Exercise-induced regional dysfunction with subcritical coronary stenosis

Jong-Dae Lee, M.D., Tsukasa Taiimi, M.D.,* Brian Guth, Ph.D., Rainald Seitelberger, M.D., Mark Miller, and John Ross, Jr. M.D.

ABSTRACT The hypothesis was tested that regional myocardial contractile dysfunction can detect subtle regional coronary blood flow maldistribution induced by exercise. In seven dogs, left ventricular pressure (micromanometer), regional systolic wall thickening (WTh, sonomicrometry), and myocardial blood flow (MBF, microspheres) were measured when mild degrees of coronary artery stenosis were produced during treadmill exercise. During exercise without coronary stenosis, WTh increased by 21 ± 12% (SD), and transmural MBF increased uniformly. In each dog, two levels of coronary stenosis were produced during exercise by adjusting the coronary hydraulic cuff: (1) St-Ex I, where WTh during exercise failed to increase significantly (average change 0 ± 7%), and (2) St-Ex II, where WTh during exercise decreased moderately from the resting control value (average −20 ± 8%). In the potentially ischemic zone coronary hyperemia occurred with each run: resting subendocardial MBF was 1.09 ± 0.30 mg/g/min, and it was 3.04 ± 0.83 during control exercise, 2.48 ± 0.75 during St-Ex I, and 1.55 ± 0.59 ml/g/min during St-Ex II (p < .01 compared with control exercise and control area). The subendocardial-subepicardial blood flow ratio fell from 1.32 ± 0.27 during control exercise to 1.07 ± 0.20 (p < .05) during St-Ex I, and to 0.64 ± 0.15 (p < .01) with St-Ex II. Changes in the subendocardial electrogram and reactive hyperemia occurred more consistently during St-Ex II than St-Ex I. Thus, failure of regional function to increase during exercise detected slight maldistribution of regional MBF, whereas reduction of regional function during exercise of 10% or more below the resting value was a reliable marker of a regional flow defect and was always associated with other evidence of ischemia. Therefore, regional dysfunction during exercise can detect subcritical but functionally significant coronary stenosis, which may allow regional wall motion to be used for detecting coronary artery disease at a relatively early stage.


EXERCISE-INDUCED ischemia has been studied in detail experimentally with analyses of regional myocardial blood flow (MBF), 1-5 regional contraction, 4-7 and overall left ventricular function. 5, 8, 9 These data and other studies in resting conscious dogs 10-12 have established that regional contractile function is responsive to reductions in MBF, especially to the subendocardium. For example, in the presence of critical coronary stenosis (normal resting flow but lack of vasodilator reserve), subendocardial coronary flow drops 50% below the resting value during exercise, with an associated 70% decrease of systolic wall thickening below the resting value. 6

In man, global or regional left ventricular function, as assessed by radionuclide imaging 13, 14 or two-dimensional echocardiography 15, 16 during exercise testing, has been shown to be abnormal in some patients with coronary heart disease. However, little is known about the sensitivity of abnormal regional wall motion for identifying mild abnormalities of subendocardial blood flow induced by exercise stress. It is known that during states of hyperemic coronary blood flow, reductions in coronary flow are caused by degrees of coronary stenosis that are considerably milder than those necessary to produce a reduction in flow in the presence of lower coronary blood flows at rest. 17 Therefore, identification of modest exercise-induced wall motion abnormalities could prove to be a means of detecting early coronary artery disease.

The purpose of this study was to test the hypothesis

From the Division of Cardiology, Department of Medicine, University of California San Diego School of Medicine, La Jolla, CA.
Supported by a National Institutes of Health, Specialized Center for Research on Ischemic Heart Disease grant HL17682.
Address for correspondence: John Ross, Jr., M.D., Department of Medicine, University of California, San Diego School of Medicine, La Jolla, CA 92039.
Received July 29, 1985; revision accepted Dec. 5, 1985.
*Present address: Fukui Medical School, 23 Shomoaisuzaki, Matsuoka-cho, Yoshiida-gun, Fukui-ken Fukui 910-11, Japan.
that a regional wall motion abnormality that develops during exercise indicates subtle maldistribution of transmural regional coronary blood flow, of the type that would accompany relatively mild coronary artery stenosis associated with some vasodilator reserve. Therefore, we studied regional myocardial function and coronary blood flow distribution during treadmill exercise in conscious dogs before and after varying degrees of subcritical coronary stenosis were created by adjusting an hydraulic cuff on the left circumflex artery. The ensuing changes in regional wall thickening were analyzed in the posterior (ischemic) and anterior (normal) regions of the left ventricle by sonomicrometry and were compared with the associated alterations in regional MBF distribution as determined by the microsphere technique.

**Methods**

**Experimental preparation.** In each of seven dogs (18 to 34 kg, average 28.6 kg), a left lateral thoracotomy was performed through the left fifth intercostal space under sodium pentobarbital anesthesia (26 mg/kg). The pericardium was opened to expose the heart. The left circumflex coronary artery was dissected free near its origin and a hydraulic occluder was placed around it, and a Doppler flow probe was placed proximal to the occluder for monitoring coronary blood flow velocity. A high-fidelity micromanometer (Konigsberg P7) was inserted into the left ventricular chamber through the ventricular apex together with a Tygon tube (1.27 mm, internal diameter) for zero pressure reference and calibration of the micromanometer. Two silicone rubber catheters were positioned, one in the left atrial appendage (for injection of radioactive microspheres) and the other in the descending aorta (for withdrawing a reference blood sample). Pairs of ultrasonic crystals were implanted in the anterior (control) and the posterior (ischemic) left ventricular walls for the measurement of regional contractile function by assessing regional wall thickening. The endocardial crystal of each pair was inserted obliquely through a diagonal tract and the epicardial crystal, attached to a Dacron patch, was sewn to a site where the ultrasonic transit time was the shortest. All wires and tubing were passed subcutaneously to the back of the animal and exteriorized. The location of the crystals was carefully examined at the time of autopsy to verify correct alignment, and in all animals reported they were appropriately positioned opposite one another. Among the 14 crystal pairs in the seven dogs, all subendocardial crystals were found to lie within 3 mm of the endocardial surface, spanning an average of 79% of the full wall thickness. There was no gross infarction between crystals.

**Subendocardial electrocardiogram (ECG).** In six of the seven animals, a satisfactory subendocardial ECG was recorded from the subendocardial crystal of the ischemic wall and analyzed for ST segment changes and Q wave amplitude. The isoelectric line was defined at the onset of Q wave, and ST segment changes were measured 20 to 30 msec after the J junction. To minimize the effect of baseline shifts caused by respiration, analysis was performed with digitized data from an average of 20 consecutive cardiac cycles.

**Regional MBF.** Measurements of regional MBF were made with the use of serial injections of tracer-labeled microspheres (10 to 15 μm diameter, New England Nuclear), as previously described. Approximately 6 × 10⁶ microspheres were injected for each blood flow determination using one of six available isotopes (¹⁴Ce, ⁵¹Cr, ¹¹⁵Sn, ¹⁰³Ru, ⁹⁰Nb, ⁶⁰Sc). Each injection was followed by a 5 ml warm saline flush. The reference arterial blood sample was withdrawn via the aortic catheter at a constant rate (8.0 ml/min) with a Sage Instruments pump (model 351) beginning before microsphere injection into the left atrium and continuing for a total of 2 min. Data from injections were used when no arrhythmias and no significant changes in hemodynamic and dimensional characteristics were observed during the microsphere injection and the withdrawal period. After the experiment each dog was killed with an overdose of pentobarbital anesthesia. The heart was fixed with 10% formalin to facilitate sectioning.

A transverse slice of the left ventricle containing the posterior wall crystals was divided circumferentially into six or seven full-thickness pieces. In five dogs, one slice contained both posterior and anterior crystals; in two dogs, the piece containing anterior wall crystals was obtained from a separate transverse slice of the ventricle. Each piece was divided into three samples of approximately equal thickness from endocardium to epicardium, and the tissue pieces containing the crystals were cut to include the tissue between crystal pairs. Each sample of tissue was recorded, weighed, and placed in a counting vial for assay of radioactivity with a Packard Autogamma Spectrometer (model 5912). After the counts in each tissue sample were corrected for background and overlapping spectra with a matrix inversion technique, MBF was calculated with the following equation:

\[ Q_m = (C_m \times Q_r)/C_r \]

where Qm is myocardial blood flow (ml/min), Cm is counts per minute in the tissue sample, Qr is withdrawal rate of the reference blood sample (ml/min), and Cr is counts per minute in the reference blood sample. Flow per gram of tissue was calculated by dividing flow by the weight of the appropriate sample.

**Experimental protocol.** The animals were studied at least 10 days after surgery when they exhibited normal activity, were afebrile, and were capable of repeated runs on the treadmill. Control recordings and the first microsphere injection were performed when the dogs were standing quietly on the treadmill. Each was then run for 5 to 8 min with microsphere injections between 3 and 7 min into the run. The treadmill speed (8 to 11.2 km/hr, 5% grade) was adjusted to increase heart rate approximately twofold (control exercise). After the end of the control exercise period (without coronary stenosis), at least 30 min was allowed for the dog to recover. Thereafter, following recording of resting hemodynamic and dimensional data, the treadmill run was repeated at the same speed and grade while coronary stenosis was produced. One to two minutes after the beginning of a period of running, a desired level of coronary stenosis was produced by adjustment of the hydraulic occluder, guided by the percent change in systolic wall thickening calculated on-line by a computer system developed in our laboratory. After steady-state conditions were achieved, characterized by the decrease in percent wall thickening from that during the control exercise period, another microsphere injection was performed. Additional slight adjustments of the occluder were performed when needed to keep stable conditions. After the end of the blood sample withdrawal, the occluder was released completely and exercise was continued to test for reactive hyperemia by the monitoring of Doppler coronary blood flow velocity. The run was stopped 1 min after release of the stenosis. After a rest period and full recovery, the treadmill run was repeated in the same manner with a different degree of coronary stenosis. Three or four runs were carried out on the same day to achieve the desired levels of coronary stenosis.

**Data analysis.** Recordings for each experiment were made...
on a Brush forced-ink recorder and on magnetic tape for subsequent analysis. Representative tracings are shown in figure 1. Measurements of end-diastolic dimensions were taken at the nadir of the pressure tracing after atrial contraction (at the time dP/dt crossed zero), and end-systolic dimensions were taken at their maximum value, within 20 msec before peak negative left ventricular dP/dt. The parameters analyzed were heart rate, left ventricular systolic pressure, peak positive dP/dt, end-diastolic wall thickness, end-systolic wall thickness, extent of wall thickening (calculated as the difference in millimeters between end-diastolic and end-systolic wall thickness), percent systolic wall thickening (defined as percentage change from end-diastolic wall thickness), regional MBF, and the ECG from the subendocardial crystal of the posterior (ischemic) wall thickness pair. Hemodynamic data, dimensions, and the ECG were digitized from magnetic tape with a computer system (PDP/11/03). Data from 20 consecutive cardiac cycles were collected and averaged for each intervention. When microspheres were injected, the beats just following the completion of injection were used for analysis.

Exercise data from pairs of ischemic wall crystals were categorized into two groups based on the extent of reduction in systolic wall thickening during exercise with coronary stenosis: (1) percent wall thickening during exercise unchanged (10% or less variation) from the control resting value (St-Ex I), and (2) percent thickening decreased by more than 10% and less than 35% from the control resting value (St-Ex II). Thus, data from runs with coronary stenosis in which percent wall thickening increased by more than 10% or decreased by more than 35% were discarded.

Statistical comparisons of data obtained before and during running without or with coronary stenosis were performed by an analysis of variance for repeated measures. The level of statistical significance used was $p < .05$, and all data are presented as the mean $\pm$ SD.

Results

Hemodynamics. An example of recordings in a representative dog is shown in figure 1, and average hemodynamic data are shown graphically in figure 2. During control exercise, heart rate increased from the resting value of 101 $\pm$ 10 to 192 $\pm$ 24 beats/min, left ventricular systolic pressure increased from 120 $\pm$ 10 to 152 $\pm$ 6 mm Hg, and left ventricular end-diastolic pressure was elevated to 21.1 $\pm$ 2.5 from 10.9 $\pm$ 2.0 mm Hg. Peak positive dP/dt also increased significantly (3201 $\pm$ 352 vs 5391 $\pm$ 665 mm Hg/sec, $p < .01$). After recovery, all variables returned to the preexercise values.

![Figure 1](http://circ.ahajournals.org/)

**FIGURE 1.** Representative recordings at fast paper speed from one experiment. Tracings are left ventricular pressure, left ventricular dP/dt, posterior (ischemic) wall thickness, anterior (control) wall thickness, and subendocardial ECG during control standing, control exercise, and exercise at two levels of circumflex artery stenosis. Serial changes in wall thickness were assessed from measurements taken at end-diastole (ED) and at end-systole (ES), as indicated by the solid vertical lines. During control exercise, systolic wall thickening increased significantly in both posterior and anterior areas. The two panels on the right show two levels of regional contractile dysfunction in the posterior area in which systolic wall thickening failed to increase (run 1) and decreased from the control value (run 2); the latter tracing shows hypokinesia and considerable postejection wall thickening typical of moderate ischemia.
During running with mild coronary stenosis, hemodynamic parameter values increased significantly and there were no significant differences among the three runs (control and two runs with coronary stenosis) (figure 2).

**Regional myocardial function.** Dimension data are presented in table 1. End-diastolic wall thickness was not significantly changed throughout the experiment in either control (anterior) or ischemic (posterior) walls of the left ventricle. During control exercise, percent systolic wall thickening increased significantly in both areas (by 21 ± 12% in the posterior wall and 35 ± 20% in the anterior wall). In the control wall, the effect of running on regional function was not significantly changed by circumflex coronary artery stenosis (table 1, figure 1).

The average percent systolic wall thickening in the ischemic area during St-Ex I was unchanged from the resting value (average 100 ± 7%, range 91 to 109% of the resting value), but it was significantly lower than that during control exercise (table 1). During St-Ex II, average percent thickening was reduced by 20% (−20 ± 8%, range −10 to −35%), a significant decrease from the resting value as well as from that during control exercise (table 1). The percent wall thickening was somewhat higher during the control run without coronary stenosis in the posterior region than in the anterior region, and therefore the percent wall thickening during St-Ex I was not significantly different from that in the anterior region; however, during St-Ex II the percent wall thickening was significantly lower than that in the anterior wall (table 1).

**MBF.** Average blood flow data are presented in table 2. Absolute flows in the endocardial and epicardial layers of the ischemic zone are shown in figure 3, and all data are summarized graphically in figure 4. During control exercise, MBF was increased in each layer, in both anterior and posterior areas. In the anterior (control) area, regional MBF during the runs with coronary stenosis remained at the same levels as during the control run and the subendocardial/subepicardial blood flow ratios were not changed throughout the experiment (table 2, figure 4).

In St-Ex I, subendocardial flow in the posterior re-
TABLE 1
Regional function at rest and during running

<table>
<thead>
<tr>
<th>Region</th>
<th>EDWTh</th>
<th>ESWh</th>
<th>%ΔWTh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>11.73 ± 2.77</td>
<td>14.36 ± 3.29</td>
<td>22.8 ± 4.7</td>
</tr>
<tr>
<td>CEX</td>
<td>11.60 ± 2.91</td>
<td>15.05 ± 3.54A</td>
<td>30.4 ± 5.8A</td>
</tr>
<tr>
<td>C</td>
<td>11.62 ± 2.60</td>
<td>14.47 ± 3.20</td>
<td>24.8 ± 5.4</td>
</tr>
<tr>
<td>St-Ex I</td>
<td>11.52 ± 2.80</td>
<td>15.03 ± 3.46A</td>
<td>31.2 ± 7.5A</td>
</tr>
<tr>
<td>C</td>
<td>11.76 ± 2.77</td>
<td>14.64 ± 3.33</td>
<td>24.6 ± 5.4</td>
</tr>
<tr>
<td>St-Ex II</td>
<td>11.52 ± 2.83</td>
<td>15.05 ± 3.44A</td>
<td>31.5 ± 7.5A</td>
</tr>
<tr>
<td>Ischemic region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>11.46 ± 3.26</td>
<td>14.58 ± 3.59</td>
<td>28.5 ± 7.5C</td>
</tr>
<tr>
<td>CEX</td>
<td>11.58 ± 3.38</td>
<td>15.39 ± 3.96A, C</td>
<td>34.2 ± 9.3A, C</td>
</tr>
<tr>
<td>C</td>
<td>11.58 ± 3.25</td>
<td>14.77 ± 3.81C</td>
<td>29.6 ± 7.3C</td>
</tr>
<tr>
<td>St-Ex I</td>
<td>11.57 ± 3.43</td>
<td>14.85 ± 3.93B</td>
<td>29.4 ± 7.2B</td>
</tr>
<tr>
<td>C</td>
<td>11.61 ± 3.25</td>
<td>14.36 ± 3.77</td>
<td>28.9 ± 7.1C</td>
</tr>
<tr>
<td>St-Ex II</td>
<td>11.43 ± 3.43</td>
<td>13.97 ± 3.74A-C</td>
<td>23.3 ± 6.5A-C</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD (n = 7).

C = control at rest; CEX = control exercise without coronary stenosis; %ΔWTh = percent systolic wall thickening; EDWTh = end-diastolic wall thickness; ESWh = end-systolic wall thickness.

* p < .01 vs control at rest; ** p < .01 vs control exercise, † p < .05 vs corresponding value in control region.

region during exercise was considerably higher than the resting value (figure 3), but was 18 ± 14% lower (p > .05) than that during control exercise (figure 4), whereas midwall and subepicardial flows were not different from those during control exercise; these regional flow changes were consistent among dogs, but the subendocardial flows did not differ significantly from those in the anterior wall (control area) (table 2, figure 4). In St-Ex I, the subendocardial/subepicardial blood flow ratio was decreased compared with that during the control run, but because of a relatively high value before stenosis it was not less than unity in St-Ex I (table 2). The subendocardial/subepicardial flow values, plotted together with the percent changes in systolic wall thickening, are shown during control exercise and St-Ex I in figure 5. When a decrease of subendocardial flow to greater than 10% below the control exercise value was taken as an indicator of a significant flow defect, two of the seven dogs in the St-Ex I group showed less than a 10% decrease; thus, failure of regional function to increase above the resting value during exercise indicated a significant flow deficit in 71% of dogs. Subendocardial flow was decreased by more than 20% below the control exercise level in only three of seven dogs.

In St-Ex II, subendocardial flow in the posterior region still increased significantly from the resting value (figure 3), but it averaged 49 ± 15% below the control exercise level (figure 4). The midwall flow was also significantly lower (table 2, figure 4). Subendocardial flow in the posterior zone during St-Ex II was also significantly lower than in the control (anterior) region (table 2). Subepicardial flow was not different from that during control exercise (figure 3), and the

TABLE 2
Regional MBF (ml/g/min)

<table>
<thead>
<tr>
<th>Region</th>
<th>ENDO</th>
<th>MID</th>
<th>EPI</th>
<th>TMBF</th>
<th>ENDO/EPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior (control region)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>0.85</td>
<td>0.85</td>
<td>0.69</td>
<td>0.79</td>
<td>1.25</td>
</tr>
<tr>
<td>±0.16</td>
<td>±0.23</td>
<td>±0.16</td>
<td>±0.17</td>
<td>±0.10</td>
<td></td>
</tr>
<tr>
<td>CEX</td>
<td>2.50A</td>
<td>2.52A</td>
<td>2.05A</td>
<td>2.31A</td>
<td>1.21</td>
</tr>
<tr>
<td>±0.77</td>
<td>±0.64</td>
<td>±0.46</td>
<td>±0.56</td>
<td>±0.21</td>
<td></td>
</tr>
<tr>
<td>St-Ex I</td>
<td>2.43A</td>
<td>2.53A</td>
<td>1.92A</td>
<td>2.30A</td>
<td>1.25</td>
</tr>
<tr>
<td>±0.60</td>
<td>±0.34</td>
<td>±0.38</td>
<td>±0.34</td>
<td>±0.09</td>
<td></td>
</tr>
<tr>
<td>St-Ex II</td>
<td>2.53A</td>
<td>2.61A</td>
<td>2.06A</td>
<td>2.40A</td>
<td>1.22</td>
</tr>
<tr>
<td>±0.47</td>
<td>±0.14</td>
<td>±0.20</td>
<td>±0.26</td>
<td>±0.36</td>
<td>±0.12</td>
</tr>
<tr>
<td>Posterior (ischemic region)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1.09P</td>
<td>0.92</td>
<td>0.74</td>
<td>0.92</td>
<td>1.46</td>
</tr>
<tr>
<td>±0.30</td>
<td>±0.20</td>
<td>±0.14</td>
<td>±0.20</td>
<td>±0.25</td>
<td></td>
</tr>
<tr>
<td>CEX</td>
<td>3.04A,E</td>
<td>2.70A,D</td>
<td>2.32A,E</td>
<td>2.69A,E</td>
<td>1.32</td>
</tr>
<tr>
<td>±0.83</td>
<td>±0.57</td>
<td>±0.53</td>
<td>±0.59</td>
<td>±0.57</td>
<td></td>
</tr>
<tr>
<td>St-Ex I</td>
<td>2.48A,C</td>
<td>2.62A</td>
<td>2.31A,E</td>
<td>2.43A</td>
<td>1.07B,E</td>
</tr>
<tr>
<td>±0.75</td>
<td>±0.63</td>
<td>±0.50</td>
<td>±0.64</td>
<td>±0.20</td>
<td></td>
</tr>
<tr>
<td>St-Ex II</td>
<td>1.55A,C</td>
<td>1.97A,C</td>
<td>2.38A,E</td>
<td>1.97A,E</td>
<td>0.64C</td>
</tr>
<tr>
<td>±0.59</td>
<td>±0.71</td>
<td>±0.57</td>
<td>±0.58</td>
<td>±0.15</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD (n = 7).

ENDO = subendocardium; MID = midmyocardium; EPI = subepicardium; TMBF = mean transmural blood flow; other abbreviations as in table 1.

* p < .01 vs control at rest; ** p < .05; † p < .01 vs control run; ‡ p < .05; § p < .01 vs the control region.
somewhat during transmural Mean stenosis, but the decrease statistically significant. flow ratio decreased subendocardial/subepicardial II) (cross-hatched bars). and the during St-Ex running segments were not significantly elevated during standing at rest. During control exercise, the ST segments were slightly but not significantly elevated. During St-Ex I, ST segments were elevated compared with those at control exercise in four of six dogs, they were unchanged in one, and they were depressed in the remaining dog; the average change was not significant (table 3, figure 6). During St-Ex II, the ST segments during running were elevated above those during exercise in all dogs. In two dogs the change was small and overlapped those during St-Ex I, but the average value was significantly increased compared with that at rest and control exercise (table 3, figure 6).

**FIGURE 3.** Absolute MBF values in the subendocardial (ENDO) and subepicardial (EPI) layers during standing at rest (open bars), and during the control (cont.) run or with two degrees of coronary stenosis (I and II) (cross-hatched bars).

subendocardial/subepicardial flow ratio decreased significantly during St-Ex II from 1.32 to 0.64 (figure 5). Mean transmural blood flow in the ischemic area also decreased somewhat during the runs with coronary stenosis, but the change from the control run was not statistically significant. In St-Ex II, however, transmural flow in the ischemic area was significantly below that in the control (anterior) region (table 2). In all seven dogs in the St-Ex II group, subendocardial flow was decreased by more than 20% below the control exercise level. Thus, a significant decrease in regional function below the resting level was a reliable marker of a substantial flow defect in the ischemic area compared with flow during control exercise and in the control region in the same heart.

**Subendocardial ECG.** A subendocardial ECG was recorded in six of seven dogs (table 3, figure 2). The ST segments were not significantly elevated during standing at rest. During control exercise, the ST segments were slightly but not significantly elevated. During St-Ex I, ST segments were elevated compared with those at control exercise in four of six dogs, they were unchanged in one, and they were depressed in the remaining dog; the average change was not significant (table 3, figure 6). During St-Ex II, the ST segments during running were elevated above those during exercise in all dogs. In two dogs the change was small and overlapped those during St-Ex I, but the average value was significantly increased compared with that at rest and control exercise (table 3, figure 6).

**FIGURE 4.** Average changes in subendocardial (ENDO), midwall (MID), subepicardial (EPI), and mean transmural blood flow (TMBF) in the posterior (ischemic) and the anterior (control) areas. Values during control exercise are expressed as 100%.

When regional myocardial function failed to increase normally during exercise (St-Ex I, closed symbols), there was a reduction in subendocardial blood flow to 18% below the control exercise levels. When regional myocardial function was reduced by an average of 20% below the resting control value (St-Ex II, open symbols), subendocardial blood flow was 49% lower and midwall blood flow was also reduced compared with that during control exercise. No significant changes were observed in the control area.
FIGURE 5. Average changes in percent systolic wall thickening in the ischemic area shown by closed symbols and solid line (%ΔIWTh, expressed as a percent of the control value before running) during control exercise (CEX) and at the two levels of coronary stenosis with exercise. The corresponding subendocardial/subepicardial blood flow ratios (ENDO/EPI ratio) are shown by open symbols and the dashed lines. *p < .01; †p < .05 vs control run.

There was no significant change in Q wave amplitude during control exercise or St-Ex I. However, during St-Ex II, Q wave amplitude was significantly decreased compared with that at rest and control exercise (table 3).

Coronary blood flow velocity. In four of seven dogs the circumflex coronary blood flow velocity could be adequately recorded. During control exercise without coronary stenosis, mean velocity increased to 42.6 ± 6.0 cm/sec from the resting value of 27.4 ± 3.8 cm/sec. It was decreased to averages of 37.8 ± 3.1 and 31.7 ± 5.4 cm/sec during St-Ex I and St-Ex II, respectively. After the stenosis was released during running, flow velocity immediately increased to 45.6 ± 8.2 (range 37.5 to 55.0) cm/sec and 53.0 ± 10.4 (range 40.0 to 68.5) cm/sec during St-Ex I and St-Ex II, respectively. In St-Ex I, this increase averaged 21 ± 18%, but one dog showed no reactive hyperemia. In St-Ex II, mean flow velocity was increased by 69 ± 24% (range 44% to 93%), with all dogs showing reactive hyperemia. A statistical analysis was not done because of the small sample size.

Discussion

The hypothesis of this study, that mild exercise-induced regional myocardial dysfunction reflects suble regional coronary blood flow maldistribution, was shown to be correct. Vasodilator reserve was demonstrated in all transmural layers during exercise, indicating relatively mild coronary stenosis, and epicardial flow increased normally at both levels of stenosis; nevertheless, subendocardial blood flow was lower than that during control exercise, with smaller reductions in average transmural flow. Studies of this type are not yet feasible in man, but they indicate the potential of altered regional contractile function for detecting coronary flow abnormalities due to subcritical coronary stenosis.

A potential limitation of these studies is that simultaneous angiographic assessment of the degree of coronary artery stenosis was not possible. However, in this conscious dog preparation it would not have been technically practical to attempt coronary angiography during treadmill exercise; moreover, angiographic studies were not carried out after exercise because the protocol used called for adjustments of the hydraulic occluder during exercise, with release of the stenosis for study

**TABLE 3**

Subendocardial ECG in the ischemic region

<table>
<thead>
<tr>
<th></th>
<th>ST (mV)</th>
<th>Δ ST (mV)</th>
<th>Q (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>0.5 ± 0.7</td>
<td>0.3 ± 0.4</td>
<td>9.7 ± 2.9</td>
</tr>
<tr>
<td>CEX</td>
<td>0.8 ± 0.8</td>
<td>0.4 ± 0.3</td>
<td>9.7 ± 2.9</td>
</tr>
<tr>
<td>C</td>
<td>0.6 ± 0.7</td>
<td>0.5 ± 0.7</td>
<td>10.1 ± 2.8</td>
</tr>
<tr>
<td>St-Ex I</td>
<td>1.0 ± 0.8</td>
<td>0.4 ± 0.3</td>
<td>8.9 ± 2.6</td>
</tr>
<tr>
<td>C</td>
<td>0.5 ± 0.7</td>
<td>1.4 ± 1.2</td>
<td>10.3 ± 3.1</td>
</tr>
<tr>
<td>St-Ex II</td>
<td>1.9 ± 1.5 ab</td>
<td>1.4 ± 1.2 ab</td>
<td>7.6 ± 2.0 ab</td>
</tr>
</tbody>
</table>

Data are mean ± SD (n = 6).

ST = ST segment elevation; Δ ST = change of ST segment from control at rest; Q = Q wave amplitude.

*p < .01 vs control at rest; †p < .05 vs control exercise.

**FIGURE 6.** Changes in the ST segments on the subendocardial ECG during exercise with coronary stenosis, expressed as the change (ΔST) from the value during control exercise without stenosis. Open symbols ± SD represent the average values. The changes were variable when the regional myocardial function changed by less than 10% from the resting value (St-Ex I), but the average increased significantly during St-Ex II. p < .01 vs control running.
of reactive hyperemia while exercise was continued. In addition, the dogs would have required sedation for angiography, and changes in blood pressure due to sedation and postexercise changes may affect the position and caliber of the hydraulic cuff, so that angiographic measurements made after exercise need not reflect the actual vessel dimensions during exercise. However, studies have been done by others relating the degree of coronary stenosis to changes in coronary blood flow both at rest and during hyperemia, and these data can be used to make a reasonable estimate of the degree of coronary stenosis that must have existed during exercise in our studies. During control exercise (without coronary stenosis), subendocardial coronary blood flow in the posterior region increased approximately threefold over the resting value. Gould et al., 17 in experiments with acute coronary stenosis in dogs, showed that under resting conditions, coronary flow measured with a flowmeter did not fall until an 85% coronary artery stenosis was reached. However, at coronary flows three to four times the resting level produced by x-ray contrast medium, a clear reduction in the level of hyperemic flow was evident with coronary stenoses of 40% to 50%. 17 Therefore, since our study was also carried out using acute coronary stenosis with slightly lower hyperemic responses, it is reasonable to estimate that the degrees of coronary stenosis in our study were in the range of 50% to 60%.

Critical coronary stenosis (abortion of coronary flow reserve) does not generally result in regional myocardial dysfunction at rest, 4 but regional myocardial dysfunction may occur during cardiac stress such as physiologic exercise, 4-7, 26 rapid pacing, 26-28 and administration of sympathomimetic drugs. 8, 20, 29 Gallagher et al. 5 and Kumada et al. 30 using an amesiod constrictor to produce gradual coronary stenosis, described markedly abnormal wall motion during exercise with little or no dysfunction observed at rest. Postpacing myocardial dysfunction was also demonstrated with the same model. 26 Drug-induced ischemia has been reported, 8 and Battler et al. 20 and Gallagher et al. 29 described regional myocardial dysfunction and flow maldistribution caused by isoproterenol infusion in the presence of coronary artery stenosis. Thus, it is clear that abnormal wall motion during stress can provide a valuable indicator of limited coronary flow reserve.

During exercise-induced ischemia, maldistribution of regional blood flow has been demonstrated to occur, often with reduction of transmural blood flow and with the greatest flow reduction in the subendocardium. 1-5 Gallagher et al. 12 described a slightly curvilinear relationship between systolic wall thickening and subendocardial (or mean transmural) blood flow in the conscious dog at rest, and Vatner 10 described an exponential relationship. Whereas studies during exercise by Gallagher et al. 5 suggest a nearly linear relationship between subendocardial flow and function during exercise with progressively more severe coronary stenosis, the sensitivity of such a relationship in the presence of mild stenosis with exercise remained uncertain.

In this study, we produced two levels of mild regional contractile dysfunction during exercise. This mild dysfunction was not accompanied by significant changes (compensatory increases) in systolic wall thickening or blood flow in the anterior wall. Moreover, exercise hemodynamic data were unchanged, indicating little overall left ventricular dysfunction. Subepicardial blood flow in the posterior (ischemic) area during coronary stenosis remained at the value observed during control running without coronary stenosis, while significant reductions were observed in subendocardial blood flow. However, subendocardial flow remained at significantly higher levels than the control resting values at both levels of coronary narrowing, indicating the presence of some coronary flow reserve. Therefore, subcritical coronary stenosis was produced.

Transmural redistribution of blood flow was clearly demonstrated in this study, but the subendocardial/subepicardial flow ratio was significantly higher than 1.00 during control exercise, and this ratio was still approximately unity during St-Ex I. There are several possible explanations for this relatively high ratio during control exercise. First, the scar tissue around the large epicardial crystal could lead to some underestimation of subepicardial blood flow, resulting in a high subendocardial/subepicardial ratio. However, the rim of scar tissue was carefully identified and excluded at the time of cutting the tissue sample, and an effect of scarring should be minimal. Second, Buckberg et al. 30 reported that the main source of error in measuring regional blood flow is the total number of microspheres in the organ and reference samples. Dole et al. 31 also emphasized the importance of the number of microspheres in both tissue and reference samples. We injected about 3 x 106 microspheres, and the calculated number of microspheres in the subendocardial samples from the ischemic zone was 2213 ± 1779 during the control run, 2330 ± 1448 during St-Ex I, and 1775 ± 1695 during St-Ex II. In the subepicardial samples from ischemic zone, these counts were higher. Thus, it is not likely that errors occurred due to insufficient
numbers of microspheres in tissue samples. Several authors have reported subendocardial/subepicardial ratios during exercise with unrestricted coronary flow. Ball et al., using dogs, reported that in no region was this ratio significantly less than 1.00, and in some areas it was considerably higher than unity. Sanders et al., using pigs, found an average ratio of 1.14 ± 0.03 (SE) during control exercise, which was not significantly different from the resting value of 1.26 ± 0.05. Similar results were observed in the dog by Gallagher et al. In any case, the finding of a ratio significantly lower than 1.00 (in St-Ex II) can be considered to indicate an ischemic response.

Both wall thickening and regional blood flow in the posterior wall were greater than in the anterior wall at rest (tables 1 and 2). Therefore, only during St-Ex II were systolic wall thickening and subendocardial blood flow in the posterior wall lower than those in the anterior wall. Because there was no gross damage between control crystals and the crystals were correctly positioned, we believe that the difference between posterior and anterior areas is dominantly related to normal regional nonuniformity of left ventricular function and MBF.

During St-Ex II, the 20% average decrease in regional function compared with the resting level was associated not only with subendocardial and midwall blood flow values significantly below the control exercise levels, but also with elevation of the subendocardial ST segments during exercise above the changes with control exercise. Reactive hyperemia was also evident after releasing the coronary stenosis during exercise in all four dogs in which it could be measured, further supporting the view that ischemia existed during St-Ex II. Therefore, mild subendocardial ischemia can be detected by a fall of regional contractile function of 10% or more below the resting value during exercise. The subendocardial and transmural flows were significantly below those in the anterior region, suggesting that such a flow defect might be detectable by external radionuclide perfusion imaging, although the normal subepicardial flow might render detection difficult by present techniques.

Failure of regional function to increase during exercise (St-Ex I) may also be indicative of subendocardial ischemia, but midwall and subepicardial blood flow increased normally under this condition; subendocardial blood flow also rose significantly, but to a less than normal degree in some animals. Whether or not this change in function is related to true ischemia, or perhaps to other factors such as a change in wall turgidity due to altered flow distribution, cannot be answered with certainty at this time. The change in subendocardial flow in St-Ex I was also not significantly different from that in the anterior area because of the lower flows in that region, a finding presumably reflecting normal inhomogeneity of blood flow. Associated ST segment changes were not consistent (small and not statistically significant for the St-Ex I group). Changes in the subendocardial ECG were previously shown to correlate with mild changes in regional wall motion produced by coronary stenosis at rest, although changes in the ST segments on the body surface ECG did not occur with prolonged mild stenosis. Other measures of ischemia, such as regional lactate production, may be required to further clarify this question.

The modest abnormalities in regional contractile function observed in this study during exercise would undoubtedly be difficult to detect by conventional echocardiographic or nuclear angiographic analysis of regional wall motion. However, recent studies using two-dimensional echocardiography with hyperemia at rest produced by dipyridamole readily demonstrated induced regional contraction abnormalities in patients with coronary stenoses of 70% or greater. Newer techniques such as tomographic gated blood pool radionuclide ventriculography, nuclear magnetic resonance imaging, or digital processing of intravenous ventricular fluorographic images during exercise or hyperemia eventually may allow reliable detection of such minor contraction abnormalities in patients with subcritical coronary stenosis.

The findings in this study indicate that regional wall motion is reliable for detecting subcritical coronary stenosis with coronary flow maldistribution and other evidence of ischemia provided that a definite decrease in wall motion below the resting level occurs during exercise. Thus, a decrease of regional wall motion of 10% or more during exercise indicates inadequate subendocardial perfusion. These results suggest that analysis of regional wall motion alone during hyperemia may be useful for detecting coronary artery disease at relatively early and perhaps preclinical stages.

References
LABORATORY INVESTIGATION—VENTRICULAR PERFORMANCE


Exercise-induced regional dysfunction with subcritical coronary stenosis.
J D Lee, T Tajimi, B Guth, R Seitelberger, M Miller and J Ross, Jr

Circulation. 1986;73:596-605
doi: 10.1161/01.CIR.73.3.596
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 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/73/3/596

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/