Exercise thallium-201 scintigraphy in dogs: effects of long-term coronary occlusion and collateral development on early and late scintigraphic images

MICHAEL V. COHEN, M.D., AND RICHARD M. STEINGART, M.D.

ABSTRACT To examine the effects of coronary collateral development on thallium-201 (201Tl) distribution the left circumflex coronary artery was ligated in eight dogs. Three days later these animals ran on a treadmill, and 201-thallous chloride was injected into the right atrium at peak exercise. Scintigraphic scanning was begun within 10 min and continued for 3 hr. Scanning was repeated weekly for 6 weeks. In the last week radioactive microspheres were injected into the left atrium at peak exercise to measure regional myocardial blood flow. The scintigraphically determined disparity between perfusion of the ischemic and normal myocardium was most marked at 3 days after ligation. This difference gradually lessened over the first 4 weeks until there was no difference in 201Tl distribution to normally perfused myocardium and tissue distal to the ligation. Concomitant with the improvement in the scintigrams, exercise hemodynamics also improved over this 4 week period with significant increases in cardiac output and decreases in left atrial pressure. Serial coronary angiographic studies in two animals demonstrated the appearance of collaterals in the initial weeks after coronary occlusion, and by 4 weeks the left circumflex artery distal to the obstruction was completely opacified by collateral flow. The ratio of directly measured exercise blood flow to the left circumflex and normally perfused tissues was 0.89 ± 0.08 at 6 weeks after ligation. Scintigraphic 201Tl redistribution after 3 hr also changed over the weeks after ligation. Three days after ligation washout from the ischemic area was significantly slower than that from the normal myocardium. By 6 weeks loss of 201Tl from the two regions occurred at nearly equal rates. Thus myocardial perfusion and function during exercise after coronary occlusion are dynamic events that change with time. It is likely that coronary collateral development is responsible for these phenomena. Therefore coronary collaterals do have salutary effects in the dog.

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THE FUNCTIONAL SIGNIFICANCE of coronary collaterals has been debated for many years. On the basis of analysis of clinical presentation and myocardial function in patients with coronary artery disease, several investigators have concluded that coronary collaterals are merely markers of the underlying disease.

However, other clinical studies have concluded that coronary collaterals are indeed able to prevent infarction, preserve myocardial function, and prolong survival. Perhaps the reasons for these conflicting conclusions rest in the difficulties encountered in designing an appropriate clinical study to answer the question and in the almost impossible task of selecting nearly identical subjects differing only in the presence or absence of collaterals. Because of these problems, animal preparations in which variables can be closely controlled have been used to study the significance of coronary collaterals.

Coronary collaterals in the experimental animal do limit infarction, restore blood flow to ischemic myocardium, preserve myocardial function, and improve survival after coronary occlusion. However, most studies have compared groups of animals with poorly developed coronary collaterals to those with well-developed collaterals. These group comparisons suffer from many of the same doubts raised by the clinical studies. Only a few investigators have studied the longitudinal effects of collateral development in the same individual animals. To better examine the sequential functional effects of coronary
collateral development after coronary occlusion, we used exercise thallium-201 (201Tl) scintigraphy in chronically instrumented dogs to make multiple observations in the same animal during a period that is known to encompass dramatic histologic changes in collateral structure. Our results demonstrate the functional counterpart of these anatomic changes and define the ability of coronary collaterals to limit the intensity of stress-induced myocardial ischemia.

Methods

Experimental preparation. Eight mongrel dogs (20 to 30 kg) were anesthetized with sodium pentobarbital (30 mg/kg) and intubated. Through a left thoracotomy, 15-gauge polyethylene catheters were inserted into the left atrial appendage and descending thoracic aorta and secured with purse-string sutures. The left circumflex coronary artery (LCf) was isolated immediately beyond the first major marginal branch. After premedication of the dogs with quindeine gluconate (6 mg/kg im) and lidocaine (40 mg iv) and initiation of a continuous intravenous infusion of lidocaine (1 mg/min), the LCf was totally ligated. Ventricular premature contractions were treated with 20 mg iv bolus injections of lidocaine. The LCf was incised immediately distal to the ligature and an 18-gauge catheter inserted and advanced to a point proximal to the next marginal branch where it was secured. The edges of the pericardium were approximated and the chest was closed in layers. All catheters were brought out through the chest wall and filled with a dilute solution of sodium heparin (1000 U/ml).

Experimental protocol. One or 2 days before any operative intervention a catheter was inserted into a foreleg vein of all animals. The dogs ran on a treadmill at increasing speeds and inclines until heart rate stabilized at approximately 220 beats/min. Two millicuries of 201-thallous chloride was then injected intravenously. The animals ran for an additional minute and after a brief cool down period were anesthetized with sodium pentobarbital. Scanning commenced 10 min after injection of radioisotope.

Three to 4 days after surgery and occlusion of the LCf, all dogs were able to run on the treadmill and underwent repeat exercise 201Tl scintigraphy. Heart rate and phasic and mean left atrial and aortic pressures were recorded while the dogs were resting quietly. Cardiac output was measured in duplicate by the indicator dilution method. A bolus of indocyanine green was injected into the left atrium while arterial blood was withdrawn by a Harvard constant withdrawal pump and sampled by a Gilford densitometer (1031R) inserted in the line. After completion of the baseline recordings, the treadmill was started and the speed and incline were slowly increased. Although the goal was to reproduce the heart rate attained during the preoperative exercise study, animals rarely performed as well during this initial postoperative exercise session. Two millicuries of 201Tl was injected after heart rate plateaued, and the animal continued to run 1 min longer. Scanning was begun 10 min after the completion of exercise.

The exercise studies and 201Tl scans were repeated weekly for 6 weeks in all eight dogs every 2 weeks for an additional 6 weeks in three animals. After the initial postoperative scan, all dogs were able to exercise to heart rates of at least 220 beats/min.

Myocardial scintigrams. The dogs were scanned with the right chest on the table. A gamma camera (Picker Nuclear) equipped with an all-purpose collimator was positioned parallel to the left chest and centered approximately 1 inch above the cardiac impulse. Placement of three 57Co markers on the chest wall at specified reference points assisted in centering the heart in the camera field and ensured reproducible orientation in all serial studies. A 15% energy window centered at 77 keV was used to collect 201Tl scintigraphic data. Data were acquired in a 64 × 64 pixel matrix on a PDP 11/34 computer (Digital Equipment Corp). Scanning was begun 10 min after 201Tl injection and continued for 36, 5 min frames with the camera-animal relationship held constant. The initial 5 min frame contained a minimum of 450,000 counts, with at least 75,000 counts in the region of the left ventricle. This scintigraphic procedure was duplicated for each of the control and six or seven postligation studies.

Before the exercise studies, 0.1 mCi of 201Tl was injected into the LCf catheter to determine the scintigraphic perfusion territory of the LCf. The animals were then positioned under the gamma camera and a 10 min acquisition was begun. In this way the territories of the LCf (active) and left anterior descending coronary artery (LAD) (inactive) were clearly and reproducibly circumscribed.

All postexercise scans were processed in a blinded fashion. A region of interest was drawn manually around the perimeter of the left ventricle with the operator designating the pixel on the circumference corresponding to the left ventricular apex. The operator also designated a rectangular background region of interest situated four pixels from the edge of the ventricle. A computer algorithm then determined the centroid of the left ventricle and generated 24 radials, at 15 degree increments, from this centroid to pixels on the circumference. By conversion, that point on the circumference opposite the apex was designated radius 1, with numbering proceeding clockwise around the ventricle. Guided by the results of the intracoronary 201Tl injections, which helped to demarcate the perfusion territory of the distal LCf, average counts within radials 3 to 11 (30 to 150 degrees) were designated as LCf activity, whereas counts from radials 14 to 18 (195 to 255 degrees) were designated as LAD activity. Radials 12 and 13 were not included in the analysis because LAD and LCf distributions tend to overlap in this region.

Background subtraction was accomplished with a modification25 of the bilinear interpolation algorithm first described by Goris et al.26 Because the gamma camera-animal relationships were not changed over the 3 hr of scanning, these same regions of interest were used to analyze each of the 36 frames with background determined separately for each frame.

For analysis of LAD and LCf count activity within the initial 5 min scan, count data were expressed as a percentage of the highest average radial activity in the heart. For analysis of 201Tl “washout” within the LAD and LCf distributions, data were expressed as a percentage of the average LAD 201Tl activity in the initial 5 min frame from that scan.

Scintigraphic measurement of the LCf/LAD 201Tl activity ratio at 10 to 14 min after exercise provides a measure of the distribution of blood flow at peak exercise.27 Scintigraphic analysis of subsequent redistribution can be used to distinguish between hyperperfusion of viable myocardium and infarction as a cause of the initial flow disparity.28

Coronary angiography. In two animals coronary angiograms were obtained 2 days after coronary occlusion and again 2 and 4 weeks later. Two days after the operative procedure the dogs were reanesthetized with sodium pentobarbital (15 to 20 mg/kg) and transported to the coronary angiographic suite where a femoral cutdown was performed. The animal was placed in a lateral position, with the right chest closest to the image intensifier (Phillips). A previously described preformed Kifa catheter29 was inserted into the femoral artery and advanced with fluoroscopic guidance into the aortic root and then
into the ostium of the left coronary artery. Five to 7 ml of contrast agent (meglumine diatrizoate) was injected by hand into the coronary artery, and the image was recorded on 35 mm film at a rate of 50 frames/sec. After completion of the procedure, the Kifa catheter was removed and thrombus was extracted proximal and distal to the arterial incision with a balloon catheter. The vessel was then repaired. Subsequent angiographic procedures were performed by cutting down on the same or contralateral femoral artery after anesthetizing the dogs with sodium pentobarbital (30 mg/kg).

Radioactive microspheres. In the sixth week after coronary ligation, myocardial blood flow was measured during exercise with radioactive microspheres before the 201TI injection. Two to 4 \times 10^6 radioactively labeled 15 \mu m microspheres suspended in 10 ml of 6% dextran to which 2 drops of polysorbate 80 (Tween 80) had been added to prevent aggregation were agitated in an ultrasonics bath for at least 20 min before injection. With the animal running on the treadmill and after the target heart rate was reached, hemodynamics were recorded and a timed constant-rate withdrawal of arterial blood was begun. Shortly thereafter the microspheres were injected into the left atrium, followed immediately by a bolus of indocyanine green for measurement of cardiac output.

Preparation of myocardial samples. After completion of the longitudinal exercise/scanning protocol, the dogs were anesthetized with sodium pentobarbital (30 mg/kg) and the heart was exposed through a left thoracotomy. Coincident with the left atrial administration of 20 ml of a saturated solution of KCl to arrest the heart, 2 to 3 ml of a concentrated solution of Evans blue dye was injected into the distal LCf to outline its perfusion territory. The heart was extirpated and the atria were trimmed away. After filling of the ventricular chambers with gauze, the heart was frozen and then sliced from apex to base into 0.5 cm thick slices. The left ventricular rings were separated into stained (LCf perfusion territory distal to the ligature) and unstained portions. These pieces were then divided into wedges and each wedge was subdivided into inner (or endocardial) and outer (or epicardial) halves. Isotope activity of all myocardial pieces and reference arterial blood samples was counted in a gamma spectrometer (Nuclear Chicago Model 1185), and the counts per minute and counts per minute per gram were determined by standard computer programs after correction for decay and overlap of isotope energies.

**TABLE 1**

<table>
<thead>
<tr>
<th>HR (bpm)</th>
<th>AoP (mm Hg)</th>
<th>LAP (mm Hg)</th>
<th>CO (1/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preligation</td>
<td>96 ± 5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Postligation</td>
<td>135 ± 7()</td>
<td>96 ± 8</td>
<td>7.5 ± 2.6</td>
</tr>
<tr>
<td>3 days</td>
<td>123 ± 8()</td>
<td>95 ± 7</td>
<td>9.6 ± 1.0</td>
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<tr>
<td>1 wk</td>
<td>118 ± 8</td>
<td>101 ± 6</td>
<td>11.4 ± 2.8</td>
</tr>
<tr>
<td>2 wk</td>
<td>122 ± 9()</td>
<td>105 ± 7</td>
<td>7.5 ± 2.2</td>
</tr>
<tr>
<td>3 wk</td>
<td>115 ± 5</td>
<td>103 ± 8</td>
<td>8.1 ± 2.2</td>
</tr>
<tr>
<td>4 wk</td>
<td>122 ± 6()</td>
<td>107 ± 6</td>
<td>8.5 ± 1.8</td>
</tr>
<tr>
<td>5 wk</td>
<td>115 ± 9</td>
<td>99 ± 6</td>
<td>8.9 ± 2.4</td>
</tr>
<tr>
<td>6 wk</td>
<td>—</td>
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**Exercise**

<table>
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<th>CO (1/min)</th>
</tr>
</thead>
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<tr>
<td>229 ± 8()</td>
<td>111 ± 9</td>
<td>23.1 ± 4.2()</td>
<td>6.1 ± 0.7()</td>
</tr>
<tr>
<td>204 ± 4()</td>
<td>107 ± 9</td>
<td>21.0 ± 4.1()</td>
<td>8.3 ± 0.9()</td>
</tr>
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<td>230 ± 3()</td>
<td>117 ± 9</td>
<td>15.1 ± 2.2()</td>
<td>8.0 ± 0.8()</td>
</tr>
<tr>
<td>231 ± 4()</td>
<td>115 ± 7</td>
<td>11.1 ± 2.0()</td>
<td>8.1 ± 0.8()</td>
</tr>
<tr>
<td>228 ± 4()</td>
<td>111 ± 8</td>
<td>10.7 ± 2.2()</td>
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<tr>
<td>219 ± 8()</td>
<td>115 ± 9</td>
<td>10.5 ± 2.0()</td>
<td>8.5 ± 0.9()</td>
</tr>
<tr>
<td>221 ± 5()</td>
<td>109 ± 9</td>
<td>11.2 ± 1.8()</td>
<td>8.6 ± 1.1()</td>
</tr>
</tbody>
</table>

AoP = mean aortic pressure; CO = cardiac output; HR = heart rate; LAP = mean left atrial pressure.

Statistical significance of paired differences between rest and exercise states: \(^p < .005\); \(^p < .001\).

Statistical significance of differences between first and subsequent postligation studies: \(^p < .05\).

Statistical significance of differences between preligation and postligation heart rates: \(^p < .05\); \(^p < .005\).

**TABLE 2**

<table>
<thead>
<tr>
<th>Type of exercise</th>
<th>HR (bpm)</th>
<th>AoP (mm Hg)</th>
<th>LAP (mm Hg)</th>
<th>CO (1/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td>96 ± 5</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Preligation</td>
<td>135 ± 7()</td>
<td>96 ± 8</td>
<td>7.5 ± 2.6</td>
<td>2.8 ± 0.3</td>
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<tr>
<td>Postligation</td>
<td>123 ± 8()</td>
<td>95 ± 7</td>
<td>9.6 ± 1.0</td>
<td>3.3 ± 0.3</td>
</tr>
<tr>
<td>3 days</td>
<td>118 ± 8</td>
<td>101 ± 6</td>
<td>11.4 ± 2.8</td>
<td>3.2 ± 0.3</td>
</tr>
<tr>
<td>1 wk</td>
<td>122 ± 9()</td>
<td>105 ± 7</td>
<td>7.5 ± 2.2</td>
<td>3.3 ± 0.2</td>
</tr>
<tr>
<td>2 wk</td>
<td>115 ± 5</td>
<td>103 ± 8</td>
<td>8.1 ± 2.2</td>
<td>3.5 ± 0.3</td>
</tr>
<tr>
<td>3 wk</td>
<td>122 ± 6()</td>
<td>107 ± 6</td>
<td>8.5 ± 1.8</td>
<td>3.6 ± 0.3</td>
</tr>
<tr>
<td>4 wk</td>
<td>115 ± 9</td>
<td>99 ± 6</td>
<td>8.9 ± 2.4</td>
<td>3.8 ± 0.3</td>
</tr>
<tr>
<td>5 wk</td>
<td>—</td>
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<tr>
<td>6 wk</td>
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back to 230 beats/min (table 1) and double product was higher (figure 1). Exercise cardiac output rose to 8.3 liters/min by week 1, significantly greater than the 3 day level (p < .05), and thereafter plateaued. Left atrial pressure during peak exercise began to decrease by 1 week after ligation. At 3 weeks peak atrial pressure was only 11.1 mm Hg, significantly lower than at 3 days (p < .05). This improvement in cardiac function was accompanied by increasing ability to run for longer periods at faster speeds and steeper inclines. Although exercise double products increased progressively up to 3 weeks after coronary ligation, these changes were not statistically significant. There were no significant differences in double product, exercise tolerance, or hemodynamics between weeks 6 and 12 in the three dogs that continued the protocol.

The myocardium in the perfusion territory of the occluded vessel, or risk area, averaged 22.6 ± 4.6% of the entire left ventricle. Because of likely resorption of necrotic myocardium and possible replacement by fibrous tissue at 6 weeks in these dogs, we believed that infarct size immediately after occlusion could not be determined accurately. Exercise myocardial blood flow to the normal tissue 6 weeks after coronary occlusion was 3.11 ± 0.09 ml/min/g, whereas perfusion to the LCf tissue averaged 2.75 ± 0.34 ml/min/g without appreciable radial flow gradient. Thus the ratio of ischemic to normal blood flow was 0.89 ± 0.08. Transmural flow distribution favored the endocardium in the normally perfused regions (inner/outer left ventricular wall flow ratio 1.12 ± 0.07), whereas mild redistribution of flow toward the epicardium was still apparent in the myocardium beyond the coronary occlusion 6 weeks after LCf ligation (inner/outer left ventricular wall flow ratio 0.94 ± 0.06).

Figure 2 illustrates mean 201Tl radial activity 10 to 14 min after exercise in the scans acquired before and 3 days and 6 weeks after LCf ligation. The data are expressed as a percentage of the highest mean radial activity in a given heart. Before ligation, the circumferential profile plot demonstrated a peak in 201Tl activity within the circumflex distribution. Three days after LCf ligation, activity in the LCf distribution was markedly reduced relative to control, whereas LAD activity was relatively increased. By 6 weeks after LCf occlusion, LCf 201Tl activity in the initial frame was intermediate between that observed before and at 3 days after LCf ligation, whereas LAD activity was unchanged from the 3 day scan. No further changes were noted in weeks 7 to 12.

The ratios of mean LCf/LAD activity (mean ± SE) 10 to 14 min after injection of 201Tl for the preligation scan and the exercise scintigrams done at 3 days and 2, 3, 4, 5, and 6 weeks after LCf ligation are shown in figure 3. Before ligation, LCf and LAD activities were equal. At 3 days after LCf ligation, LCf activity in the initial frame of the 3 hr study was 73.6 ± 6.6% of LAD activity (p < .02). During the next 2 weeks, LCf activity remained significantly lower. By 4 weeks LCf activity was 87.4 ± 4.6% of LAD activity (p = NS), and there was no further change in subsequent weeks. The LCf/LAD activity ratios at 3 days and 2 weeks after LCf ligation were significantly lower than the ratio before ligation (p < .05). By the third week after ligation and thereafter, the LCf/LAD ratios in the initial frame of the 3 hr studies were no longer significantly different from preligation values. Thus the large exercise scintigraphic defect apparent 3 days after coronary occlusion showed progressive shrinkage in subsequent weeks until perfusion of the identified abnormal region became nearly indistinguishable from that of normal myocardium.

Dynamic changes in the rate of 201Tl loss from the LAD and LCf distributions were observed over the 6 weeks after LCf ligation. Figure 4 illustrates the mean LCf and LAD 201Tl activities for the eight dogs in each
Three activities LAD (figure 4, B). Val washout curves lower than LAD initially was activity. The difference in LAD and LCf distributions, LAD and were convergence of some activities before LCf ligation, LCf distributions were equal, averaging 52.5 ± 5.5% and 54.5 ± 5.5% over 3 hr for the LAD and LCf distributions, respectively (figure 5, A). Three days after LCf ligation, the loss of 201Tl from the LCf distribution (49.9 ± 6.1%) was significantly slower than that from the LAD distribution (68.5 ± 9.2%) (p < .025) (figure 5, A). The time-activity curves therefore converged over the 3 hr observation period (figure 4, B). During the ensuing 5 study weeks, the rate of 201Tl loss from the LAD distribution remained constant, whereas that from the LCf distribution tended to increase. When the differences in the postligation LAD and LCf washout rates were compared with the preligation values, marked change was noted at 3 days (figure 5, B). The difference in LAD and LCf washout rates then gradually disappeared over the ensuing 5 weeks and was no longer significantly different from the preligation value at 6 weeks after LCf ligation.

In two animals coronary collateral development was monitored with serial angiograms. Two days after coronary occlusion there was no opacification of the LCf beyond the site of ligation (figure 6, A). Contrast agent remained in the LCf stump distal to the last patent marginal branch for several minutes after disappearance from the other vessels. Two weeks later col-
lateral vessels were evident and contrast agent could be seen in the distal LCf, but washout was still delayed. By 4 weeks abundant collateral channels from the proximal LCf, including the sinoatrial node artery and the mid and distal LAD, were present. Furthermore, the entire LCf distal to the ligation was well opacified (figure 6, B), and the crux and atroventricular node arteries could be easily identified. Dye washout from the distal LCf was only slightly slower than that from the LAD. In figure 6 these changes in the angiogram...
are compared with the changes in the thallium scintigraphic images recorded 1 day after the respective angiograms in the same dog. Three days after coronary occlusion, when few collaterals were apparent, a large scintigraphic defect corresponding to the region of absent or poor myocardial perfusion was obvious (figure 6, A). However, by 4 weeks (figure 6, B), when coronary collaterals had become abundant and accounted for substantial restoration of flow to the distal LCf perfusion territory, the scintigram was nearly normal.

Discussion

In this study, large, reversible, exercise-induced scintigraphic defects were apparent shortly after coronary occlusion. Exercise in these animals resulted in dramatic increases in left atrial pressure and only modest rises in cardiac output. In subsequent weeks scintigraphic defects shrank, and after 4 weeks there was no statistically significant difference in radiisotope uptake or washout by normal tissue and myocardium in the perfusion territory of the ligated vessel. Hemodynamics and exercise performance also improved in the initial 4 weeks after occlusion. Exercise elicited smaller increases in left atrial pressure and larger rises in stroke volume and cardiac output.

Numerous studies have demonstrated that directly measured myocardial thallium distribution shortly after intravenous injection is proportional to blood flow.\textsuperscript{31–33} In particular this has been clearly demonstrated in an exercising canine preparation similar to the one used in this study.\textsuperscript{31} Our previous work has extended these conclusions to scintigraphic measurements of myocardial thallium activity.\textsuperscript{27} Therefore, increasing LCf/LAD (ischemic/normal) myocardial scintigraphic \textsuperscript{201}Tl ratios correlate with increasing tissue perfusion of the once ischemic myocardium. At 6 weeks, when scintigraphic defects were nearly absent, myocardial blood flow to muscle in the distribution of the occluded vessel was practically normal even during the stress of exercise. These flow data confirm earlier observations.\textsuperscript{21} Persistent small scintigraphic and flow deficits at 6 weeks are probably related to replacement of infarcted tissue by poorly vascularized fibrous tissue and the fundamental inability of coronary collaterals to deliver normal flows during stress.\textsuperscript{34–37} Scintigraphic studies up to 12 weeks after coronary occlusion showed no additional improvement.

The most likely explanation for the improvement in exercise scintigraphic images, exercise performance, and hemodynamics in the weeks after coronary occlusion is development of coronary collaterals. The time course of the improvement in the dogs in this study parallels the three-phase collateral transformation demonstrated by Schaper et al.,\textsuperscript{38–41} in which a thin-walled 40 μm conduit is eventually converted into a 1 mm thick-walled arteriole. Hence coronary collateral development could account for the gradually increasing perfusion of the ischemic tissue with subsequent lessening of exercise-induced myocardial dysfunction and improvement in hemodynamics. Previous studies\textsuperscript{31, 22} have clearly demonstrated a significant correlation between increasing coronary collateral flow and improved hemodynamic performance during exercise. Thus coronary occlusion in exercising dogs with initially low collateral flow caused cardiac failure with a rise in left atrial pressure to nearly 30 mm Hg and a significant decrease in cardiac output.\textsuperscript{21} With further collateral development, coronary occlusion in the same running dogs resulted in a much smaller rise in

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left atrial pressure and a smaller fall in cardiac output, thus documenting the ability of collaterals to preserve myocardial perfusion despite interruption of normal antegrade sources and to attenuate the effects of this interruption on cardiac function. The serial coronary angiographic studies in this investigation further demonstrate that coronary collateral development parallels the improvement in exercise hemodynamics as well as in the exercise thallium scintigrams (figure 6). Furthermore, nearly normal exercise flows in the ischemic region at 6 weeks attest to the ability of coronary collaterals to rapidly restore perfusion of myocardium after coronary occlusion.

Explanations for the serial changes in hemodynamics and scintigraphic images other than increasing collateral blood flow are possible but less likely. Decreased exercise performance in the initial postsurgical study could have been related in part to anesthesia and thoracotomy performed just 3 days earlier. Decreased exercise capacity at this time because of discomfort or the detraining effect of surgery might have limited the rise in cardiac output, although the increase in left atrial pressure would also have been attenuated. Further recovery from the surgical insult might have accounted for better exercise performance and the increased cardiac output in later studies, but left atrial pressure and cardiac output remained essentially normal.

FIGURE 6. A. Unretouched Polaroid picture of a $^{201}$ Tl scintigram taken 10 min after cessation of exercise performed 3 days after coronary occlusion. A frame from a coronary angiogram completed 1 day earlier appears beneath the scintigram. There is a large scintigraphic defect apparent in the distribution of the LCf. The arrow in the angiographic frame indicates the site of LCf ligation. The radiopaque contrast agent injected into the ostium of the left coronary artery flowed only to the point of arterial obstruction. There were no visualized collateral channels and no contrast agent was ever observed in the distal LCf. B. Scintigraphic and angiographic frames from studies performed 4 weeks after those presented in A. Only a small scintigraphic defect remains, and the improvement after the initial study is obvious. The level of the LCf ligation is again indicated by the straight arrow. But now the entire distal LCf (curved arrow) is normally opacified by numerous intracoronary and intercoronary collateral channels. Because of the slightly different projection, the short marginal artery originating just before the site of ligation in A is in part superimposed on the initial segment of the collateralized LCf. Runoff from the distal LCf was only slightly slower than that from normal vessels.
pressure would also have been expected to increase rather than decrease, as seen in the experimental animals. The gradual and significant decline in left atrial pressure during exercise over the initial 3 to 4 weeks of study is more consistent with an improvement in left ventricular function, and the limitation of early performance more likely the result of acute cardiac failure. To support this contention, parallel studies in four dogs similarly instrumented except that the LCF was not ligated revealed that aortic and left atrial pressures, cardiac output, and double product as well as exercise performance did not change significantly from 3 days to 10 to 14 days after surgery, a period during which the most impressive changes in hemodynamics were occurring in the experimental animals described above.

Compensatory hypertrophy of normal myocardium theoretically could result in improvement of global left ventricular function. However, improvement was evident between the first evaluation at 3 days and the second at 7 days after coronary ligation, hardly enough time for significant hypertrophy to occur.

It is also possible that changes in ventricular geometry rather than increasing collateral blood flow over time were responsible for the apparent shrinking of the scintigraphic defect. Gewirtz et al. demonstrated that short-term aortic constriction that doubled left atrial pressure and caused substantial decreases in distal aortic pressure could result in left ventricular dilatation. 201Tl scintigrams obtained during the aortic constric-
tions showed prominent apical defects, presumably caused by thinning of the tissue. However, in the present experiments imaging was begun 10 min after exercise in anesthetized dogs. Blood pressure in these animals had returned to or had fallen slightly below baseline levels and therefore would not have been responsible for thinned, count-deficient myocardium. Alternatively, a large scintigraphic defect in the initial study might have been caused by bulging of a large LCF scar. But if the diminution of LCF counts was simply caused by bulging of a scar, one would have expected the left ventricular cavity to have dilated and the LCF myocardium to have thinned. As seen in figure 6, left ventricular size was not grossly different at 3 days and 4 weeks after coronary ligation and the count-deficient area in the LCF distribution had normal thickness. Furthermore, the heart size did not change over the 3 hr scanning interval, and the circumferential region of interest closely approximated the ventricular borders. If the LCF distribution were largely scarred, the documented marked redistribution of 201Tl activity over the 3 hr of scanning would not have been observed. Finally, since there was only a small flow deficit at 6 weeks and the amount of infarcted tissue at postmortem examination was small, it is unlikely that changes in compliance of infarcted tissue or contraction of scar would account for improvement of the scintigrams done several weeks after coronary ligation. Nevertheless, a small contribution of these mechanical effects cannot be completely excluded.

If absolute blood flow to the normal myocardium were highest in the initial exercise study after coronary occlusion and then during subsequent weeks were lower, the ischemic/normal 201Tl activity ratio would have appeared to increase even if ischemic-myocardial uptake had been unchanged. However, previous studies have demonstrated that normal myocardial flows are lower in the exercising dog shortly after coronary occlusion than in the same animals with long-standing occlusions exercising at similar workloads. Presumably cardiac failure and poor exercise tolerance in the early exercise studies limit the rise in myocardial flow in the noninvolved segments. The flow increases are seen later after long-term coronary occlusion when the limitations are no longer present. These changes in normal tissue flow, if unaccompanied by changes in perfusion of ischemic myocardium, would have produced a fall, rather than the observed increase, in the ischemic/normal activity ratio over 6 weeks and cannot account for the observed improvement in scintographic images.

In the routine performance of exercise 201Tl scintigraphy in patients with severe coronary obstructive disease, occasional subjects will have no evidence of scintigraphic defects. In fact, several investigators have already concluded that collaterals in man may attenuate or eliminate 201Tl defects as well as modify redistribution, although agreement is not universal. Buda et al. did serial 201Tl scintigrams in patients 3 weeks and 3 months after myocardial infarction. Similar to the present observations in dogs, scintigraphic defects were significantly smaller in the follow-up studies despite greater rate-pressure products. They also postulated that increased myocardial perfusion related to collateral development was the most likely explanation. Patients studied by Kondo et al. with collateral vessels were significantly more likely to have complete or partial 201Tl redistribution than patients without anastomotic vessels (p < .02). As demonstrated by Khaw et al. in animal preparations, delayed distribution of 201Tl is a function of the distribution of viable myocardium. Therefore the presence of collateral vessels is associated with the maintenance of myocardial viability.
To the extent that collaterals do have these effects on early and late $^{201}$Tl distribution, attempts to predict the severity of coronary artery disease from exercise scintigrams$^{11}$ are consigned to failure. As demonstrated in this investigation in dogs with the same coronary lesion throughout the study, the magnitude of the $^{201}$Tl defect was greatly influenced by the degree of collateral development. Thus it must be recognized that $^{201}$Tl scintigrams are likely to be affected by the collateral circulation as well as by the severity of the lesions.

Our results provide evidence that coronary collaterals in an experimental preparation can restore blood flow to ischemic myocardium and improve global cardiac function. These observations further strengthen the contention that coronary collaterals have salutary effects. By diminishing myocardial ischemia, collaterals attenuate initial scintigraphic defects and in turn may alter the pattern of redistribution. These latter observations should not be overlooked when clinical scintigrams are being evaluated.

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LABORATORY INVESTIGATION–MYOCARDIAL BLOOD FLOW


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