Impaired Function of Salvaged Myocardium: Two-dimensional Echocardiographic Quantification of Regional Wall Thickening in the Open-chest Dog

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Summary This study was designed to examine the functional properties of myocardium subjected to acute coronary occlusion but surviving the ischemic insult. Ten conscious mongrel dogs underwent mid-circumflex coronary occlusion and were treated for 6 hours with prostacyclin, 540 ng/kg/min, and ibuprofen, 110 μg/kg/min, or diprydiamole (7-9.7 μg/kg/min). At 7 days, each dog was anesthetized, the chest was opened, and cross-sectional two-dimensional echocardiograms were obtained through the middle of the occluded vascular bed. A computer-aided contouring system was used to assess percent systolic thickening in 16 equally spaced segments around the left ventricle. Metal markers sewn to the epicardium permitted precise regional correlation of histology, percent systolic thickening, and flow, as measured by radioactive microspheres. Necrosis was minimal, averaging only 2.2 ± 0.8% (±SEM) of the left ventricular ring corresponding to the echocardiographic cross section. Percent systolic thickening was 28.6 ± 4.7 in the nonischemic anterior wall, but was reduced to −4.5 ± 3.1 in the occluded bed (p < 0.01). In individual echo segments, percent systolic thickening correlated with local flow (r = 0.69, p < 0.001), but was still depressed even when flow was normal. In six segments within the occluded bed that had normal histology and flow, percent systolic thickening was 52% less than that in the nonischemic region (p < 0.02). Thus, coronary artery occlusion combined with drug treatment results in myocardium that, although histologically normal and supplied by normal myocardial blood flow, remains functionally abnormal 7 days after occlusion.

Methods

Animals

We studied 10 of 30 dogs prepared during a series of experiments investigating the ability of dipyridamole or prostacyclin and ibuprofen to reduce infarct size after coronary occlusion. They differed from the larger group in that they had no visible myocardial necrosis by gross inspection of the heart.

Instrumentation

Mongrel dogs that weighed 18–24 kg were instrumented under pentobarbital anesthesia. A left thoracotomy was performed and an occluder snare was placed around the mid-circumflex coronary artery past the first large marginal branch. This location was chosen so as to produce a relatively small occluded bed. The snare consisted of a silk thread that attached to a plastic tube at one end and looped around the coronary artery before exiting through the same plastic tube. To mark the center of the occluded bed, the artery was transiently occluded and a superficial 4-0 silk suture was sewn epically around the center of the region of cyanosis. Polyethylene catheters were placed in the external jugular vein, common carotid artery and left atrium. The distal ends of these catheters and the tube containing the snare thread were externalized at the back of the neck through a subcutaneous tunnel. Penicillin, 1 million U, and streptomycin, 1 g, were given intramuscularly after surgery and the catheters were filled with heparinized normal saline.

Controls

Two control dogs were subjected to the entire protocol except that coronary occlusions were not performed and microspheres were not injected.
Experiment

After 1 week of recovery from the thoracotomy, the conscious dogs stood in a restraining sling and morphine, 0.25 mg/kg i.v., was given for sedation and analgesia. Continuous recordings of left atrial and aortic pressure (Statham P23Db transducers) and lead II of the ECG were made on a direct-writing recorder (Gould, Inc). Myocardial blood flow measurements were made using 7–10-μ diameter radioactive microspheres, with Tween-80 added, labeled with 125I, 147Ce, 85Sr, 86Nb or 46Sc (3M Co.). Microsphere vials were agitated for 3–5 minutes before use. Approximately 2 million microspheres, followed by a 5-ml saline flush, were injected into the left atrium for each measurement. Starting just before the injection and continuing for 2 minutes afterwards, reference blood samples were withdrawn at a constant rate by a calibrated Harvard pump. The first myocardial blood flow measurement was made 40 minutes after the morphine was given. Lidocaine, 1 mg/kg i.v., was then administered. Five minutes later, coronary occlusion was established by tightly pulling the free external end of the silk thread and then clamping the thread to the plastic tube. A second microsphere measurement was made 5 minutes after occlusion. The dogs then received one of the experimental treatments. In the first five dogs, dipyridamole was given as an initial i.v. bolus of 5 mg (obtained in 2-ml ampules containing 10 mg of dipyridamole, 4 mg of tartaric acid, and 100 mg of polyethylene glycol 600, Boehringer Ingelheim), followed by a continuous infusion of 0.084 mg/min. In the second five dogs, prostacyclin and ibuprofen were given by continuous infusion into the left atrium and jugular vein, respectively. Prostacyclin, 0.18 mg/kg, was mixed in 50 ml of saline and given in a dose of 5.8 μg/kg/min for the first 3 minutes and 540 mg/kg/min thereafter. Ibuprofen, 37.5 mg/kg, was also mixed in 50 ml of saline and given as 1.2 mg/kg/min for 3 minutes, followed by 110 μg/kg/min. Microsphere flow measurements were repeated 1 and 6 hours after treatment. Phasic and mean arterial and left atrial pressures were recorded before and after each microsphere injection. No attempt was made to suppress ventricular ectopy after occlusion. After 6 hours, the drug infusions were stopped and the dogs were returned to their cages.

Echocardiographic Studies

Seven days after coronary occlusion, the dogs were brought back to the laboratory and general anesthesia was produced with pentobarbital, 20–25 mg/kg. A midline thoracotomy was performed, the pericardium opened, and the beating heart exposed. Two ultrasound-dense metal beads (3/16-inch stainless steel shot with holes drilled to allow a suture to pass through) were sewn to the epicardium (fig. 1). One bead was sewn posteriorly in the center of the occluded bed at the site of the previously placed silk suture. The second bead was sewn anteriorly at the same distance from the cardiac apex as the posterior bead.

Two-dimensional echocardiography (Varian V-3000 Ultrasonograph) was then performed on the anesthetized, open-chest dogs. The specially modified echo probe consisted of a transducer head surrounded by a standoff device with a polyethylene membrane. The epicardium was in direct contact with the outer surface of the membrane and the entire space between the inner surface of the plastic and the echo transducer was filled with mineral oil. The echocardiographic probe was angulated until a cross-sectional view of the left ventricle was obtained that contained both metal markers. Visualization of the markers usually necessitated a transient reduction in transmit gain levels (fig. 2). Data were stored on 1-inch videotape (60 fields/sec, International Video Corp.).

Heart rate, mean arterial pressure and left atrial pressure were then recorded. A final myocardial blood flow measurement was made, after which the dogs were given a lethal dose of anesthetic; the hearts were removed, washed free of blood and weighed.

Determination of Mass of Occluded Bed, Regional Myocardial Blood Flow, and Myocardial Injury

The size of the occluded coronary bed was measured by postmortem angiography. Cannulas were placed in the origins of the right, left anterior descending and circumflex coronary arteries and simultaneous injections were made of a barium sulfate–gelatin mass at a controlled pressure of 160 mm Hg. After packing with gauze, the hearts were fixed in formalin and stereoscopic radiographs prepared. Completeness of occlusion was confirmed by inspecting the angiograms.

Each heart was sliced into four or five transverse sections. The section containing the 2 metal beads was 1 cm thick and other sections were 1–1.2 cm thick. Pairs of wire markers were placed at opposite points through the wall of the ventricle in each section and paired stereoscopic radiographs were made. Using the whole-heart images and the radiographs for each slice, an independent observer marked the boundaries of the occluded coronary bed by following the course of each major coronary branch from ring to ring and examining the patterns of interdigitation of terminal branches. Retrograde filling of the occluded bed through collaterals from the nonoccluded vessels enabled definition of the border between coronary branches.

The formalin-fixed heart slices were dissected free of the atria, right ventricle, large epicardial vessels and fat. After weighing each slice, the top and bottom surfaces were traced on plastic transparencies, thereby outlining the left ventricle. The tracing of each ring was superimposed on the corresponding radiograph to permit transfer of the marked boundaries of the occluded bed. Tracings and radiographs were aligned using natural markers (cavity and wall shape), the wire markers and the metal beads.

Myocardial Blood Flow Determinations

Sampling for regional myocardial blood flow was made transmurally in the ring containing the metal beads. The ring was divided into 16 equally spaced segments by a radial grid. All segments within the occluded bed (three or four per dog), segments from
myocardium adjacent to the occluded bed (two per dog), as well as a control segment outside the occluded bed, were sampled. Tissue samples were divided into endocardial and epicardial halves, weighed, placed in vials that contained formalin, and counted for radioactivity along with reference blood samples in a well-type gamma scintillation counter (Packard model 5986) at energy windows adjusted to the peak emission from each of the five nuclides. Regional myocardial blood flow was calculated using the formula \( R \times \) \((Cm/ Cr)\) (ml/min/g), where \( R = \) reference blood flow pump withdrawal rate, \( Cm = \) counts per gram in myocardial tissue sample and \( Cr = \) counts in reference blood sample. Flows were then corrected for true and apparent microsphere loss.\(^{10, 11}\) The preocclusion content of microspheres in each ischemic region expressed relative to that in the nonischemic area was used as a quantitative measure of the combined effects of microsphere loss, local edema, hemorrhage and inflammatory cell infiltrate. Subendocardial flow values were corrected using preocclusion subendocardial anterior wall flows, and subepicardial flow values were corrected using subepicardial flows. Thus, the following formula was used: \( Fc = F \times (A/P)\), where \( Fc = \) corrected flow, \( F = \) uncorrected flow, \( P = \) preocclusion flow in region of interest and \( A = \) preocclusion flow in corresponding nonischemic region.

**Histologic Studies**

Longitudinal slices through the center of each myocardial sample were prepared for histology and stained with hematoxylin-eosin. The amount of necrosis was determined from microscopic examination with estimations of the percent of each histologic section involved by infarct. This was done without knowledge of gross appearance, function or regional myocardial blood flow.

**Analysis of Two-dimensional Echocardiograms**

For correlation of the echocardiographic, pathologic and flow data, the echocardiographic image was recalled from videotape and displayed on a television screen. The left ventricular image was centered on a plastic transparency with a radial grid that contained 16 equidistant radii corresponding to the 16 radii generated by the contouring system, and the position of the two metal beads was marked (fig. 1). The transparency was then placed over the left ventricular slice containing the beads, aligned so that the beads and marked bead positions coincided, and the left ventricular ring was traced. The occluded bed boundary was then transferred from the transparency described earlier.

Two-dimensional echocardiograms were transferred to a videodisc (VAS) and displayed on a high-resolution \( x, y, z \) oscilloscopic screen for computer-
Computer analysis permitted spline-fit contouring of both endocardium and epicardium, and calculations of percent systolic thickening, an index of regional function, could be made for each of the 16 point pairs. Regional percent systolic thickening was defined, after the method of Lieberman et al., as wall thickness at end-systole minus thickness at end-diastole divided by thickness at end-diastole times 100. End-diastolic thickness was measured by QRS onset. Negative values meant systolic thinning.

Average percent systolic thickening was examined in five regions in each dog (fig. 1). The 16 equally spaced segments were grouped by location. Segments that lay totally within the occluded bed (three or four per dog) comprised the occluded bed center. Those segments traversed by the boundary of the occluded bed (usually two per dog) comprised the occluded bed edge or lateral zone. The control region (nonischemic anterior wall) contained the three or four segments directly opposite to the occluded bed center. The remaining six to eight segments were divided into adjacent zone 1 (segments directly adjacent to the occluded bed edge) and adjacent zone 2 (segments adjacent to the control region but outside the occluded bed).

Statistics

The significance of differences across time for hemodynamic data and flows, and of differences in percent systolic thickening in the various myocardial regions, was calculated by repeated-measures analysis of variance with orthogonal contrasts for trends. Linear regression analysis was used to compare percent systolic thickening and histologic necrosis. Values are given as mean ± SEM.
TABLE 1. Hemodynamic Values

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart rate (beats/min)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Left atrial pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>101 ± 7</td>
<td>111 ± 5</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>Postocclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>111 ± 10</td>
<td>116 ± 5</td>
<td>9 ± 1</td>
</tr>
<tr>
<td>1 hr</td>
<td>105 ± 11</td>
<td>116 ± 6</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>6 hr</td>
<td>109 ± 9</td>
<td>106 ± 6</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>7 days (under anesthesia)</td>
<td>157 ± 9*</td>
<td>85 ± 5*</td>
<td>8 ± 2</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
*p < 0.01, 7-day value vs others combined (analysis of variance); control through 6-hour values not significantly different using repeated-measure analysis of variance.

Results

Of the 10 dogs included in the current study, five were treated with prostacyclin plus ibuprofen and five with dipyridamole. As no significant differences occurred between the two groups, the results in the 10 dogs were combined.

Hemodynamics (table 1)

During the first 6 hours after occlusion, heart rate, mean arterial pressure, and mean left atrial pressure did not change. At the time of two-dimensional echocardiography 7 days later, the dogs were anesthetized and hemodynamic values were therefore significantly different from those obtained on the day of the initial experiment. Heart rate was higher (157 ± 9 vs 101 ± 7 beats/min, p < 0.01) and mean arterial pressure was lower (85 ± 5 vs 111 ± 5 mm Hg, p < 0.01), while left atrial pressure was similar.

Regional Myocardial Blood Flow (table 2)

After coronary occlusion, blood flow decreased throughout the occluded bed in all regions except the subepicardial portion of the lateral zone. The reduction in flow was greatest in the center zone of the occluded bed, and the subendocardium showed a greater reduction than subepicardium. In individual dogs, the subendocardial flow ranged from 0.15–0.81 ml/g/min (11.5–92.0% of simultaneous nonischemic anterior wall flow) and in eight dogs flow was less than 50% of nonischemic flow. There were no significant reductions in flow in the nonischemic region. During infusion of the experimental agents, myocardial blood flow increased in all regions within the occluded bed at 1 and 6 hours. Analysis of variance revealed that the flow across time increased significantly in the center of the occluded bed and in the subendocardial portion of the lateral zone. The nonischemic region showed no significant changes in flow at 1 and 6 hours during drug infusion.

At 7 days, with the dogs anesthetized, regional myocardial blood flow was reduced in all nonischemic and ischemic regions of the myocardium compared with the original control flows. However, expressed relative to the nonischemic region, flow in the occluded bed was significantly reduced only in the subendocardium. For the subendocardium, flow averaged 74.9 ± 10.1% of nonischemic flow in the center, and 83.8 ± 5.3% in the lateral zone (p < 0.05 and 0.02, respectively, vs nonischemic region). For the subepicardium, values were 95.9 ± 7.7% and 103.5 ± 10.5%, respectively.

Gross and Microscopic Infarction

Occluded bed size, measured from postmortem radiographs, was 10.8–23% of the left ventricular mass (mean 16.6 ± 4.8%). No myocardial infarction was grossly visible on the cut surface of any myocardial ring in any dog. However, one dog that received ibuprofen plus prostacyclin had small foci of gross necrosis visible when the ring was cut by perpendicular slices. Although microscopically, the percent of left ventricular ring infarction was higher in this dog than in the others (7% vs 1.7%), this dog was included in all analyses. The amount of microscopic necrosis in each dog was 0–7% of the left ventricle, with an average

TABLE 2. Regional Myocardial Blood Flow

<table>
<thead>
<tr>
<th></th>
<th>Occluded bed</th>
<th>Lateral zone</th>
<th>Nonischemic region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subendo</td>
<td>Subepi</td>
<td>Subendo</td>
</tr>
<tr>
<td>Control</td>
<td>1.27 ± 0.15</td>
<td>1.24 ± 0.15</td>
<td>1.27 ± 0.15</td>
</tr>
<tr>
<td>Postocclusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 min</td>
<td>0.45 ± 0.07</td>
<td>0.83 ± 0.09</td>
<td>0.80 ± 0.12</td>
</tr>
<tr>
<td>1 hr</td>
<td>0.78 ± 0.13</td>
<td>1.06 ± 0.15</td>
<td>0.96 ± 0.17</td>
</tr>
<tr>
<td>6 hr</td>
<td>0.86 ± 0.12†</td>
<td>1.06 ± 0.14†</td>
<td>1.03 ± 0.14†</td>
</tr>
<tr>
<td>7 days (under anesthesia)</td>
<td>0.55 ± 0.09*</td>
<td>0.74 ± 0.09*</td>
<td>0.60 ± 0.07*</td>
</tr>
</tbody>
</table>

Values are in ml/min/g (mean ± SEM).
*p < 0.01, 7-day value vs others combined (analysis of variance).
†For control through 6 hours, analysis of variance shows a significant change with time (p < 0.00001 for subendocardium, p < 0.05 for subendocardium lateral zone and subepicardium center). A significant quadratic relationship was found (p < 0.002, p < 0.05, p < 0.03 for subendocardium center, subendocardium lateral zone, subepicardium center, respectively).
percent necrosis of 2.2 ± 0.8%. The two sham controls had no microscopic infarction.

**Regional Myocardial Function by Echocardiogram**

(Table 3, Fig. 3)

Percent systolic thickening was least in the center of the occluded bed, averaging −4.5 ± 3.1% (representing systolic thinning). At the edge of the occluded bed there was 1.2 ± 2.5% systolic thickening (NS vs center). The adjacent region demonstrated an intermediate level of function, with 17.4 ± 3.7% systolic thickening in adjacent zone 1 and 24.3 ± 5.2% systolic thickening in adjacent zone 2 (p < 0.05 for adjacent zone 1 or 2 vs occluded lateral zone). The control regions demonstrated 28.6 ± 4.7% systolic thickening (p < 0.05 vs adjacent zone). Analysis of variance revealed that the overall differences in function between regions was highly significant (p < 0.0001). The sham controls had 34% and 36% systolic thickening for their entire ventricular rings.

Figure 4 shows the relationship between percent systolic thickening (normalized for systolic function in the control region) and regional myocardial blood flow at 7 days. Three segments within the occluded bed have been plotted for each dog. Regional myocardial function and regional myocardial blood flow were lin-

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**Table 3. Average Regional Percent Systolic Thickening 7 Days After Coronary Occlusion in Dogs Without Gross Necrosis**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Occluded bed center</th>
<th>Occluded bed lateral zone</th>
<th>Adjacent 1</th>
<th>Adjacent 2</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>12.5</td>
<td>6.25</td>
<td>21.75</td>
<td>27.5</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>−0.5</td>
<td>21.75</td>
<td>56.5</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>12</td>
<td>10.25</td>
<td>38.5</td>
<td>16.5</td>
</tr>
<tr>
<td>4</td>
<td>−24</td>
<td>−11</td>
<td>28.5</td>
<td>35.25</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>−0.25</td>
<td>2.25</td>
<td>17</td>
<td>22.75</td>
<td>33.7</td>
</tr>
<tr>
<td>6</td>
<td>10.5</td>
<td>−1</td>
<td>38</td>
<td>11.25</td>
<td>14.25</td>
</tr>
<tr>
<td>7</td>
<td>−9.5</td>
<td>−10</td>
<td>29.5</td>
<td>32.75</td>
<td>37.5</td>
</tr>
<tr>
<td>8</td>
<td>−14</td>
<td>4</td>
<td>13.5</td>
<td>11.75</td>
<td>29.5</td>
</tr>
<tr>
<td>9</td>
<td>−7.5</td>
<td>−2</td>
<td>−2.25</td>
<td>9</td>
<td>10.5</td>
</tr>
<tr>
<td>10</td>
<td>−3.5</td>
<td>6</td>
<td>11.5</td>
<td>3.75</td>
<td>21.5</td>
</tr>
</tbody>
</table>

Mean ± SEM: −4.5 ± 3.1 1.2 ± 2.5 17.4 ± 3.7* 24.3 ± 5.2 28.6 ± 4.7†

Overall differences in systolic thickening in various regions significantly different by analysis of variance (p < 0.0001). Brackets indicate mean values that are not significantly different from one another using Waller-Duncan K-ratio multiple-comparisons test.

*p < 0.01 compared with both occluded bed center and occluded bed lateral zone.

†p < 0.05 compared with adjacent zone 1, p < 0.01 compared with occluded bed center and lateral zone.
early correlated (\( y = -98.0 + 137.4x, r = 0.70, p < 0.0001 \)). Even at a normalized flow of 100\%, the value for regional thickening was only 39.4\% of normal regions, with 95\% confidence limits of 23.9\% and 54.9\%.

Of the 30 segments examined within the risk zone, a total of six segments from four dogs showed normal regional flow and histology. Percent thickening for these segments was reduced by 52\% compared with control regions (\( p < 0.02 \)).

Normalized percent thickening was not significantly correlated with percent local necrosis (\( r = 0.125 \)), heart rate, left atrial pressure or mean arterial pressure.

**Discussion**

In this study, we found impaired function of histologically salvaged myocardium. Other investigators have found that after experimental coronary occlusion, the amount of functionally abnormal myocardium exceeds the amount of ischemic or necrotic myocardium. Wyatt et al.\(^1\) found that both adjacent ischemic and remote nonischemic regions of myocardium were functionally affected for up to 30 minutes after acute coronary occlusion. Dysfunction measured by length gauges was inversely proportional to distance from the occlusion. Kerber et al.,\(^2\),\(^5\) using one-dimensional echocardiography, noted reductions in systolic septal velocity, septal excursion and thickening in both ischemic and adjacent nonischemic regions for up to 45 minutes after coronary ligation, although radioactive microspheres confirmed normal regional myocardial blood flow in abnormally functioning nonischemic regions. Roan et al.,\(^1\)\(^9\) using microcrystal techniques in dogs subjected to acute coronary occlusion, found that substantial functional impairment could exist even in myocardial segments in which necrosis was absent. Our studies\(^6\),\(^8\) have shown that two-dimensional echocardiography consistently overestimates the amount of necrosis found at autopsy in animals and man, suggesting that histologically normal, albeit functionally abnormal, regions of myocardium exist.

Functional abnormalities in histologically normal myocardium adjacent to ischemic or infarcted tissue may be attributed to a mechanical tethering of infarcted or ischemic tissue to adjacent normal tissue. In the present experiment, minimal or no infarction was present within the occluded coronary bed. Functional abnormalities could not, therefore, be explained by the mechanical effects of adjacent infarction. Although impaired function within the occluded bed may be partially explained by local ischemia in those segments with diminished flow, the dysfunction of segments with both normal histology and flow must be otherwise accounted for. In these, tethering to noninfarcted but ischemic regions seems a plausible mechanism of impaired thickening. Likewise, tethering to ischemic tissue most likely accounts for the reduction in thickening of the adjacent zone, where function was reduced although this zone was not within the occluded bed. Thus, although this study appears to eliminate tethering to infarcted tissue as a mechanism of impaired function, tethering to ischemic tissue may be a mechanism of dysfunction in normally perfused regions both within and without the occluded bed.

The dogs in this study were subjected to a relatively mild ischemic insult in order to maximize the chance for obviating necrosis within the occluded bed. Thus, regional myocardial blood flow in the subendocardium in the center of the occluded bed 5 minutes after coronary occlusion was only modestly reduced, to an average 0.45 ml/g/min, although in individual dogs the flow was as low as 0.15 ml/g/min and eight of the 10 dogs had flow less than 50\% of that in nonischemic myocardium. At least a small infarct was therefore expected in most of the dogs.\(^9\) Because of the small occluded bed sizes, mild degrees of ischemia, and lack of unmedicated control dogs, we cannot be certain to what extent the lack of necrosis in the occluded bed was due to "natural salvage" (i.e., natural increase in collateral flow) or drug intervention. However, dipyriramole,\(^17\) ibuprofen,\(^18\) and prostacyclin\(^19\) all individually reduce infarct size.

A number of studies have reported prolonged functional abnormalities in myocardium subjected to transient myocardial ischemia. Heyndrickx et al.\(^20\) found that a transient 15-minute occlusion produced functional changes persisting at 6 hours, although function was normal at 24 hours. Theroux et al.\(^21\) described functional abnormalities persisting for up to 45 minutes after only 2 minutes of transient occlusion. The pressure-length loops of Tyberg et al.\(^22\) were abnormal at least 2 hours after transient 30-minute coronary occlusion. Puri\(^23\) found that 1 hour of temporary occlusion followed by reperfusion produced substantial functional deficits at 2 hours and an incomplete, although substantial, return of ventricular function at 2 weeks. In that study, histology was normal in four of the six dogs examined. Klener et al.\(^24\) noted that 15 minutes of transient coronary occlusion followed by reperfusion produced systolic shortening abnormalities that persisted for 3 days.

Biochemical or ultrastructural abnormalities may explain the prolonged functional deficits noted in transiently ischemic myocardium. Wood et al.\(^25\) found decreased glycogen content after 60 minutes of reperfusion that followed 10 minutes of ischemia. DeBoer et al.\(^26\) and Klener et al.\(^27\) reported decreased content of adenosine triphosphate and total purines as well as abnormal ultrastructure (areas of localized sarcoplasmic reticular and intermyofibrillar edema and glycogen loss) 72 hours after a 15-minute ischemic episode. Further studies by this group\(^24\) demonstrated return of function and adenosine triphosphate content by 7 days. Schaper et al.\(^28\) found that 15–90 minutes of global ischemia in the isolated dog heart produced a depression of function that persisted through 50 minutes of reperfusion, associated with depression of adenosine triphosphate, but not of phosphocreatine. Various degrees of ultrastructural injury were found, although the changes identified as "reversible" were gone by 120 minutes of reperfusion.

Ventricular function in this experiment was deter-
mined 7 days after occlusion, while the dogs were anesthetized. Hemodynamic values therefore differed considerably from those determined during the original control period. Mean arterial pressure was lower, producing the possible confounding effects of improved thickening through decreased afterload and worsened thickening through decreased myocardial perfusion. Heart rate was higher, increasing myocardial demand and possibly exacerbating the degree of functional impairment. Thus, the absolute level of impairment in the occluded bed was likely influenced in this model by these factors, although control regions were under the same hemodynamic constraints. Postextrastolic potentiation or the infusion of dopamine or isoproterenol might have uncovered an inotropic reserve. Lengthening the period between occlusion and functional assessment might have enabled further functional recovery. Nevertheless, under the conditions of this study, salvaged myocardium was clearly not the functional equivalent of normal myocardium. The model system of the present study may, of course, not be applicable to human conditions, and our results should not be extrapolated to the clinical situation.

Impaired wall thickening within the occluded bed may have been related to a localized functional abnormality in subendocardially located cells. After coronary occlusion, ischemia was most severe in this region, increasing the likelihood of cellular injury. After 7 days, flow was normal in the subepicardium, but reduced in the subendocardium. The concept that subendocardial injury may impair transmural function is supported by the study of Lieberman et al., in which abrupt deterioration of systolic thickening occurred when the transmural extent of infarction was 1–20%; systolic thinning ensued when the transmural extent of infarction exceeded 20%, with no further augmentation of thinning as infarction increased from 21% to 100% (threshold phenomenon). In addition, Gallagher et al. reported that small changes in subendocardial flow have profound transmural effects on regional function. Therefore, a functional abnormality limited to the subendocardium could produce transmural contraction abnormalities.

Although salvage of some ischemic myocardium is feasible, this and other studies point to functional abnormalities of the salvaged tissue that persist for hours to days. Indeed, some efforts need to be focused on the full return of this tissue to normal. To do this, a complete functional assessment of such regions, the natural history of the dysfunction, and the biochemical basis must be investigated.

References

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Echocardiographic Detection of Infarct-localized Asynergy and Remote Asynergy During Acute Myocardial Infarction: Correlation with the Extent of Angiographic Coronary Disease

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SUMMARY To determine whether during acute myocardial infarction (MI), ischemia and asynergy can develop in areas remote from the infarct zone, we undertook a two-part study. In part 1, 51 patients with recent infarction (15.6 ± 4.1 days after MI) and one-vessel disease of ≥70% stenosis by angiography underwent two-dimensional echocardiography (2-D echo). Using an 11-segment ventricular model, the 2-D echocardiograms were read blind and then compared with angiography to establish the distribution of regional asynergy for MI involving each of the three major coronary arteries. In part 2, 30 patients underwent 2-D echo 10.8 ± 3.1 hours after onset of symptoms of acute MI. All 30 patients underwent coronary angiography before discharge and 19 had repeat 2-D echo 4–13 days after MI. One-vessel asynergy was defined as abnormal motion confined to a single vascular region; remote asynergy was designated when abnormal motion was present in two or more vascular regions.

Of 30 patients with acute MI, eight had one-vessel disease (1VD) and 22 had multivessel disease (MVD) by angiography. Remote asynergy by 2-D echo was found in 17 patients with MVD (77%), but in none with 1VD (p < 0.01). Of the five MVD patients without remote asynergy, four had only a 70% stenosis of a second coronary vessel. Compensatory hyperkinesis was seen in four of the 1VD patients (50%), but in only one of the MVD patients (4.5%) (p = 0.005). Follow-up 2-D echo in 19 patients revealed improvement in the extent of asynergy in two of five 1VD patients (33%) and in 10 of 13 MVD patients (77%) (p = 0.06).

Thus, MI in the distribution of a single coronary vessel produces a distinctive, recognizable pattern of asynergy. The stress of infarction may induce compensatory hyperkinesis in 1VD patients, whereas in MVD patients this stress may exceed the perfusion capacity of the additionally stenosed vessels and result in remote asynergy. Finally, the extent of early asynergy during acute myocardial infarction overestimates the extent of asynergy present after recovery from the infarct.

DURING acute myocardial infarction, left ventricular asynergy and ischemia may occur outside the acute infarct zone. This remote asynergy may be an important contributor to overall ventricular dysfunction in some patients with an acute infarction. Remote asynergy may be a marker of stenosis in another coronary vessel, indicating multivessel disease and a poorer short- and long-term prognosis after myocardial infarction. We examined segmental wall motion during the acute phase of myocardial infarction and correlated regional myocardial function with the location and number of coronary stenoses. Segmental wall motion was reassessed in the convalescent period to determine the significance of changes in wall motion over time. To accomplish these aims required a two-part study.

First, we had to establish the predicted distribution of echocardiographically determined asynergy after a one-vessel infarct. Hence, two-dimensional echocardiograms (2-D echoes) were obtained in 51 patients...
Impaired function of salvaged myocardium: two-dimensional echocardiographic quantification of regional wall thickening in the open-chest dog.
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