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**Beneficial Effect of Physical Training on Blood Flow to Myocardium Perfused by Chronic Collaterals in the Exercising Dog**

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**SUMMARY** To determine the effect of physical training on collateral blood flow, we measured regional myocardial blood flow (MBF) by injecting 15 μ radioactive microspheres at rest and during exercise in 14 dogs with chronic coronary occlusive lesions. Seven dogs subsequently trained for 6 weeks while the other seven remained in kennels. Training effect was documented by decrease in heart rate during exercise that averaged 35 beats/min. MBF studies were repeated after 6 weeks. Myocardial samples were obtained from normally perfused zones (NZ) and from regions supplied via collaterals (collateral dependent zones or CZ). Initially, endocardial blood flow in CZ averaged 1.10 ml/min/g (83% of NZ, P < 0.05) at rest and 1.36 ml/min/g (69% of NZ, P < 0.05) during exercise, indicating relative underperfusion. Epicardial blood flow was equal in NZ and CZ. After 6 weeks MBF was not significantly changed in control animals. After training, however, MBF to underperfused endocardium of CZ during exercise was 39% greater than it had been prior to training. The epicardial portion of CZ (not exhibiting underperfusion) showed no change in MBF during exercise after training.

Our data suggest that beneficial effects of training in coronary disease may include improvement in MBF to underperfused collateral-dependent portions of myocardium.

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**THE INFLUENCE OF PHYSICAL TRAINING** on chronic coronary artery disease has not been fully defined.1, 2 Patients with limitation by angina pectoris due to coronary artery disease frequently have substantial increases in exercise capacity following a program of physical training.3, 4 This beneficial effect of training is, in part, related to a decrease in heart rate for any given submaximal work load. Such a decrease causes reduction in myocardial metabolic activity, and consequently a favorable influence on the balance of myocardial oxygen demand and myocardial oxygen delivery via the coronary arteries. It is possible, however, that physical training may also exert a beneficial effect by improving coronary blood flow to potentially underperfused regions of the myocardium. Eckstein5 demonstrated a higher index of coronary collateral function in previously trained open chest dogs with chronic single vessel coronary occlusive lesions than in similarly prepared dogs without prior physical training. However coronary collateral blood flow has not been measured directly during exercise before and after physical training in animals with chronically occlusive coronary lesions.

Recently, use of radioactive microspheres has permitted accurate measurement of coronary blood flow in conscious unmedicated dogs at rest and during exercise before and after acute partial constriction of a coronary artery.6 Microsphere flow data are particularly valuable in that they

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permit an assessment of regional blood flow in endocardial and epicardial portions of the left ventricular myocardium.\(^*\) They also permit quantitation of coronary blood flow arriving via collateral channels. To expand our understanding of the influence of physical training, we employed a radioactive microsphere technique to measure regional blood flow, at rest and during exercise, before and after a six week physical training program in dogs with surgically induced chronic, multivessel coronary occlusive lesions.

**Methods**

**Selection**

One to three year old foxhounds weighing 20 to 30 kg were screened for ability to run on a treadmill. Approximately 80% of animals tested quickly learned to run continuously for six minutes and were, accordingly, selected for surgical preparation. Animals excluded from study differed from the study group only in their inability to cooperate with the investigators.

**Surgical Preparation (fig. 1)**

A sterile left thoracotomy in the fourth intercostal space was performed in 28 dogs under nitrous oxide/halothane general anesthesia. A heparin filled 24" vinyl catheter, i.d. 0.17 mm, was sealed at its distal end, and its proximal end was inserted into the ascending aorta via the left internal mammary artery. A similar catheter was inserted into the left atrium via the atrial appendage. An ameroid constrictor, i.d. 1.5 mm, was placed around the left anterior descending coronary artery (LAD) just distal to its first major diagonal branch. Previous experience has shown that the hydrophilic properties of ameroid result in complete obliteration of the lumen within five days. A single electrode was inserted into left ventricular myocardium for monitoring of cardiac rhythm. The left circumflex coronary artery (LCCA) was dissected free from surrounding tissues about 1" from its origin. A 1-0 silk suture was tied snugly around both the artery and a 1.5 mm diameter metal rod to produce complete arterial obstruction. The rod was then withdrawn leaving a fixed stenosis, subsequently measured as 60 to 90% obstruction, in every animal. The insulated electrode lead and the distal end of arterial and left atrial catheters were brought out through the chest wall incision and secured in a subcutaneous pouch at the back of the neck. The thoracotomy was closed and the dogs were allowed a two week recovery period during which they remained in cages. Surgery was associated with a 10% mortality due to ventricular fibrillation, usually occurring soon after creation of the LCCA constriction. An additional 40% mortality occurred during the first week of the recovery period. Necropsy of animals dying at this time usually showed a recent anterior or posterior myocardial infarction. Of the 14 survivors, seven were males and seven were females.

**Regional Myocardial Blood Flow**

Using radioactively labelled microspheres myocardial blood flow was measured at rest and during treadmill exercise at 3 mph 5% grade two weeks ("baseline" studies) and eight weeks ("follow-up" studies) after surgery. Approximately one million tracer microspheres, 15 ± 5 microns diameter, labelled with cerium-141, ytterbium-169, strontium-85, or scandium-46 (3 M Company) suspended in 3 ml saline were injected steadily into the left atrial catheter over a period of approximately 20 seconds. In no instance were significant hemodynamic or clinical changes observed in conjunction with microsphere injection. For each myocardial blood flow determination, an arterial reference sample was begun approximately 10 seconds before microsphere injection and continued for exactly three minutes at 7.6 ml/min utilizing a Harvard infusion/withdrawal pump. For determinations during exercise, dogs were run at 3 mph, 5% grade for 3 min to reach a steady state prior to microsphere injection; dogs continued to run at this same speed and grade throughout the 3 min arterial sampling period. All dogs were able to run at 3 mph 5% grade without coercion for the required 6 min of study.

After completion of myocardial blood flow measurements during the follow-up study, dogs were sacrificed utilizing a lethal dose of sodium pentobarbital and the hearts excised. A normal zone of myocardium (NZ) with unimpaired blood flow was defined anatomically (fig. 1) as that tissue bounded by 1) the LAD proximal to the ameroid, 2) the diagonal branch of the LAD with origin just proximal to the ameroid, 3) the LCCA, and 4) a line parallel to LAD from LCCA at the point of stenosis to the diagonal branch just described. The collateral dependent zone (CZ) was chosen to evaluate blood flow in regions supplied entirely via collateral channels. This zone was defined anatomically as the portion of the anterior left ventricular wall normally supplied by the LAD and bounded by 1) the LAD distal to the ameroid and 2) the diagonal branch arising from this distal portion of the
LAD closest to the ameroid (fig. 1). Depending on local anatomy and size of these regions, NZ was divided into four to six full thickness samples and CZ was divided into 9 to 12 samples. Since there was no systematic difference in flow data from samples obtained at different anatomic sites within a particular zone, flow results were averaged from all samples within a given zone. Each full thickness sample, weighing 1 to 2 grams, was separated into endocardial (end) and epicardial (epi) portions and weighed separately. These myocardial samples and blood reference samples were counted in a Packard Autogamma Spectrometer (Model 5220) using counting windows appropriate for the 4 radionuclides mentioned previously. Myocardial blood flow values were determined from the blood reference and myocardial sample counts using four simultaneous equations. Flow within each full thickness sample (transmural flow) was calculated as a weighted average of component endo and epi flows.

Student’s t-test for paired data was used for statistical analysis of hemodynamic and myocardial blood flow data. Mean flow values from each myocardial region of each dog were themselves averaged to obtain overall means.

Study Protocol

One or two days prior to baseline study (2 weeks after surgery) all dogs exercised briefly to reaquaint the animals with the treadmill. At the time of study, all dogs were free of anemia, fever or other evidence of ill health. On the day of baseline study, catheters and electrode wire were brought to the exterior from the subcutaneous pouch through a small incision made following 1% lidocaine infiltration. After a 15 to 20 minute rest period that allowed heart rate to stabilize, a multistage exercise test was performed with electrocardiographic monitoring from the intramyocardial electrode. Heart rate was measured at rest and after three minutes at each of the following exercise levels: 3 mph 0% grade, 3 mph 5% grade, and 3 mph 10% grade. Dogs were allowed a five minute rest period between each exercise level. Arterial pressure monitoring was initiated and observations were continued until stable rest values of mean arterial pressure and heart rate were achieved. Myocardial blood flow determinations were made by microsphere injection at rest and during exercise at 3 mph 5% grade as described. After completion of baseline studies, catheters were refilled with heparin and resealed. The exterior portions of the catheters and electrode lead were cleaned with antisepsic solution and replaced in the subcutaneous pouch. Antibiotics were administered routinely after baseline study. No dog developed systemic sepsis. Several dogs had localized wound infections that abated after local drainage and antibiotics.

After baseline studies, dogs were randomly allocated to either the control group (4 females, 3 males) or the physically trained group (3 females and 4 males). Dogs in the control group remained in kennels. These kennels, measuring 16’ × 4’, permitted freedom of motion but were too small to allow free running. Dogs in the physically trained group exercised for one hour on the treadmill five days a week for six weeks. Otherwise they were treated in the same manner as members of the control group. Initially, exercise was performed at 3 mph, 0% grade with rest periods as needed for fatigue. Intensity of exercise was gradually increased until all dogs ran for one hour continuously at 6 mph 5% grade by the end of the six week training period. Electrocardiographic monitoring was not performed during training sessions. However, none of the dogs appeared ill during or after a training session and there were no fatalities during the course of physical training.

After six weeks dogs in the control group were given brief warm-up exercise periods on the treadmill for two days prior to the followup study. Like the baseline study, the follow-up study consisted of an initial exercise test with electrocardiographic monitoring followed by myocardial blood flow determinations at rest and during exercise at 3 mph 5% grade. Identical follow-up studies were performed on members of the control group and members of the physically conditioned group. Follow-up studies were incomplete in one member of the physically trained group due to migration of the left atrial catheter. Data from this dog were excluded from all paired comparisons of baseline and follow-up results.

Animals were sacrificed and myocardial samples were taken from normal zone and the collateral dependent zone as described previously. There were no areas of myocardial scar in the portions of the anterior left ventricle used for sampling purposes. However, a few animals in both the control group and in the physically trained group had small areas of fibrosis in the endocardial layers of the posterior wall, especially in the region of the posterior papillary muscle.

After myocardial sampling was completed, the left main coronary artery was cannulated and flushed with acetone followed by perfusion with liquid vinyl at 100 mm Hg overnight (to allow the vinyl to harden). The vinyl cast of the left coronary artery was carefully dissected and 100% occlusion of the LAD at the ameroid was verified in each case. The fixed stenosis of the cast of the LCCA was measured in two dimensions microscopically and estimated to produce 60 to 90% reduction in arterial cross-section in every animal. In no instance did vinyl fill the LAD distal to the ameroid. Extensive myocardial sampling precluded vinyl perfusion of collateral vessels.

Results

Heart Rate and Blood Pressure Responses

Multistage exercise testing was performed to assess the influence of the physical training program on heart rate. As shown in figure 2, a 6-week interval had no influence on heart rate at rest or during any stage of exercise in the control group. Although heart rate at rest tended to be less in trained dogs (mean reduction 25 beats/min), this difference did not achieve statistical significance. At each level of follow-up exercise, however, heart rates in the physically trained group were significantly lower (average decrease 35 beats/min, P < 0.05) than heart rates at the same exercise during baseline studies. Thus 6 weeks of periodic treadmill exercise produced changes in heart rate during exercise characteristic of the physically trained state.

Aortic pressure and heart rate data obtained at the time of myocardial blood flow determination are listed in table 1. These heart rate results obtained at only one level of exercise are in agreement with the results of multistage exercise testing in that a significant decrease in heart rate from mean
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184 to mean 163 beats/min (P < 0.05) was observed in physically trained animals while a statistically significant change was not noted in the control group. Aortic pressure and rate-pressure products did not change consistently from baseline studies to follow-up studies in either the control group or the physically trained group.

No arrhythmias were observed at rest or during exercise in any of the animals studied.

Myocardial Blood Flow during Baseline Studies

As shown in figure 3, baseline studies demonstrated that normal zone (NZ) transmural myocardial blood flow (expressed as ml/min/g ± standard error) averaged for all 14 animals, was 1.22 ± 0.16 at rest increasing to 1.83 ± 0.26 (a 50% rise) with exercise at 3 mph, 5% grade. Mean NZ endo flow was 1.32 ± 0.16 at rest increasing to 1.97 ± 0.30 with exercise and mean NZ epi flow was 1.14 ± 0.16 at rest increasing to 1.68 ± 0.23 with exercise. Endo/epi flow ratios in NZ, averaging 1.16 ± 0.05 at rest, were unchanged (1.18 ± 0.05) during exercise.

In CZ, the portion of myocardium receiving blood flow exclusively through collateral channels, mean transmural flow increased by 28% (from 1.16 ± 0.12 to 1.49 ± 0.09) with exercise. The magnitude of the exercise-induced rise in myocardial blood flow tended to be less in CZ than in NZ, particularly in CZ endo, where mean flow rose by only 24%

(from 1.10 ± 0.08 to 1.36 ± 0.08) with exercise. CZ epi flow rose from 1.21 ± 0.16 at rest to 1.60 ± 0.15 with exercise. The endo/epi flow ratio in CZ tended to fall during exercise: mean values were 0.98 ± 0.05 at rest and 0.92 ± 0.09 during exercise.

Paired data analyses for NZ and CZ values from the same heart revealed no difference between mean epi flow of NZ and CZ either at rest or during exercise (table 2, fig. 4). Even at rest, however, endo flow in CZ was 0.22 ml/min/g (or 17%) less (P < 0.05) in CZ than in NZ. With exercise, mean flow was 0.61 ml/min/g (or 31%) less (P < 0.05) in endo of CZ than in endo of NZ. Endo/epi flow ratios provide further evidence that endo in CZ was relatively underperfused compared with endo in NZ. On average, endo/epi ratios were 15% less (P < 0.05) in CZ than in NZ at rest and 22% less (P < 0.05) in CZ than in NZ during exercise. Hence, baseline studies indicate that the endocardial portion of the region receiving blood flow exclusively via collateral channels was mildly underperfused at rest relative to a zone in the same heart supplied by unobstructed coronary arteries and that the degree of relative underperfusion tended to increase during exercise. The epicardial portion of the collateral dependent zone, however, exhibited no abnormality in myocardial blood flow.

The baseline data just cited were averages of the entire study population (14 dogs). There were no differences between these means and corresponding means for the control subgroup or the physically trained subgroup.

Follow-up Values of Myocardial Blood Flow

Dogs remaining in kennels for 6 weeks (control group) exhibited no statistically significant change in mean flow to any portion of the myocardium either at rest or during exercise when paired comparisons were made between baseline values and follow-up values (table 2 and fig. 5). However, endo/epi ratios for CZ were higher in control animals at follow-up studies than they had been at baseline studies.

Measurements after physical training showed no consistent alteration in mean myocardial blood flow either to endo or epi of NZ or to epi of CZ at rest or during exercise (table 2 and fig. 5). Moreover, in the physically trained group, follow-up values of flow to endo of CZ at rest were un-
changed. Comparison of results obtained during exercise, however, revealed that mean myocardial blood flow to endo of CZ had significantly increased ($P < 0.05$) from $1.32 \pm 0.30$ at baseline study to $1.84 \pm 0.18$ at follow-up determination (fig. 5). Thus, blood flow was 39% greater in the relatively underperfused endocardial portion of CZ during exercise after six weeks of physical training.

Linear regression analysis was applied to measurement of endocardial blood flow in the collateral dependent zone during exercise in individual members of the control group and the physically trained group. Change in this quantity from baseline study to follow-up study failed to correlate in either group with change in simultaneously measured heart rate, aortic pressure or rate-pressure product. Similarly, there was no correlation between change in this flow value from baseline study to follow-up study and the degree of endocardial underperfusion (quantitated as CZ endo flow/NZ endo flow) during exercise at baseline study.

Endo/epi flow ratios for the CZ rose significantly in the physically conditioned group as they had in the control group (table 2).

### Discussion

In this study we evaluated the magnitude and distribution of coronary flow to a zone of myocardium receiving its blood supply exclusively through collateral channels. The ability of collateral vessels to transport blood flow into this collateral dependent zone was restricted by a high-grade proximal, fixed stenosis of an artery that presumably served as one source of supply for collateral vessels. A substantial degree of collateral development probably occurred between the time of surgical preparation and the time that baseline studies were performed, resulting in baseline values of coronary blood flow to the epicardial portion of the collateral dependent zone that were indistinguishable at rest and during exercise from comparable values measured in zones with unrestricted coronary blood flow (fig. 4). Baseline endocardial blood flow in the collateral dependent zone, however, was significantly lower than endocardial flow in regions of the same heart perfused by unrestricted arteries, and baseline endo/epi flow ratios were abnormally low in the collateral dependent zone. Exercise-induced changes in both mean endocardial flow and mean endo/epi flow ratio of the collateral dependent zone showed that relative underperfusion tended to increase during exercise, when demand for blood flow within the portion of the myocardium perfused by normal vessels rose an average of 50%. Thus, coronary flow distribution patterns demonstrated by others to occur in ischemic regions of the hearts of awake dogs after acute coronary occlusion were evident in our chronically collateralized preparation. These findings suggest the presence of residual, physiologically meaningful insufficiency of coronary collateral function at the time of baseline studies.

Follow-up studies of control animals demonstrated only a small and inconsistent tendency for improvement in blood flow to the relatively underperfused endocardial portion of the collateral dependent zone during the six weeks when con-

### Table 2. Mean Myocardial Blood Flow Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Zone</th>
<th>Testing circumstances</th>
<th>Mean MBF (ml/min/g)</th>
<th>Mean Endo/ Epi</th>
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<tr>
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<td>Follow-up Ex</td>
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Abbreviations: MBF = myocardial blood flow; NZ = normally perfused zone; CZ = collateral dependent zone; N = number of dogs with complete data in each group; Ex = exercise; Tm = transmurial; Endo = endocardial portion; Epi = epicardial portion.

*Difference statistically significant, $P < 0.05$ (all other number pairs are not significantly different on paired $t$-testing).
Epicardial perfusion. To cause an correlation between change mand derperfused region (and showed this study, studies. Moreover, comparing baseline values with perfusion coronary activity. Since physical training is associated with decreased heart rate at a given level of exercise, it would not be anticipated that myocardial metabolic activity is augmented in the physically trained state. In our preparations, neither rate-pressure product, an index of myocardial metabolic activity, nor aortic pressure (i.e., coronary perfusion pressure) was consistently changed when comparing baseline values with those obtained at follow-up studies. Moreover, linear regression analysis failed to show a correlation between change in endocardial flow of collateral dependent zone in a given animal and simultaneous change in rate-pressure product or in aortic pressure either in members of the control or in members of the physically trained group. Hence, neither increased metabolic activity nor rise in coronary perfusion pressure appear to account for the augmentation of endocardial flow observed in the collateral dependent zones of physically trained dogs.

Improvement in flow distribution (normalization of endo/epi flow ratio) noted at follow-up study in both physically trained and control groups may have been an important factor in the augmentation of endocardial flow. Nevertheless, the consistent augmentation of endocardial flow seen in trained dogs was not observed in control dogs even though the rise in endo/epi ratio in the collateral dependent zone of control dogs equalled or exceeded the rise in trained dogs. Moreover, there was no tendency toward a rise in epicardial flow in collateral dependent zone of trained dogs that might have enhanced the significance of an increased endo-epi ratio in the trained group. Thus, it seems most likely that the improvement in blood flow to the endocardial region of collateral dependent zone of physically trained animals is due to an improvement in function of coronary collateral channels. These findings, obtained in the unmedicated, exercising dog, support similar conclusions ad-

**Figure 4.** Comparison of baseline myocardial blood flow (MBF) in normally perfused zone (NZ, stippling) and in collateral dependent zone (CZ, stripes) of 14 dogs indicates that endocardial (ENDO) flow was consistently less in CZ than in corresponding NZ (P values refer to paired data analysis) at rest (left panel) and during exercise (right panel). Transmural (TM) and epicardial (EPI) flows were not significantly different in CZ and NZ. Data represent average of 14 dogs with baseline studies. P values refer to paired data analysis.

**Figure 5.** Comparison of myocardial blood flows (MBF) during exercise in the collateral dependent zone (CZ) before (stippling) and after (stripes) a six week interval shows significantly greater endocardial (ENDO) flow in the six animals receiving physical training during this interval (right panel). Transmural (TM) and epicardial (EPI) flows in this group, however, and all flow values in seven control animals were not significantly altered. Data represent average MBF. P values refer to paired data analysis.
vanced by Eckstein on the basis of retrograde flow measurements in open chest anesthetized animals.7

Coronary collateral blood flow occurs principally during diastole.12 By prolonging diastole, interventions that decrease heart rate may improve coronary collateral function. This mechanism has been thought to account partially for an increment in coronary collateral flow noted following propranolol.13 Since physical training is generally associated with reduction in heart rate during exercise, it might be anticipated that reduction in heart rate is responsible for the observed changes in myocardial blood flow. Linear regression analysis, however, showed no correlation between increment in flow to the endocardial portion of the collateral dependent zone in each member of the physically trained group and decrement in simultaneously determined heart rate during exercise. Indeed, those three trained animals exhibiting the greatest increase in flow had heart rate decreases during exercise (when coronary blood flow determinations were made) of 10 beats/min or less. These findings suggest that physical training may improve collateral flow by mechanisms other than simple prolongation of diastole during exercise.

It is possible that the physical training program employed in this study exerted part of its beneficial influence by causing an enlargement or proliferation of collateral channels. For example, by magnifying myocardial underperfusion and its physical and biochemical consequences, regular exercise may bring about collateral flow rates,14 collateral vessel wall stresses,15 and levels of tissue hypoxia16 that favor collateral development and that occur only rarely in animals lacking physical training. This hypothesis may be particularly applicable to our experimental population, which exhibited rather modest degrees of underperfusion during the relatively mild conditions of study. In this context, however, it is interesting to note that the training-induced improvement in blood flow to the endocardium of the collateral dependent zone did not correlate with the degree of underperfusion measured in the same animal during baseline evaluation. A preliminary report suggests that physical training per se does not influence coronary collateral function in the absence of coexistent coronary occlusive lesions.17 However training has been thought to augment slightly the angiographic diameter of the circumflex coronary artery of dogs without coronary occlusions.18

Since our study was performed utilizing a limited number of experimental animals, it cannot provide a definitive assessment of the safety of physical training in the presence of coronary occlusive lesions. Nonetheless, it is noteworthy that no fatalities and no overt illness (e.g., circulatory collapse due to arrhythmia) occurred in the physically trained group despite exercise of intensity sufficient to cause measurable enhancement of coronary collateral function in animals with severe multivessel coronary occlusive lesions. Small degrees of myocardial infarction were noted in the circumflex distribution. However, these occurred with equal frequency in members of the control group. This fact and the necropsy findings in dogs dying early suggest that these infarctions developed prior to baseline studies.

Clinical studies have shown that programs of physical training improve exercise capacity in patients with angina pectoris.9,10 Although caution must be observed in extrapolating data derived from animal models to treatment of human disease, our results suggest that physical training is also capable of improving coronary collateral function, thereby augmenting myocardial blood flow to underperfused regions.

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**References**

Beneficial effect of physical training on blood flow to myocardium perfused by chronic collaterals in the exercising dog.

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