Exercise Can Promote Coronary Collateral Development Without Improving Perfusion of Ischemic Myocardium

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SUMMARY We studied the effect of exercise training on the coronary collaterals that developed in response to gradual coronary occlusion in dogs. After their proximal left circumflex coronary artery occlusion, 33 dogs were randomly assigned to exercise or sedentary groups. Coronary collateral function was evaluated 5 weeks or 8 weeks later. The exercised dogs developed better epicardial collateral connections to the occluded left circumflex as judged by higher retrograde blood flow from the distal left circumflex and lower pressure drop across the collaterals. No difference in collaterals was apparent angiographically. Microsphere data indicated that exercise dogs were not better protected against tachycardia-provoked subendocardial ischemia in the myocardium supplied by the collaterals.

INTERCORONARY collateral blood vessels grow in response to coronary ischemia. This association suggests that collateral development may be governed in part by blood flow requirements of the myocardium. If so, augmentation of myocardial blood flow requirements by repetitive exercise might promote further collateral development.

In patients whose exercise capacity is limited by angina due to coronary ischemia, exercise training increases their work threshold for angina. A possible explanation is improved collateral function. However, because of the relative bradycardia caused by training, the amount of cardiac effort and myocardial metabolic rate at any given exercise level is lower after training. Therefore, the higher work threshold for angina, alternatively, may be explained by lower coronary blood flow needs. Angiographic studies have shown no effect of exercise on coronary collaterals.

Exercise training stimulates the growth of normal coronary arteries and capillaries in rats. The effect of exercise training on coronary collaterals has been investigated in dogs with coronary ischemia. Dogs that exercised seem to have better collaterals as judged by higher retrograde blood flow from the stenosed artery, but the results were inconclusive in other experiments using the microsphere technique to determine blood flow into the distal myocardium.

A beneficial impact of exercise training on angina threshold in patients seems established. The important, unresolved question is whether exercise significantly influences coronary collateral development. We have investigated this question, using a dog model of chronic coronary occlusion in which progressive coronary collateral development was evaluated concurrently by the microsphere technique, coronary angiography, and coronary perfusion pressure and retrograde blood flow measured distal to the occlusion.

Methods

Preliminary Operative Procedure

A left thoractomy was performed using halothane anesthesia and aseptic technique. We encircled the proximal portion of the left circumflex coronary artery (LC) with an ameroid constrictor (2.77 or 3.00 mm i.d.) or a pneumatic cuff occluder and closed the chest.

Protocols

Acute LC occlusion was carried out in seven dogs 7–9 days after securing the pneumatic cuff on the LC. Observations were made while the LC was patent (verified angiographically) and 2–3 minutes after temporary acute LC occlusion induced by inflation of the pneumatic cuff.

Thirty-three dogs were allotted randomly (sealed cards) to sedentary (Sed) or exercise (Ex) groups 3 days after ameroid implantation. Sed dogs remained in their cages. Ex dogs ran 5 days per week on a treadmill, beginning on the sixth postoperative day. The intensity of exercise was increased progressively until a level of 30 minutes of continuous running at 5 m.p.h. at a 15% grade was reached 2 weeks postoperatively.

Each dog’s heart rate during submaximal exercise was measured on a motor-driven treadmill at the same workload before surgery and during the last week of the experiment. The dogs remained in their respective groups for 5 weeks (8 Sed dogs, 8 Ex dogs) or 8 weeks (8 Sed dogs, 8 Ex dogs), when their coronary collateral function was assessed and the experiment terminated.

Five other dogs were excluded: four died of unknown causes before completion of the experiment, and one 8-week Ex dog had an unsuspected healed inferior infarction found postmortem.

Coronary Collateral Evaluation

Acepromazine (Ayerst), 1 mg/kg intravenously, and morphine, 30 mg intramuscularly, were ad-
ministered for sedation, and 2% lidocaine was infiltrated subcutaneously for local analgesia. We inserted catheters into neck vessels and positioned them by fluoroscopy in the left ventricle, thoracic aorta, and coronary sinus approximately 2 cm beyond the ostium; and we retrieved the proximal end of the cuff occluder through a skin incision on the dog’s back. The following procedures were carried out with the dogs awake and breathing spontaneously; heart rate and aortic blood pressure were recorded; paired arterial and coronary venous blood samples were obtained for oxygen and lactate analyses (8-week experiments only); microspheres were injected to determine coronary blood flow distribution; and left ventriculography was filmed in the right anterior oblique projection at 60 frames/sec\(^{-1}\), using 8 ml of Renografin (meglumine diatrizoate) (8-week experiments only). Left ventricular volumes and ejection fraction were calculated by the area-length method.

The dogs were then anesthetized with pentobarbital (approximately 15 mg/kg) and left coronary angiography was performed. In 8-week experiments large cut films were obtained. The diameters of the left anterior descending (LAD) and posterior descending branch of the LC on these high-resolution cut films were measured and corrected for magnification. Collateral development between the LAD and LC also was subjectively scored (blindly), assigning 1, 2 or 3 (best) points based on the number and size of visible collateral connections and the extent and intensity of opacification of the LC system distal to its occlusion. Finally, a wide left thoracotomy was carried out and a cannula inserted into the LC immediately distal to the pulmonary cuff or aimeroid. We measured pressures simultaneously in the aorta and in the distal LC. Retrograde blood flow from the distal LC was measured by opening the cannula into a graduated cylinder.

**Microsphere Techniques**

The spheres (3M Co.) were approximately 15\(\mu\) in diameter and labeled with either strontium-85, cerium-141, or niobium-95, used in random sequence. Four hundred thousand to 1 million microspheres were introduced via the left ventricular catheter over a 15–20-second period. After the experiment, we removed the heart and separated the free wall of the left ventricle (discarding 5 g at the apex) into regions supplied by the LAD and LC, based on the distribution of visible epicardial branches. To test the adequacy of separation of LAD and LC regions by this method, in 20 experiments we cut away approximately 10 g of marginal tissue from each region where they merged (total 20 g). Exclusion of the marginal tissue slightly increased the severity of estimated LC regional ischemia in the acute but not the chronic occlusion experiments. All data presented in the tables and figures include the marginal tissue. Samples were divided into inner (subendocardial) and outer (subepicardial) halves and placed in 15-mm diameter glass tubes and weighed. Their radioactive emissions were counted in a Packard 5230 automatic gamma spectrometer system, calibrated with cesium-137 as a standard before each run. Coronary blood flow data are expressed only as distribution ratios between different regions of the heart, which depend simply upon the counts/min per gram (attributable to the isotope administered) for one region divided by that of the other.

**Histology**

The heart was examined microscopically for evidence of fibrosis in 12 of the first 13 experiments. The left ventricle was sliced horizontally into six rings and a sample extending from endocardium to epicardium was taken from the LAD and LC regions of each ring and prepared for hematoxylin and eosin staining.

**Statistics**

Statistical significance of differences was judged by a two-tailed \(t\) test, paired (changes within the same dogs) or unpaired (Ex vs Sed).

**Results**

**Exercise Training Effect**

Sed dogs gained weight (23.3 ± 0.63 to 25.4 ± 1.04 kg, mean ± sem, \(p < 0.01\)); the weight of the Ex dogs remained steady. The submaximal exercise heart rate decreased (170 ± 11.2 to 149 ± 8.4 min\(^{-1}\), in 8-week Ex dogs \(p < 0.05\), but did not change significantly in 5-week Ex dogs or in either Sed group. The final heart weight/initial body weight was 7.5 ± 0.23 for Ex dogs and 7.0 ± 0.23 g/kg × 10\(^3\) for Sed dogs (difference not significant). Left ventricular volume and ejection fraction determined angiographically in 8-week dogs with the dogs conscious in the basal resting state were not significantly different between Sed and Ex groups (54 ± 7.3 vs 70 ± 8.8 ml and 68 ± 3.7 vs 65 ± 3.3%, respectively).

**Coronary Blood Flow Distribution**

Observations were made with the dogs conscious and at rest. There were no significant differences in heart rate (71 ± 2.2 min\(^{-1}\)) or aortic blood pressure (116 ± 1.9/78 ± 1.6 mm Hg) between different groups of dogs. Microsphere data are shown in table 1 and figure 1. When the LC was patent, microsphere concentrations in LAD and LC regions were nearly equal (LC/LAD = 1.00 ± 0.027), and in each region the subendocardial (I) layer received more microspheres than the subepicardial (O) layer (I/O > 1).

Acute LC occlusion decreased the LC/LAD and I/O (LC), but did not affect the I/O (LAD). Inclusion of myocardium where the LAD and LC regions merged led to an underestimation of the severity of ischemia which occurred in the center of the LC region. The data in table 1 include this marginal tissue. When 20 g of marginal tissue were excluded, LC/LAD was 0.12 ± 0.051 and I/O (LC) was 0.44 ± 0.098 during acute occlusion.

All groups of dogs with chronic LC occlusion had
normal coronary blood flow distribution when they were in the basal resting state, as demonstrated by LC/LAD, I/O (LAD) and I/O (LC) values, which were similar to those of dogs with patent coronary arteries. Tachycardia induced by atrial pacing, however, did lead to signs of relative ischemia in the myocardium supplied by the chronically occluded LC, especially in the subendocardial layer. There was a significant decrease in LC/LAD in 5-week dogs at a heart rate of 250 beats/min (8-week dogs were paced only at 200 beats/min), and I/O (LC) was significantly lower than I/O (LAD) during tachycardia in both 5-week and 8-week dogs (table 1).

Results are presented separately for Sed and Ex dogs in figure 1. The basal resting values and the LC regional ischemia provoked by tachycardia were essentially the same for Sed and Ex groups. In chronic occlusion experiments the microsphere results were not significantly changed when the data were recalculated excluding the marginal tissue between the LAD and LC regions.

**Myocardial O₂ and Lactate Extraction**

Acute LC occlusion with the dogs conscious and at rest increased the extraction ratio of oxygen from the coronary blood (a-v/a) from 73 ± 3% (patent LC) to 79 ± 3%. Oxygen extraction in 8-week Ex dogs (66 ± 3%) was less than in dogs with patent LC (p < 0.05), but was not significantly less than in 8-week Sed dogs (70 ± 3%). Oxygen extraction did not change significantly during atrial pacing in 8-week dogs.

**Figure 1.** Coronary blood flow distribution by microsphere technique in conscious dogs. Solid symbols are for sedentary dogs; open symbols for exercise dogs. In the lower panel, circles represent the left anterior descending artery (LAD) region and triangles represent the left circumflex artery (LC) region. Values are mean ± SEM.
Table 2. Distal Left Circumflex Coronary Pressure and Retrograde Blood Flow (Chest Open)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acute LC occlusion (n = 7,6)</th>
<th>Chronic LC Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 weeks</td>
<td>8 weeks</td>
</tr>
<tr>
<td></td>
<td>Sed (n = 8,7)</td>
<td>Ex (n = 8,6)</td>
</tr>
<tr>
<td>AP (mm Hg)</td>
<td>89 ± 8.5</td>
<td>79 ± 4.7</td>
</tr>
<tr>
<td>LCP (mm Hg)</td>
<td>19 ± 2.5</td>
<td>46 ± 5.3</td>
</tr>
<tr>
<td>AP-LCP (mm Hg)</td>
<td>70 ± 6.9</td>
<td>33 ± 4.7</td>
</tr>
<tr>
<td>RBF (ml/min)</td>
<td>6 ± 1.8</td>
<td>17 ± 2.6</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
Abbreviations: AP = mean aortic pressure; LCP = mean distal left circumflex artery pressure; RBF = left circumflex retrograde blood flow.
Statistical significance:
8 weeks different from 5 weeks, *p < 0.05; †p < 0.01.
Ex different from Sed: ‡p < 0.05; §p < 0.01.

Lactate extraction by the heart at rest was similar in 8-week Sed (25 ± 10%) and Ex (21 ± 6%) dogs, and did not change significantly in either group during atrial pacing. Acute LC occlusion failed to produce a consistent change in myocardial lactate extraction (lactate production in only two of seven dogs), indicating that the coronary venous blood samples probably represented myocardium mainly in the distribution of the LAD rather than the LC.

Distal LC Pressure and Retrograde Blood Flow

Aortic pressure, distal LC pressure, and retrograde LC blood flow were measured under open chest conditions (table 2 and fig. 2). Aortic pressure was comparable for different groups of dogs. The pressure drop between the aorta and distal LC (AP-LCP) was lower and the retrograde blood flow was higher in dogs with chronic LC occlusion than in dogs with acute LC occlusion (p < 0.01), and these differences tended to progress between 5 weeks and 8 weeks. Ex dogs had lower AP-LCP and higher retrograde blood flow than Sed dogs. The statistical significance of these differences is shown in table 2.

Collaterals by Angiography

Renografin injected into the left coronary ostium with the dogs anesthetized before opening the chest opacified the LC beyond the ameroid constrictor via visible collaterals in all chronic LC occlusion dogs. Figure 3 illustrates the range that was found in angiographic display of the collaterals among different dogs. There was no significant difference between Sed and Ex 8-week dogs in the diameters of the LAD (Sed = 2.7 ± 0.12 mm, Ex = 2.9 ± 0.16 mm) or the posterior descending branch of the LC (Sed = 1.6 ± 0.16 mm, Ex = 1.4 ± 0.18 mm), nor in the extent of collateral vessel development as subjectively assessed (Sed = 2.1 ± 0.26 points, Ex = 1.9 ± 0.26 points).

Microscopic

Three 5-week Ex dogs had small discrete fibrous scars at the base of the posterior papillary muscle. The scar tissue (2–3 g) was excluded from microsphere analysis. The remainder of the myocardium appeared grossly normal in all dogs. Transmural sections taken at six levels (apex to base) in the distributions of the LC and LAD were examined microscopically in five Ex dogs and seven Sed dogs. Most sections were free of microscopic fibrosis. Three Ex dogs had slight subendocardial fibrosis in one of six LC sections, limited to the immediate subendocardium in two and extending halfway to the epicardium in one. Two Sed dogs had slight fibrosis in the immediate subendocardial layer in one of six LC sections, and one also had this condition in one of six LAD sections.
Discussion

The purpose of the acute LC occlusion experiments was to determine baseline collateral function as measured by our techniques in this animal model. Differences in results between chronic and acute LC occlusion experiments presumably reflect subsequent collateral development induced by ischemia with or without superimposed exercise.

The ameroid constrictors, initially nonobstructive, swell as they absorb body fluids and gradually occlude the encircled coronary artery. Occlusion occurred after 2-3 weeks in two preliminary dogs in which we carried out serial coronary angiography, which coincides with the interval for occlusion found by others.\(^4\)

If we estimate that enough stenosis to stimulate collaterals occurred 1 week earlier, the period available for collateral growth was 3-4 weeks in our 5-week experiments and 6-7 weeks in our 8-week experiments. Collateral growth begins within a few days of coronary ischemia\(^5\), \(^6\) and levels off 1-2 months after ameroid implantation.\(^4\), \(^7\) Our experiments covered the rapid collateral growth period. Ex dogs reached a significant intensity of running a little more than 1 week after surgery, when the LC probably was still patent. Therefore, the training periods were approximately 4 weeks and 7 weeks in the two protocols and encompassed the entire period of collateral growth.

The higher retrograde blood flow from the occluded LC in Ex dogs confirms similar observations made by Eckstein more than 20 years ago in dogs whose collaterals were induced by a fixed subtotal coronary stenosis.\(^9\) Eckstein also demonstrated that retrograde blood flow was proportional to the degree of coronary stenosis, supporting the contention that retrograde flow was a valid measure of collateral development. Nevertheless, blood flowing backwards from a coronary artery opened to the atmosphere has no simple physiologic counterpart and specifically cannot be considered directly equivalent to the collateral blood flow that would occur in more physiologic circumstances.\(^14\), \(^18\), \(^19\) When the arterial wall is intact, blood which traverses the collateral connections to the LC flows distally into the microvasculature; and the collateral flow under those conditions is influenced not only by collateral resistance but by the resistances of the arterioles and capillaries as well. Retrograde blood flow probably underestimates the perfusion of ischemic myocardium by collaterals in acute coronary occlusion\(^18\), \(^19\) and overestimates collateral perfusion when intercoronary connections have developed further during chronic occlusion.\(^18\)

We also found that Ex dogs had higher pressures in the distal LC and a lower pressure difference between the aorta and distal LC. These measurements were made while the LC was closed and transporting blood in the usual direction from its collaterals toward the distal myocardial microvasculature. Aortic pressure should be a reasonable estimate of perfusion pressure on the upstream side of the collaterals since the fall in pressure along the major epicardial arteries is only minor,\(^20\) and there was no significant difference in the LAD diameters between our Ex and Sed dogs that might have created a discrepancy in epicardial pressure gradient between the two groups. It seems reasonable to conclude, then, that the Ex dogs had a smaller pressure drop across their collaterals. The most plausible explanation for this is lower collateral resistance to blood flow. However, an alternative ex-

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**Figure 3.** Coronary angiograms in the right anterior oblique projection in three 8-week dogs, selected to illustrate the range of collateral development as subjectively assessed. The catheter tip is in the left coronary ostium, and the Renograin (meglumine diatrizoate) fills the left circumflex artery system distal to the ameroid constrictor via visible collateral connections from the left anterior descending artery. These collateral connections were graded as 1 in the left panel (exercise dog), 2 in the center panel (exercise dog), and 3 (largest) in the right panel (sedentary dog).
planation — that the Ex dogs had decreased blood flow through the collaterals due to increased resistance in the distal vascular bed supplied by the LC — cannot be completely ruled out. Either vasoconstriction or reduction in the size of the LC vascular bed could lead to increased distal resistance. Although the microsphere data eliminate the possibility of vasoconstriction and low blood flow confined specifically to the LC region, they do not preclude the possibility of generalized coronary vasoconstriction in the Ex dogs (although the low coronary (a-v/a) O\textsubscript{2} is strongly against it). Scheel et al.\textsuperscript{14} have shown that after coronary occlusion, the surviving patent coronary artery gradually encroaches upon the territory originally served by the occluded artery. A greater degree of encroachment into the LC vascular bed in the Ex dogs, if it occurred, would increase the resistance to distal LC runoff and theoretically could explain their low AP-LCP. In this case, however, blood flow per gram to the smaller myocardial mass as determined by the microsphere method should have been greater in the Ex dogs.

The microsphere data demonstrated normal regional and transmural coronary blood flow distribution at rest in both Sed and Ex dogs. In contrast to the severe ischemia produced by acute LC occlusion, within a few weeks collaterals to the gradually occluded LC met basal requirements for blood flow served by its distal vascular bed, as found previously by others.\textsuperscript{21} The coronary occlusion itself was a powerful stimulus for collateral development. Increase in heart rate to 250 beats/min in 5-week experiments, however, led to a decrease in LC/LAD and to a fall in I/O (LC) that was excessive compared with the simultaneous fall in I/O (LAD). These are signs of relative ischemia in the subendocardium supplied by the occluded LC,\textsuperscript{22} and they indicate that the collaterals could not maintain blood flow normally to the LC region during the stress of marked tachycardia. The results were virtually the same for Sed and Ex groups (fig. 2), indicating that exercise training did not stimulate the capacity for collateral blood flow beyond that which developed over the same interval in sedentary dogs.

The main cause of the lower I/O in the LC region during tachycardia was a relative paucity of microspheres in the subendocardial layer of the LC region, indicating that the LC subendocardium was ischemic relative to the LAD subendocardium. However, in the subepicardium the microsphere concentration during tachycardia was slightly greater in the LC than in the LAD region, which contributed to a minor degree to the lower I/O (LC) and suggests that the presence of well-developed collaterals may impair blood flow in the subepicardial area of the heart from which the collateral blood flow originates, as described by Flameng et al.\textsuperscript{31}

Heaton et al.\textsuperscript{13} carried out a similar investigation in dogs using the microsphere technique in a slightly different experimental design. They determined blood flow before and after 6 weeks of sedentary or exercise existence. During the 6-week interval, collateral blood flow increased slightly more in exercise dogs (37%, which was significant) than in sedentary dogs (25%, insignificant); but since no statistically significant difference between the two groups was demonstrated, no definite conclusion seems possible.

How can the results of our different methods for assessing coronary collateral function in the experiments reported here be reconciled with each other? We believe that the data for retrograde blood flow and pressure drop across the collaterals combined provide strong evidence that exercise training enhanced the development of collateral communications between the LAD and occluded LC. A difference in collaterals was not evident angiographically, probably because angiography is insensitive for quantifying collaterals. The microsphere data, which we believe furnish a relatively sensitive indicator for regional perfusion, showed that Ex dogs were not better protected against LC regional ischemia during tachycardia stress. These results imply that the enlarged macroscopic coronary collaterals to the distal LC system in the Ex dogs were unable to improve myocardial perfusion to a significant degree. This suggests that the distal microcirculation may be a limitation governing collateral blood flow.

Coronary obstruction is a recognized, potent stimulus for collateral development in humans and dogs. The present investigation was designed to provide the best opportunity for observing a supplementary influence of exercise on collateral growth. There is some question whether middle-aged patients with established symptomatic coronary heart disease can carry out enough physical exertion to achieve a meaningful stimulus beyond that caused by ischemic disease. Our results raise the additional question of whether slightly improved collateral development, even if it does occur, will significantly influence myocardial perfusion.

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References
Long-term Effects of Physical Training on Coronary Patients with Impaired Ventricular Function

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SUMMARY  
Eighteen patients with coronary heart disease and an ejection fraction of 0.40 or less were entered into an individualized exercise training program. Maximal symptom-limited exercise stress test and cardiac catheterization studies were performed initially and 12–42 months (average 18.5 months) after exercise training.

At the time of the follow-up study, the mean functional aerobic impairment (FAI) improved from 32.1 to 23.4% (p ≤ 0.01); resting and submaximal heart rates were significantly lower (p < 0.01 and 0.05, respectively). There was no significant change in the pulmonary artery or left ventricular end-diastolic pressure, cardiac index, stroke index, left ventricular end-diastolic volume or ejection fraction. Exercise training, therefore, can be beneficial even for patients with impaired ventricular function. Increase in physical work capacity was not correlated with improvement of ventricular function; on the other hand, exercise training did not cause deterioration of ventricular function.

PHYSICAL TRAINING has been shown to be beneficial to patients with coronary heart disease because it improves physical work capacity, 

improves the psychological status. The overall safety of exercise training has been documented in several studies. However, little is known about the effect of physical training on coronary patients with impaired ventricular function. Such patients are often placed on reduced physical activities based on the fear that physical training may result in further deterioration of ventricular function.

In this study we evaluated the long-term effects of exercise training on physical work capacity and cardiac hemodynamics in postmyocardial infarction patients with significant impairment in left ventricular function.
Exercise can promote coronary collateral development without improving perfusion of ischemic myocardium.
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