the concept that the interplay of mechanical forces in the nonischemic left ventricle is altered after the onset of regional acute ischemia. An imbalance of forces may selectively overstress nonischemic adjacent myocardium by mechanical tethering that results from changes in left ventricular shape during systole and contributes to the dysfunction found in these adjacent regions after total coronary occlusion.

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