Significance of Regional Wall Thickening Abnormalities Relative to Transmural Myocardial Perfusion in Anesthetized Dogs

Kim P. Gallagher, PH.D., Toshiaki Kumada, M.D., James A. Koziol, PH.D., Michael D. McKown, W. Scott Kemper, M.S.E.E., and John Ross, Jr., M.D.

SUMMARY In 15 open-chest, anesthetized dogs, regional systolic wall thickening (%ΔWT) was measured with sonomicrometry and regional blood flow was determined with tracer microspheres (7-10 μm) before and after various degrees of coronary artery narrowing were created with a hydraulic occluder. The stenoses were categorized into four groups by the effect on %ΔWT, and the corresponding myocardial blood flow (MBF) was determined in four layers across the ventricular wall (layer 1: subendocardium; layer 4: subepicardium). In group 1, %ΔWT decreased 44 ± 10% and only layer 1 MBF was significantly reduced (-28%); in group 2, %ΔWT decreased 77 ± 8% and MBF was reduced in both layers 1 and 2 (-52% and -36%, respectively); in group 3, %ΔWT decreased 104 ± 3% and MBF was reduced in the three inner layers (layer 1: -65%; layer 2: -58%; layer 3: -34%); in group 4, %ΔWT decreased 145 ± 9% (systolic wall thinning) and transmural reduction of MBF was found (layer 1: -74%; layer 2: -68%; layer 3: -58%; layer 4: -29%). We conclude that (1) up to 75% reduction in systolic wall thickening may occur when perfusion to only the inner one-half of the myocardium is decreased; (2) akinetic wall motion may be observed when perfusion remains normal in the subepicardial one-fourth of the wall; (3) dyskinesia (wall thinning) occurs when blood flow is reduced transmurally.

EXPERIMENTAL STUDIES on wall thickening dynamics have been performed using a variety of techniques.1-11 Although there has been some investigation of the relationship between coronary blood flow and abnormal systolic wall motion due to ischemia,11-16 little information is available relating regional wall motion to transmural flow distribution.11 Because overall wall motion, as reflected by systolic wall thickening or thinning, should reflect the net effect of nonuniform transmural flow, we undertook to determine the relationship between systolic wall dynamics and regional myocardial blood flow (MBF) in different layers of the myocardium in the same region. Changes in regional perfusion were created by different degrees of coronary stenosis and regional flow was measured using radionuclide-labeled microspheres. Wall thickening was studied using the ultrasonic dimension gauge technique.9

Methods

Seventeen adult mongrel dogs that weighed 22-35 kg were studied. All dogs were observed for 1 month and were free of disease, with hematocrits over 35%. The dogs were anesthetized with sodium pentobarbital (30 mg/kg), a thoracotomy was performed through the left fifth intercostal space, and the heart was suspended in a pericardial cradle. Respiration was maintained with room air using a Harvard respiratory pump set at a tidal volume of 500-600 ml and a rate of 10-12 per minute;10 care was taken to maintain full lung expansion during the study. Stable hemodynamic conditions were observed throughout each experiment.

In some dogs, a high-fidelity micromanometer (Konigsberg P-22) was implanted in the left ventricular chamber through a stab incision in the apex. In the remaining dogs, a short Tygon tube was inserted through the apex and connected to a Statham P23Db transducer for measurement of intracavitary pressure. The left circumflex coronary artery was exposed by dissection, and a hydraulic cuff was placed around it. The water-filled cuff was connected to a vernier screwdriver syringe for the production of different degrees of partial coronary narrowing. A Silastic catheter was inserted into the circumflex artery distal to the hydraulic occluder, connected to a Statham P23Db transducer and used for measurement of perfusion pressure distal to the coronary stenosis.17

For the measurement of regional wall thickening dynamics, a pair of miniature (2 mm diameter), 5-MHz ultrasonic crystals was positioned in the lateral or posterior wall of the left ventricle perfused by the circumflex coronary artery. One of the crystals was inserted tangentially through the myocardium into the subendocardium. The other crystal was sutured to the epicardial surface opposite the inner crystal at a site where the ultrasonic transit time was shortest between the two crystals.8 This allowed placement of the crystals across the left ventricular wall without damage to the tissue between the two crystals. The position of the crystals was examined at necropsy and recorded, and data from poorly positioned crystals were discarded from two dogs. Complete wall thickening data from 15 dogs were analyzed. The average distance between the crystals was 86 ± 3% (mean ± SEM) of the full wall thickness.
The reference withdrawal method was used for measurement of regional MBF. Microspheres 7–10 μm in diameter labeled with one of five randomly selected isotopes (152Ce, 51Cr, 153Sm, 68Nb and 54Sc, 3M Co.) were injected into the left atrium through a Tygon catheter and flushed with 5 ml of room temperature saline. The reference withdrawal blood sample was obtained through a large-bore catheter placed in the aorta via the femoral artery using a constant rate of blood withdrawal beginning before the injection of microspheres and ending 90 seconds afterwards. Before injection, the microspheres were vortex-agitated and ultrasonicated; adequate dispersal was determined by examining a droplet of the microsphere suspensions under a microscope before injection.

At the end of the experiments, the dogs were killed with a KCl injection. The heart was removed and plastic catheters were tied into the left circumflex and left anterior descending coronary arteries for injection of two dyes to delineate the two vascular beds. The heart was then placed in formalin for 2–5 days. Full-thickness sections were taken from the area of the left ventricle perfused by the left anterior descending artery, which served as a control region, and from the lateral or posterior wall, which contained the pair of ultrasonic crystals used to measure wall thickening in the region perfused by the circumflex artery. Each block of tissue was divided into four pieces of approximately equal thickness from the endocardial (layer 1) to the epicardial (layer 4) surface. After its location was recorded, each piece of tissue was weighed and placed in a counting vial for assay of radioactivity using a Packard Autogamma Spectrometer (Model 5912). MBF was calculated as $Q_m = (C_m \times Q_r)/C_r$, where $Q_m =$ MBF (ml/min), $C_m =$ counts in tissue sample (counts/min), $Q_r =$ wall thickening rate of the reference arterial sample, and $C_r =$ counts in the reference arterial sample. Flow per gram of tissue was calculated by dividing the blood flow by the weight of the appropriate sample. The flow calculations were performed on a programmable Hewlett-Packard (Model 9825A) calculator.

Recordings were made during each experiment on a Brush forced-ink recorder and also on magnetic tape for subsequent analysis. Wall thickening, left ventricular pressure and distal coronary pressure were recorded simultaneously. The variables analyzed were wall thickness at end-diastole (identified at the point just before the onset of the positive dP/dt signal) and end-systole (defined as the maximum systolic excursion occurring at or before 20 msec before peak negative dP/dt), extent of systolic wall thickening, left ventricular peak systolic and end-diastolic pressures, phasic and mean coronary perfusion pressures and heart rate. The extent of wall thickening was calculated as the difference in millimeters between end-diastolic and end-systolic dimensions (∆WtH) and expressed as a percentage change from end-diastolic wall thickness (%∆WtH).

Variables were recorded at a paper speed of 100 mm/sec without turning off the respirator, as this maneuver sometimes led to a rapid deterioration of systolic thickening in the ischemic area during coronary stenosis. Twenty consecutive cardiac cycles were sampled and averaged immediately after the microsphere injection during control conditions and after coronary stenosis was created.

After instrumentation, a control injection of microspheres was made, and a level of stenosis was created with the hydraulic occluder. When stable hemodynamic and wall thickening conditions were attained, a second injection of microspheres was made. Stable conditions were regarded as achieved when no changes in hemodynamic variables and regional systolic thickening were observed for at least 3 minutes before injection of the microspheres. The stenosis was released and the dog was allowed to recover for at least 30 minutes. A second, and occasionally a third, stenosis was created, and microsphere injections were repeated, using the same stability and recovery criteria. Because it was difficult to create the same levels of stable stenosis in each dog, the degrees of coronary stenosis were categorized on the basis of effects on systolic wall thickening and each category was analyzed separately. The levels of coronary stenosis were divided into four groups: (1) wall thickening reduced less than 60% (moderate hypokinesia), (2) wall thickening reduced 60–90% (severe hypokinesia), (3) wall thickening reduced 90–110% (akinesia), and (4) wall thickening replaced by systolic thinning (dyskinesia, or systolic thinning greater than 10% of end-diastolic wall thickness). Dimensional and hemodynamic data were analyzed with a nonparametric procedure, the Wilcoxon paired sample test, to compare data in the control state with that after each level of stenosis associated with injection of microspheres. We selected a nonparametric test because the same control blood flow data were used in comparing changes between more than one degree of stenosis. Complete recovery of wall thickening was confirmed before proceeding with the second or third stenosis in each dog; previous studies indicate that recovery of function is associated with restored regional blood flow. The Wilcoxon paired sample test was also used to detect differences between blood flow data during control and stenotic conditions.

Standard linear regressional analysis was used to relate changes in systolic wall thickening to alterations in regional MBF. A stepwise regression procedure was also used to determine which blood flow, in individual layers or in combinations of layers, could best explain wall thickening changes. Wall thickening and blood flow data (expressed as fractions of control values) from the eight dogs with control observations and three levels of stenosis were used for this analysis.

**Results**

**Hemodynamic Variables**

The effect of the four levels of coronary artery stenosis on hemodynamic function are summarized in table 1. No significant changes from the control state were observed in heart rate, but a small reduction
(8.6%, p < 0.05) in systolic left ventricular pressure occurred in group 4, accompanying the most marked wall thickening abnormality. Left ventricular end-diastolic pressure increased a small amount in groups 3 and 4. The prominent hemodynamic feature at each level of stenosis was a reduction in coronary perfusion pressure measured distal to the obstruction created by the hydraulic occluder.

Wall Thickening

A representative example of recordings from one of the dogs is shown in figure 1 to illustrate wall thickening during control conditions and at three levels of stenosis. Wall thickening during ischemia was characterized by early systolic thinning and post-ejection thickening, as well as by reduced excursion during ejection.

### TABLE 1. Hemodynamic Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Heart Rate (beats/min)</th>
<th>LV systolic pressure (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>Systolic coronary pressure (mm Hg)</th>
<th>Diastolic coronary pressure (mm Hg)</th>
<th>Mean coronary pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (n = 6)</td>
<td>C 128 ± 8</td>
<td>114 ± 8</td>
<td>5.3 ± 2.5</td>
<td>111 ± 8</td>
<td>96 ± 7</td>
<td>105 ± 7</td>
</tr>
<tr>
<td>S 132 ± 8</td>
<td>NS</td>
<td>110 ± 8</td>
<td>5.4 ± 0.7</td>
<td>78 ± 10</td>
<td>33 ± 5</td>
<td>55 ± 7</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>2 (n = 5)</td>
<td>C 134 ± 11</td>
<td>109 ± 9</td>
<td>6.7 ± 1.1</td>
<td>105 ± 10</td>
<td>90 ± 8</td>
<td>98 ± 9</td>
</tr>
<tr>
<td>S 137 ± 10</td>
<td>NS</td>
<td>107 ± 10</td>
<td>8.4 ± 1.1</td>
<td>64 ± 9</td>
<td>27 ± 3</td>
<td>46 ± 6</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>3 (n = 10)</td>
<td>C 141 ± 8</td>
<td>114 ± 6</td>
<td>6.0 ± 0.8</td>
<td>111 ± 7</td>
<td>95 ± 6</td>
<td>103 ± 6</td>
</tr>
<tr>
<td>S 146 ± 7</td>
<td>NS</td>
<td>109 ± 7</td>
<td>8.5 ± 1.3</td>
<td>59 ± 6</td>
<td>23 ± 2</td>
<td>41 ± 4</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>0.05</td>
<td>0.005</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>4 (n = 7)</td>
<td>C 131 ± 8</td>
<td>117 ± 7</td>
<td>6.2 ± 0.8</td>
<td>117 ± 6</td>
<td>100 ± 6</td>
<td>108 ± 6</td>
</tr>
<tr>
<td>S 136 ± 5</td>
<td>NS</td>
<td>107 ± 6</td>
<td>9.0 ± 1.7</td>
<td>50 ± 5</td>
<td>21 ± 2</td>
<td>36 ± 3</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>0.025</td>
<td>0.05</td>
<td>0.025</td>
<td>0.025</td>
<td>0.025</td>
</tr>
</tbody>
</table>

**Abbreviations:** LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; C = control; S = stenosis; p = probability of difference between control and stenosis conditions (based on Wilcoxon paired sample test).
Table 2. Summary of Wall Thickening Data

<table>
<thead>
<tr>
<th>Group 1 (n = 6)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>S</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>EDWTh (mm)</td>
<td>9.70 ± 0.79</td>
<td>11.62 ± 1.06</td>
<td>1.91 ± 0.34</td>
<td>19.3 ± 2.8</td>
</tr>
<tr>
<td>ESWTh (mm)</td>
<td>9.84 ± 0.84</td>
<td>10.92 ± 0.99</td>
<td>1.08 ± 0.22</td>
<td>10.8 ± 2.0</td>
</tr>
<tr>
<td>ΔWT (mm)</td>
<td></td>
<td></td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td>%ΔWT</td>
<td></td>
<td></td>
<td>0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2 (n = 5)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>S</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>EDWTh (mm)</td>
<td>12.61 ± 1.38</td>
<td>14.78 ± 1.46</td>
<td>2.18 ± 0.24</td>
<td>17.9 ± 2.6</td>
</tr>
<tr>
<td>ESWTh (mm)</td>
<td>12.30 ± 1.42</td>
<td>12.77 ± 1.39</td>
<td>0.47 ± 0.04</td>
<td>4.1 ± 0.6</td>
</tr>
<tr>
<td>ΔWT (mm)</td>
<td></td>
<td></td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>%ΔWT</td>
<td></td>
<td></td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 3 (n = 10)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>S</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>EDWTh (mm)</td>
<td>10.80 ± 0.57</td>
<td>12.77 ± 0.65</td>
<td>1.97 ± 0.18</td>
<td>18.4 ± 1.5</td>
</tr>
<tr>
<td>ESWTh (mm)</td>
<td>10.32 ± 0.54</td>
<td>10.23 ± 0.51</td>
<td>-0.09 ± 0.05</td>
<td>-0.8 ± 0.5</td>
</tr>
<tr>
<td>ΔWT (mm)</td>
<td></td>
<td></td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>%ΔWT</td>
<td></td>
<td></td>
<td>0.005</td>
<td>0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 4 (n = 7)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>S</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>EDWTh (mm)</td>
<td>11.74 ± 0.63</td>
<td>14.07 ± 0.70</td>
<td>2.32 ± 0.18</td>
<td>20.0 ± 1.6</td>
</tr>
<tr>
<td>ESWTh (mm)</td>
<td>10.47 ± 0.42</td>
<td>9.56 ± 0.40</td>
<td>0.91 ± 0.16</td>
<td>-8.7 ± 1.6</td>
</tr>
<tr>
<td>ΔWT (mm)</td>
<td></td>
<td></td>
<td>0.025</td>
<td>0.025</td>
</tr>
<tr>
<td>%ΔWT</td>
<td></td>
<td></td>
<td>0.025</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Abbreviations: C = control; S = stenosis; p = probability of difference between control and stenosis conditions (based on Wilcoxon paired sample test); EDWTh = end-diastolic wall thickness; ESWTh = end-systolic wall thickness; ΔWT = ESWTh - EDWTh; %ΔWT = (ΔWT/EDWTh) × 100.

Wall thickening data are presented in table 2 and are shown graphically as relative changes in figure 2. In group 1, wall thickening was reduced by 44 ± 5% (p < 0.03); in group 2, wall thickening was reduced by 77 ± 3% (p < 0.01); in group 3, systolic wall thickening ceased (−104 ± 3%, p < 0.005); and in group 4, wall thickening was replaced, during systole, by substantial thinning (−145 ± 9%, p < 0.025). No change in end-diastolic wall thickness was observed in group 1, but significant thinning (expressed as a percentage of control end-diastolic wall thickness) of 2.5% in group 2 (p < 0.02), 4.4% in group 3 (p < 0.01), and 10.8% in group 4 (p < 0.01) were observed with more severe stenoses (table 2).

MBF and Wall Thickening

Regional blood flow data are presented in table 3. The patterns of transmural MBF in each group are shown in figure 3.

No significant change in mean transmural MBF was detected in group 1, although systolic wall thickening decreased by approximately 45%; only subendocardial (layer 1) MBF was significantly lower than control (−28%, p < 0.05). In group 2, MBF was reduced in layers 1 and 2 (−52%, p < 0.05 and −36%, p < 0.05, respectively), but the outer half of the myocardial wall was perfused at control levels; nevertheless, there was severely hypokinetic wall motion. Systolic wall thickening ceased (akinesia) in group 3 (fig. 2). The inner three-quarters of the myocardial wall were perfused at significantly reduced levels (layer 1: -65%, p < 0.003; layer 2: -58%, p < 0.003; layer 3: -34%, p < 0.003), but subepicardial MBF was not altered. Substantial systolic thinning characterized group 4 (dyskinesia), and MBF was decreased significantly in all four layers across the ventricular wall of this region (layer 1: -74%, p < 0.025; layer 2: -68%, p < 0.025; layer 3: -55%, p < 0.025; layer 4: -29%, p < 0.025). No significant changes were detected in MBF to the anterior wall of the left ventricle (control region) except in group 4, in which a significant elevation was observed in subendocardial (layer 1) MBF (table 3).

Changes in subendocardial (layer 1) and subepicardial (layer 4) blood flow were plotted against relative changes in systolic wall thickening (fig. 4) to illustrate the close relationship between subendocardial MBF and wall thickening and poor association of subepicardial blood flow data with wall thickening.

Regression Analysis of %ΔWT on MBF

In eight dogs, data during control conditions and at three levels of stenosis were available, enabling us to
perform a four-point regression analysis. Individual regression equations were determined with y equal to relative changes in systolic wall thickening (expressed as a fraction of control wall thickening) and x equal to blood flow (expressed as a fraction of control MBF). We thereby obtained eight regression equations for the relation of systolic thickening to subendocardial blood flow and for blood flow in each of the other three layers. Only subendocardial blood flow correlated significantly with wall thickening in all eight dogs (r = 0.92–1.00, p < 0.05).

A stepwise regression procedure performed to determine which MBF data best explained wall thickening changes confirmed that changes in %ΔWT were best predicted by alterations in subendocardial (layer 1) MBF alone. The overall regression equation for systolic wall thickening on layer 1 MBF was y = 0.96x - 0.30 (r = 0.64), where y equals relative systolic wall thickening and x equals blood flow, both expressed as fractions of control values. Subendocardial blood flow also predicted changes in %ΔWT better than did mean transmural blood flow or the ratio of endocardial to epicardial (endo/epi) blood flow, although both of the latter were statistically significant correlations (r = 0.49 and 0.55, respectively).

**Discussion**

We used sonomicrometry in this study because of its high sensitivity and fidelity, ease of calibration, and stability characteristics. Accurate measurement of wall motion depends on correct placement of the crystals, which we verified at necropsy. However,
translational motion of the crystals related to shear may have occurred, which is indistinguishable from radial motion measured with a unidirectional technique. A single subendocardial crystal with a triangu-

Figure 3. Average transmural distribution of myocardial blood flow (MBF) in the four categories of wall thickening reductions due to coronary stenosis. On the x-axis are plotted the four layers into which each transmural section of myocardial tissue was divided, from subendocardium (layer 1) to subepicardium (layer 4). Asterisks indicate significant differences between control and stenotic conditions: *p < 0.05, **p < 0.01.

Figure 4. Graph of relative changes in subendocardial (layer 1) and subepicardial (layer 4) blood flow plotted against relative changes in systolic wall thickening. Significant changes in blood flow are indicated with asterisks. Subendocardial blood flow was closely related to reductions in wall thickening, but subepicardial blood flow was decreased significantly in only the fourth (dyskinetic) category. *p < 0.05, **p < 0.01. %ΔWT = systolic wall thickening; MBF = myocardial blood flow; ISCH = ischemia; CONT = control.

Figure 5. Comparison of our data on the relationship of mean transmural blood flow to systolic wall thickening with that presented by Kerber et al.15 and Stowe et al.14 Data are presented as percentages of control blood flow and control systolic thickening. The data from Kerber et al.15 were taken from Table 1, Ref. 13, and normalized to conform with our presentation of data and that of Stowe et al.
wall thickness measurements of less than 0.5% of end-diastolic wall thickness. Using a different method, Feigl and Fry also concluded that shearing strain during ejection is relatively small. Recently, Fenton et al., using an array of lead beads implanted in the myocardium and tracked by cineangiography to measure transmural myocardial deformation, determined that the shear components of wall thickening were negligible as well. In a recent preliminary study Osakada et al., using the technique described by Kemper et al., verified that shear effects are small during ischemic conditions created by coronary occlusions in anesthetized dogs. Thus, artifact due to translational motion of the crystal pairs is probably inconsequential.

The sonomicrometers did not, in every case, span the entire wall thickness, which could have led to some error in relating transmural blood flow to wall thickening. The magnitude of this error is probably minor because an average of 85% of the wall wassubtended by the crystals, but it cannot be disregarded in evaluating the data. The average systolic wall thickening was 17.8% in this open-chest preparation, which is somewhat less than that observed in animals chronically instrumented with ultrasonic crystals for measuring wall thickness. The difference is probably due to the effects of thoracotomy, anesthesia and acute implantation of the crystal pairs.

The results of this study are consistent with previous studies in that blood flow reductions were greatest in the subendocardial region during each degree of stenosis. As subendocardial blood flow was reduced in our study by more severe degrees of stenosis and significant blood flow reductions were observed in the remaining layers, the decrement in systolic wall thickening increased. Subepicardial blood flow was not significantly reduced until the fourth group, when mean coronary perfusion pressure decreased to 36 mm Hg, at which point substantial systolic wall thinning occurred. A 45% decrease in systolic wall thickening was observed with a significant flow reduction in only the subendocardial quarter of the myocardium and a 75% decrease was associated with normal blood flow in the outer half of the ventricular muscle. Even akinesia was associated with nontransmural ischemia in that subepicardial perfusion was not significantly reduced from control levels, so that under these circumstances sustained perfusion of the outer muscle did not produce systolic wall thickening. The degree of wall dysfunction with milder degrees of inner myocardial ischemia might have been worse, however, had not subepicardial perfusion been sustained. Ball and Bache suggested that maintained or augmented subepicardial blood flow accompanying subendocardial ischemia may reflect increased subepicardial mechanical function compensating for subendocardial ischemia. Thus, contraction in the subepicardium may have limited extension of the deep myocardial layers, reducing the adverse effect of regional systolic bulging on ventricular pumping efficiency.

Inner myocardial ischemia exerted a substantial, progressive negative influence on regional systolic wall thickening. We recently reported preliminary results of a study in which a direct relation between decrements in regional blood flow and systolic shortening in the subendocardium occurred when coronary inflow was reduced by stenosis of the circumflex artery in anesthetized dogs. We concluded that outer myocardial fibers may be viable in these circumstances but have insufficient mass to counteract the force of contraction in adjacent nonischemic regions. Because systolic wall thickening represents the net effects of active shortening of all myocardial contractile elements across the ventricular wall, the results of the present study, focusing on wall thickening dynamics rather than regional segmental function, support the view that inner myocardial ischemia can exert transmural effects on contraction by a complex interplay between normally and abnormally perfused muscle fibers.

Some investigators have focused on the relationships of total coronary blood flow to systolic wall thickening, but few have examined the transmural distribution of MBF. However, there is indirect evidence to support our findings that inner myocardial ischemia exerts substantial effects on overall wall function. Kerber et al. measured wall motion with echocardiographic techniques and simultaneously determined MBF with microspheres in anesthetized dogs. Relative reduction in mean transmural MBF correlated significantly with changes in wall velocity and systolic excursion during graded circumflex artery obstruction. Although they did not report the distribution of regional blood flow across the left ventricular wall, the regional perfusion deficits created by Kerber et al. were probably most substantial in the subendocardium. A comparison of their mean MBF data with ours shows a striking similarity, especially at the first level of stenosis (fig. 5). Approximately 50% reductions in wall thickening were associated with nonsignificant changes in mean MBF. This response may reflect the tendency for subepicardial flow to increase during milder degrees of stenosis (fig. 4), although this change was not statistically significant. Kerber et al. also observed dyskinesia in normally perfused regions adjacent to areas rendered ischemic by coronary occlusion. Mean transmural blood flow remained at control levels although wall motion was dyskinetic; possibly, the subendocardial region was not adequately perfused, which may explain the abnormal wall motion. Alternatively, MBF could have been normal transmurally, the dyskinetic wall motion reflecting ill-defined consequences of tethering between ischemic and nonischemic myocardium.

Stowe et al. produced stepwise reductions in coronary blood flow through the left anterior descending artery using a flowmeter in anesthetized pigs and found a significant linear relationship between total coronary inflow and systolic wall thickening measured with sonomicrometers. Wall thickening decreased approximately 55% with a 25% reduction in coronary flow, and systolic thinning was observed
when flow was less than 25% of the control value. These results appear similar to our own (fig. 5), but exact comparison is difficult because Stowe et al. measured arterial inflow rather than regional blood flow. The disparity evident in figure 5 may be due to collateral blood flow, which is not accounted for by arterial inflow measurements made with a flowmeter.

Heyndrickx et al. related systolic wall thickening to the distribution of myocardial blood flow, expressed as the endo/epi ratio, during and after 15-minute coronary occlusions. Mean transmural blood flow, reduced by 75% during coronary occlusion, remained significantly lower than control for 1 hour after release of the occlusions and was associated with decreased systolic wall thickening. After 3 hours of reperfusion, mean transmural blood flow had returned to control levels, but the endo/epi ratio was significantly lower than control, indicating that subendocardial blood flow was not yet restored. Systolic wall thickening also remained below the preocclusion values, which suggested that reductions in MBF limited to the subendocardial region may affect overall wall thickening, as we observed. As the authors acknowledged, however, transient but reversible biochemical and/or contractile protein damage is an alternative explanation for their observations.

In a clinical study, Massie et al. reported asynergy at rest on biplane contrast left ventriculograms in a substantial proportion (57%) of segments in patients with coronary artery disease having normal perfusion scintigrams (thallium-201) at rest. Perfusion abnormalities were evident in these segments during exercise. The asynergy at rest may have been due to undetected perfusion defects, particularly if they occurred in the subendocardium (as we observed), which probably would not be discernible on scintigraphy.

Thus, several lines of indirect evidence support our finding that a marked decrease in regional wall thickening may occur with reductions in blood flow localized to the inner myocardial layers. This effect may be due to tethering of adequately perfused subepicardial regions to adjacent regions of normally contracting muscle or inadequate mass of subepicardial myocardium, leading to mechanical constraint of wall motion. Our major conclusions may be summarized as follows: (1) severe wall thickening dysfunction, including akinesia, can occur with nontransmural regional ischemia and (2) dyskinesia or systolic wall thinning occurs when blood flow reduction is transmural.

Acknowledgment

We thank Dan McKown for technical assistance and Marilyn Cornwall and Eileen Perin for secretarial assistance. We also thank Frank White and Joe Andrews of the Department of Pathology for aid with the preparation and processing of microsphere data.

References

The Relationship of Vascular Injury and Myocardial Hemorrhage to Necrosis After Reperfusion

MICHAEL C. FISHBEN, M.D., JACOB Y-RIT, M.D., ULF LANDO, M.D., KATSUO KANMATSUSE, M.D., JEAN C. MERCIER, M.D., AND WILLIAM GANZ, M.D., C.SC.

SUMMARY Early reperfusion may salvage ischemic myocardium; late reperfusion often intensifies morphologic changes of necrosis and causes hemorrhage. To determine whether hemorrhage after reperfusion increases the extent of myocardial infarction, six closed-chest, anesthetized dogs underwent balloon occlusion of the left anterior descending coronary artery for 5.5 hours, followed by 30 minutes of reflow. Colloidal carbon was injected distal to the balloon before reperfusion to label injured vessels. After sacrifice, the area of myocardial necrosis was measured by planimetry of 1-cm-thick serial slices of left ventricle stained with triphenyl tetrazolium chloride. Areas of hemorrhage and vascular injury were also measured. In all hearts, the extent of hemorrhage and vascular injury was less than the extent of necrosis (10.2 ± 4.6% vs 19.8 ± 8.6% [mean ± SD], p < 0.01). Further, hemorrhage was always within the area of necrosis, primarily in the subendocardial portion. Hemorrhage after reperfusion occurred only in necrotic tissue where carbon labeling indicated severe vascular injury before reperfusion, suggesting that the hemorrhage was the consequence of preexisting microvascular injury, not its cause.

RESTORATION of blood flow to ischemic myocardium would seem to be a rational way of limiting the extent of ischemic injury. Studies in dogs have shown that if reperfusion is instituted less than 20 minutes after coronary occlusion, normal myocardial blood flow, function and morphology eventually return. However, if 40 minutes or more elapse before flow is restored, normal perfusion may not be restored, function may not recover fully or may even worsen temporarily and the morphologic signs of myocardial injury may be more pronounced than would be expected after occlusion of the same duration not followed by reperfusion. Morphologically, with reperfusion one may observe marked cell swelling and disruption, extensive deposition of calcium, diffuse contraction band change and marked vascular damage with marked hemorrhage into the myocardium; when coronary occlusion is not followed by reperfusion, these changes are unusual or not extensive. Whether reperfusion merely makes already irreversibly injured myocardium look worse or whether it actually extends myocardial necrosis is controversial. Because surgical bypass and transluminal angioplastic techniques are applied now for early reperfusion of myocardium in patients with evolving myocardial infarction, this matter is clinically relevant.

The goal of this study was to determine whether reperfusion hemorrhage actually extends infarction or occurs in myocardium that was already irreversibly injured before reperfusion.

METHODS

Six mongrel dogs that weighed 22–25 kg were anesthetized with morphine (1.5 mg/kg), followed 45–60 minutes later by i.v. pentobarbital (30 mg/kg) supplemented by doses of 2 mg/kg every 30 minutes. The dogs were intubated and artificially ventilated 10 times/min at tidal volumes of 20 ml/kg. Heparin (100 IU/kg) was given hourly for anticoagulation. Aortic
Significance of regional wall thickening abnormalities relative to transmural myocardial perfusion in anesthetized dogs.

K P Gallagher, T Kumada, J A Koziol, M D McKown, W S Kemper and J Ross, Jr

*Circulation.* 1980;62:1266-1274
doi: 10.1161/01.CIR.62.6.1266

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1980 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/62/6/1266

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/