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The Effect of Daily Exercise on Regional Myocardial Flow of Proximal Coronary Constriction Dogs and Its Mechanism

Ming Hsiung Hwang
Loyola University Chicago

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THE EFFECT OF DAILY EXERCISE ON REGIONAL MYOCARDIAL FLOW OF PROXIMAL CORONARY CONSTRICITION DOGS AND ITS MECHANISM

by

Ming Hsiung Hwang, M.D.

A Thesis Submitted to the Faculty of the Graduate School of Loyola University of Chicago in Partial Fulfillment of the Requirements for the Degree of Master of Science January 1980
To the Chairman of my Thesis Committee, John B. Pace, Ph.D., M.D.
and the other members of the Committee, Walter C. Randall, Ph.D., Henry S.
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and to Mr. Glenn Miller for his technical assistance.

Finally, I am grateful to Miss Marge Tautkus and Miss Adele Von Druska
for their splendid secretarial support.
The author, Ming Hsiung Hwang, is the son of Tsain-Shar and Wan Zu Hwang. He was born March 29, 1943 in Changhua, Taiwan. He received his elementary education in the public schools of Changhua, Taiwan, and secondary education at Provincial Senior Changhua High School, also in Changhua, where he graduated in 1960.

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From July 1968 to June 1969 he was a medical officer in the Chinese Army. In July 1969 he went to Changhua Christian Hospital for two years of medical residency training in Internal Medicine, and became Chief Resident for another year.

In July 1972 he went to Michael Reese Hospital, Chicago, Illinois for one year of internship and two years of residency in Internal Medicine, which was completed in July of 1975. Beginning July 1, 1975 he began a combined clinical Cardiology fellowship and Graduate School Program at Loyola University Medical Center in Maywood, Illinois. The Cardiology Fellowship was completed on June 30, 1977.

Dr. Hwang is now an Assistant Professor of Medicine at Stritch School of Medicine, Loyola University of Chicago, and a Staff Cardiologist at Hines Veterans Administration Hospital, Hines, Illinois. He is a member of several medical societies. He received certification in Internal Medicine in 1975, and in Cardiovascular Disease in 1977, and became a Fellow of the American College of Cardiology in 1979.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>ii</td>
</tr>
<tr>
<td>VITA</td>
<td>iii</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>vi</td>
</tr>
<tr>
<td>CHAPTER</td>
<td></td>
</tr>
<tr>
<td>I. INTRODUCTION (and review of literature)</td>
<td>1</td>
</tr>
<tr>
<td>II. PROCEDURE</td>
<td>9</td>
</tr>
<tr>
<td>Phase I</td>
<td>9</td>
</tr>
<tr>
<td>Phase II</td>
<td>13</td>
</tr>
<tr>
<td>III. RESULTS</td>
<td>17</td>
</tr>
<tr>
<td>A. Physiological Data</td>
<td>17</td>
</tr>
<tr>
<td>B. Transmural Myocardial Blood Flow</td>
<td>20</td>
</tr>
<tr>
<td>C. Regional Myocardial Blood Flow</td>
<td>24</td>
</tr>
<tr>
<td>D. Postmortem Coronary Angiograms</td>
<td>32</td>
</tr>
<tr>
<td>E. Thioflavin-S Fluorescent Data</td>
<td>32</td>
</tr>
<tr>
<td>IV. DISCUSSION</td>
<td>35</td>
</tr>
<tr>
<td>SUMMARY</td>
<td>42</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>44</td>
</tr>
<tr>
<td>APPROVAL</td>
<td>48</td>
</tr>
<tr>
<td>Table</td>
<td>Page</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>1. Physiological Data: Control Group</td>
<td>18</td>
</tr>
<tr>
<td>2. Physiological Data: Exercise Group</td>
<td>19</td>
</tr>
<tr>
<td>5. Myocardial Blood Flow ml/min/gm: Chronic Exercise Group (8) (Open Chest)</td>
<td>25</td>
</tr>
<tr>
<td>6. Regional Myocardial Blood Flow - ml/min/gm of Myocardium</td>
<td>27</td>
</tr>
<tr>
<td>7. Comparison of the Flow Ratio of Subendocardial to Subepicardial Layer Between the Anterior and Posterior Wall</td>
<td>30</td>
</tr>
</tbody>
</table>
## LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Diagram of Left Coronary Artery at Left Thoracotomy</td>
<td>10</td>
</tr>
<tr>
<td>2.</td>
<td>Electrocardiographic Monitoring during Constricting Circumflex Artery</td>
<td>11</td>
</tr>
<tr>
<td>3.</td>
<td>Left Ventricular Wall Dissection</td>
<td>14</td>
</tr>
<tr>
<td>5.</td>
<td>Regional Myocardial Flow: Posterior Wall</td>
<td>33</td>
</tr>
</tbody>
</table>
INTRODUCTION

In the year 1772, Heberden\textsuperscript{1} reported a patient essentially cured of a painful disorder of the breast by a six-month period of sawing wood for half an hour each day. About thirty years later, in reviewing symptoms and treatment of angina pectoris, Parry\textsuperscript{2} discussed the benefit of moderate exercise. These early clinical observations implied that exercise is beneficial for patients with coronary artery disease.

In the 1950s these observations received new interest when Morris\textsuperscript{3,4} reviewed the mortality records in England and Wales, and related these to the occupation of the patient. He concluded that the physical activity required by the occupation related inversely to mortality from coronary artery disease. The physical activity required by the occupation was graded by several industrial experts. In a later study,\textsuperscript{5} he observed that the age-adjusted incidence of coronary artery disease was 1.5 times greater, while sudden death and three-month mortality from myocardial infarction were doubled in drivers of buses as compared to conductors of buses in the London Transport System. He concluded that the physical activity required of a conductor on a double-deck bus was much greater than that of the driver, and suggested that this accounted for the difference.

In this country, Breslow\textsuperscript{6} made similar observations relating mortality and morbidity from coronary artery disease to the level of physical activity required by the occupation. This again was done through an analysis of census and death certificates in California. In 1962, Taylor\textsuperscript{7} reviewed death certificates of male railroad employees and found that men in
sedentary jobs had a higher mortality from coronary artery disease than those engaged in moderate to heavy labor. In 1963, Kahn\textsuperscript{8} studied the mortality records of Washington, D.C. male postal employees from 1906 to 1940 and stated that these sedentary clerks had a mortality from coronary artery disease 1.4 to 1.9 times greater than the active mail carriers.

From the Western Collaborative Group study of 3,000 healthy males ages 35 to 59 years\textsuperscript{9,10} it was found that annual incidents of new angina, myocardial infarction or electrocardiographic changes were greater in the group without regular exercise habits. Those subjects in the age range of 50 to 59 years who exercised had one-third fewer coronary events than did their sedentary counterparts. In the Framingham Study, by grading the physical activity index from resting heart rate, vital capacity, hand grasp strength and relative weight, the sedentary cohort had increased coronary artery disease and mortality rates.\textsuperscript{11,12} These observations were also documented by the Coronary Drug Project,\textsuperscript{13} where, after myocardial infarction, those subjects with a historical sedentary life style had an increase in five-year mortality. These studies demonstrate that patients, particularly males, with a proclivity for coronary artery disease appear to have a lower incidence of coronary events if their life style or occupation includes moderate to severe physical activity.

We will focus our discussion of coronary artery disease on comparison of sedentary versus exercise-oriented life styles. Based on a seven-year prospective study of the effects of physical fitness on coronary artery disease, Hellerstein\textsuperscript{14} reported a mortality rate of 2\% per year in the exercise group, compared to 5\% per year in the conventionally treated group.
Similar results were reported from Israel by Gottheiner\textsuperscript{15} from his cardiac rehabilitation program of males with coronary artery disease. In post-infarction males, Rechnitzer\textsuperscript{16} found recurrence rates of angina to be 13\% per year and mortality 3.5\% per year in an exercise group. This compared to 28\% per year recurrence rates and 11\% per year mortality in a control group. These clinical studies suggest the beneficial effects of exercise during rehabilitation of patients with coronary artery disease.

How does daily exercise benefit patients with coronary artery disease? Physical conditioning increases maximal oxygen consumption and decreases heart rate response to submaximal exercise.\textsuperscript{17} Redwood\textsuperscript{18} reported that by physically conditioning a group of coronary patients, the heart rate-blood pressure product (a hemodynamic index of myocardial oxygen consumption) was lowered for any given level of exercise for 6 weeks, and that, after conditioning, the patients could achieve greater double products before the onset of angina. Ferguson\textsuperscript{19} and Kennedy\textsuperscript{20} have shown that in groups of coronary patients physical training can increase the exercise capacity and total body maximum oxygen consumption approximately 25\%. However, these investigators do not consider development of coronary collaterals as an explanation for the beneficial effects of exercise since they were not able to demonstrate an increase in collateralization by serial coronary angiography.

Because of difficulty in demonstrating new collateral supply in the human, investigators have turned to animal models which we will now review. After partial constriction of the proximal left circumflex coronary artery with silk, Eckstein\textsuperscript{21} divided dogs into two groups. One group was placed in a program of treadmill exercise of 5-7 mph, 10\% inclination, for 45 minutes daily, 5 days a week. A control group of dogs was kept caged. After 4-6 weeks the dogs were
anesthetized and a left thoracotomy was performed. The circumflex artery was isolated and divided beyond the constriction. Eckstein found that although antegrade blood flow was inversely related to the degree of constriction, retrograde blood flow was directly related. The exercised dogs had a higher retrograde blood flow than the sedentary dogs, and, therefore, presumably had greater collaterals. Kaplinsky et al.\textsuperscript{22} did not show the effects of exercise on promoting collateral formation. Their model included post-mortem angiography on dogs with total left anterior descending occlusion. Burt and Johnson\textsuperscript{23} found no difference in collateral blood flow in the circumflex arteries of dogs with normal coronary arteries after one month of treadmill exercise as compared with sedentary controls. Cobb et al.\textsuperscript{24} failed to demonstrate any effect on infarct size or incidence of arrhythmias following total occlusion of previously partially stenosed left anterior descending arteries after a period of exercise. By a cast and corrosion technique, Tepperman and Pearlman\textsuperscript{25} demonstrated in exercised rats increased heart/body weight ratios and increased coronary tree-cast weight/heart weight ratios in comparison to a sedentary control group. Finally, Heaton et al.\textsuperscript{26} attached an Ameroid constrictor to the left anterior descending coronary artery after the first diagonal branch. This produced total occlusion of the artery in two weeks and was combined with constriction of the proximal left circumflex. Baseline myocardial flow determinations were made at rest and at exercise at 3 mph and 5% inclination. Animals were randomly placed into control and exercise groups. After 6 weeks of treadmill exercise or rest, repeat myocardial blood flow determinations were made at rest and exercise. On comparing the myocardial flow in the normal coronary perfused area (normal) to the area supplied only by collaterals (collateral), it was found that the endocardial flow of the collateral area was 83% of the normal area at rest and 69% during exercise with reversal of transmural myocardial
distribution (epicardial > endocardial layer). After 6 weeks both groups had similar myocardial flow in the normal and collateral areas at rest and during exercise with normal transmural myocardial distribution (endocardial > epicardial layer). Because of the higher endocardial flow during exercise in the exercise group as compared to the non-exercise group, Heaton concluded that physical training may have a salutary effect on myocardial blood flow to underperfused collateral-dependent areas of the myocardium. The results of these various reports are equivocal and often contradictory in defining the effects of exercise on the development of collaterals and myocardial blood flow.

In 1967, Rudolph and Heyman developed the microsphere method to study the fetal circulation of sheep and goats in utero. Carbonized microspheres of 50 μ diameter with various radioactive isotope labels were injected into different venous sites in the fetus. The various fetal organs were placed in the gamma scintillation counter with specific window adjusted to the peak energy emission of the isotope. From the constant monitoring of maternal arterial pressure and fetal umbilical or femoral arterial pressure and serial determinations of pH, pCO₂, and pO₂, they found no alteration of circulatory physiology during or after each microsphere injection. Using electromagnetic flowmeters on two umbilical veins and radioactive counts of blood, they verified that the distribution of spheres to an organ is proportional to the blood flow to the organ. By the constant infusion of antipyrine into the fetal limb vein and measuring the placental arterio-venous concentration differences, they could calculate the fetal umbilical blood flow applying the Fick principle. Relating this to the placental flow and radioactive count, it was possible to determine the actual flow to every fetal organ. Finally,
they performed inferior vena caval injections in the guinea pig, mouse, or rat, and demonstrated that 99.5% of the total body count was in the lungs with no significant recirculation of microspheres. Two years later, Kaihara et al. applied this method to measure the distribution of cardiac output in the dog. By injecting microspheres into the left atrium, left ventricle and aortic root, they were able to show that only left atrial injections had the homogenous mixing of microspheres. When microspheres with two different radioactive labels were mixed in one injection, the radioactive counts of the two nuclides for one specific organ had a correlation coefficient of 0.965. Again, they demonstrated that nearly 100% of the microspheres were extracted during the first transit through the pulmonary or systemic capillary beds. Later, Domenech et al. applied these principles to measuring the total and regional coronary blood flow in dogs. They injected microspheres of various diameters (14 to 61 μ) into the left atrium and withdrew arterial blood from the peripheral artery at 20 ml/min simultaneously. From the right heart bypass model, the direct measured coronary sinus return had linear relationship with the calculated flow from the microsphere technique with a correlation coefficient of 0.99. The radioactivity of the coronary sinus blood was always under 0.5%, and usually less than 0.1%, of the total radioactivity in the heart. This study showed that microspheres were completely trapped in the myocardial capillary system. In the conscious animal they found the proportions of total coronary blood flow to the left ventricular free wall plus septum, the right ventricular free wall, or the atrium were almost constant and were similar to the right heart bypass animals. However, when they measured the ratio of radioactivity between the subendocardial and subepicardial layers of the myocardium, the ratio was 2.5 for microspheres of 51 to 61 μ; 1.4 for
microspheres of 20 - 23 μ and 1.3 for 14 μ microspheres. This
distribution difference was documented and resolved by Utley et al and Yipintsoi et al. Using microspheres in sizes of 9, 15, 25 and 50 μ to measure myocardial blood and comparing this to a diffusible indicator, they found that regional myocardial flows were only very slightly different between the indicator and a 15 μ or less microsphere. Finally, Buckberg et al studied the limitation of microsphere method in measuring the myocardial blood flow. Whenever each single sample had more than 400 microsphere particles, it would reach the 95% confidence level and 10% precision of the non-randomness of the sample. The regional myocardial flow measurement varied within 20% for different radionuclide injections. The greatest precision of difference to less than 5% was obtained when 10,000 particle microspheres were injected into the left atrium.

Thioflavin-S is a water soluble yellow dye which fluoresces a bright yellow-green under ultraviolet light. It had been used by Schlegel to visualize the blood vessel and lymphatics of various organs. In 1974 and again in 1975, Kloner et al applied Thioflavin-S to estimate myocardial flow during coronary occlusion. After intravenous injection of 4% Thioflavin-S solution, the dye rapidly permeated the endothelium of all vessels through which it flowed. The heart was arrested 10 seconds after Thioflavin-S injection with highly concentrated KCL solution. From the area of fluorescence and nonfluorescence, one could qualitatively delineate the perfused and non-perfused areas.

This thesis is focused on the effect of daily exercise on the myocardial blood flow in the dog with fixed proximal coronary artery constriction applying the microsphere technique and Thioflavin-S method. It is the objective of these experiments to determine if chronic physical exertion
can alter the forward or collateral retrograde coronary flow in this animal model.
PROCEDURE

PHASE I

Mongrel dogs weighing 20 ± 5 kg were anesthetized with pentobarbital (30 mg/kg i.v.). Utilizing aseptic techniques, a left thoracotomy was performed. Respiration was maintained with a Bird respirator. The pericardium was opened, and all visible epicardial coronary collaterals connecting the left anterior descending with the left circumflex arteries were ligated with silk sutures (Figure 1). The proximal left circumflex coronary artery was isolated 1.0 cm distal to its origin from the left main coronary artery. A 16-18 gauge needle was placed over this, and the artery and needle were tied with silk ties. The needle was withdrawn. This caused 80-90% luminal constriction, and interference with flow was documented by 1½ to 2 mm S-T segment elevation or depression from baseline (Figure 2).

An indwelling catheter was placed through the left atrial appendage and the proximal end was positioned in a subcutaneous pouch. The chest was closed and the dogs allowed to recover. Procaine penicillin and streptomycin were given for 4 to 5 days post-operatively to prevent infection. After the dogs recovered from surgery an indwelling aortic catheter was introduced through the omocervical artery to the ascending aorta, and the proximal end was positioned in a subcutaneous pouch.

On the fifth to seventh post-operative day, the dogs were divided randomly into 2 groups: 1) a control group, consisting of 8 dogs that remained sedentary for the next 4 to 6 weeks; and 2) an exercise group, consisting of 7 dogs placed in a daily treadmill exercise program. The exercise program consisted of running 4 to 6 mph at 10% inclination, 45 minutes per day, 5 days a week for 4 to 6 weeks.
FIGURE 1

DIAGRAM OF LEFT CORONARY ARTERY
AT LEFT THORACOTOMY

LEFT ATRIAL CATHETER
L.A.

LEFT CIRCUMFLEX
R.V.

L.A.D.

X = LIGATION OF PRE-EXISTING COLLATERALS
★ = PARTIAL STENOSIS OF LEFT CIRCUMFLEX
L.A. = LEFT ATRIUM
R.V. = RIGHT VENTRICLE
L.A.D. = LEFT ANTERIOR DESCENDING ARTERY
FIGURE 2

ELECTROCARDIOGRAPHIC MONITORING DURING CONSTRICTING CIRCUMFLEX ARTERY

BEFORE CONSTRICTION

AFTER CONSTRICTION

CONTROL

TCO TIGHT

GOOD STENOSIS
Five to 7 weeks after surgery, the indwelling left atrial and aortic catheters were recovered from the subcutaneous pouches. The aortic catheter was connected to a Harvard constant withdrawal pump and, via a three-way stopcock, to a Statham P-23D pressure transducer. Systemic arterial pressure was recorded on a Grass Model 7 polygraph.

Each dog was placed on the treadmill and resting blood pressures and electrocardiograms were recorded. Approximately 2 million particles of 7 to 10 μm microspheres (3M Company) labelled with either Sr-85, Ce-141, or I-125 were injected over a 20 to 30 second period into the left atrial catheter with 10 to 20 ml of normal saline. The microspheres were homogenized in suspension using an ultrasonic vibrator prior to injection. Arterial reference blood was withdrawn from the aortic catheter at a constant rate of 23 ml/min beginning 7 to 20 seconds prior to the onset of the microsphere injection and continuing for a total of 90 seconds.

Following resting flow determinations, the dogs were exercised at 5 to 7 mph for 30 minutes to achieve a heart rate of approximately 200 beats/min. After 20 minutes of exercise, and with the dogs continuing to run, blood pressure and diagonal lead electrocardiograms were recorded. At this point, a second microsphere injection with a different radioisotope label was made using the technique described above. Following the second microsphere injection and arterial reference blood sample, exercise was stopped. The dogs were killed with pentobarbital and their hearts were removed and fixed in formalin.

The right ventricular free wall and both atria were removed from the formalin-fixed hearts. After removing the chordae tendinae and the epicardial fat, the left ventricle was divided into four equal cross-sections. The apical
portion was discarded. Each cross-section of myocardium was sectioned again, and the anterior and posterior walls, including the papillary muscles, were taken for study. Each of these sections were then subdivided into subepicardial, midmyocardial, and subendocardial layers (Figure 3). Each myocardial specimen and arterial reference blood sample were placed in a gamma scintillation counter with a specific window adjusted to peak energies for I-125, Ce-141 or Sr-85. The myocardial blood flow to each area was calculated using the following formula:

\[ FM = FA \times \frac{Cm}{Ca} \]

*FM*: Myocardial blood flow (ml/min/gm of myocardium)  
*FA*: Arterial reference blood flow (ml/min)  
*Cm*: Radioactive counts of myocardium (counts/gm of myocardium)  
*Ca*: Radioactive counts of arterial reference blood

**PHASE II**

Three additional groups of dogs underwent left thoracotomy, left circumflex constriction, and epicardial collateral ligation as described above. In 6 dogs (acute coronary group) radioactive microsphere myocardial blood flow measurements were performed immediately following the operation. A second myocardial blood flow determination was done after total occlusion of the constricted circumflex artery. During each myocardial blood flow measurement left atrial pressure, aortic pressure, and diagonal electrocardiograms were recorded. Sixteen dogs divided into chronic sedentary (8) and chronic exercise (8) groups were allowed to recover from the surgery and were treated in a manner identical to the Phase I dogs. Five to 7 weeks after surgery each dog underwent a second left thoracotomy, and the constricted circumflex artery was isolated. Myocardial blood flow measurements were then performed. Following complete occlusion of the stenotic circumflex a second myocardial blood flow determination was
FIGURE 3

LEFT VENTRICULAR WALL DISSECTION

A
ANTERIOR

B
SEPTAL WALL

C
POSTERIOR

D
LATERAL WALL

1 = SUBENDOCARDIAL LAYER
2 = MIDMYOCARDIAL LAYER
3 = SUBEPICARDIAL LAYER
performed. During each myocardial flow measurement left atrial, aortic pressure, and diagonal electrocardiograms were recorded.

Just before the animals were killed, 1 mg/kg of 4% Thioflavin-S solution was injected intravenously over 10-20 seconds. Ten seconds later the dogs' hearts were arrested using a concentrated potassium chloride solution, and the hearts were removed.

Immediately following removal of the heart, the proximal left circumflex was cannulated with a Swan-Ganz catheter, the balloon was inflated to occlude the origin of the left circumflex to the catheter tip, and Renografin-76 was injected at a pressure of 90 mmHg. Cine or cut film angiograms were taken after the contrast injection. The coronary angiograms were used to quantitate the degree of circumflex stenosis. The films were analyzed without information as to group by two independent observers. The animals with less than 50% constriction or total occlusion of the circumflex were excluded from the study.

After post-mortem coronary angiograms, the hearts were fixed in formalin and the left ventricles were isolated. After removing the epicardial fat, vessels, and chordae tendinae, the left ventricle was sectioned into 4 equal pieces along the long axis. The apical ring was discarded. Each donut cross-section of myocardium was divided, and the anterior and posterior walls (including papillary muscle) were taken for study (Figure 3). The anterior and posterior wall sections from each animal were photographed under ultraviolet light. Perfused capillary endothelium could be identified by fluorescence of the Thioflavin-S stain under ultraviolet light. The amount of fluorescence was semi-quantitated and served as an index for collateralization. Photographs were analyzed without information as to the group from which the animal came.
The anterior and posterior wall sections were then subdivided into subepicardial, midmyocardial, and subendocardial layers (Figure 3). The myocardial specimen and arterial reference blood samples were placed in a gamma scintillation counter and myocardial flow calculations were done in the same manner as Phase I of the study.
RESULTS

A. PHYSIOLOGICAL DATA:

PHASE I

Control Group: This group of animals ran at an average speed of 5.5 ± 0.13 (mean ± standard error) mph and increased their heart rate from 96 ± 3 beats/min at rest to 213 ± 4 beats/min during exercise. The mean arterial pressure, which did not change significantly, was 83 ± 4 mmHg at rest and 84 ± 6 mmHg at exercise (Table 1).

Exercise Group: These animals ran at an average speed of 6.4 ± 0.19 mph. The heart rate increased from 86 ± 6 beats/min to 202 ± 6 beats/min, and mean arterial pressure increased from 89 ± 4 mmHg to 94 ± 4 mmHg (Table 2).

Thus, at the time of the study, the exercise group ran faster than the control group, but the control group had a slightly faster heart rate during exercise as well as at rest.

The product of heart rate times mean arterial pressure (double product) in the control group was 8.0 ± 0.5 × 10^3 mmHg x beats/min at rest, and increased to 18.9 ± 1.0 × 10^3 mmHg x beats/min during exercise. The double product in the exercised group was 7.3 ± 0.7 × 10^3 mmHg x beats/min at rest, and increased to 19.0 ± 0.6 × 10^3 mmHg x beats/min during exercise. The differences in double product between the groups were not significant statistically.

PHASE II

Acute Coronary Group: The average heart rate of these animals at the time of partial coronary stenosis was 144 ± 11 beats/min, and 141 ± 11 beats/min after total occlusion. Systolic arterial pressure increased from 108 ±
TABLE 1

PHYSIOLOGICAL DATA

<table>
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<tr>
<th>EXERCISE CAPACITY</th>
<th>HEART RATE</th>
<th>MEAN BLOOD PRESSURE</th>
<th>SUBENDOCARDIAL/SUBEPICARDIAL FLOW RATIO</th>
</tr>
</thead>
<tbody>
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<td>BEAT/MIN</td>
<td>mmHg</td>
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</tr>
<tr>
<td></td>
<td>R</td>
<td>E</td>
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<td>E</td>
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<td></td>
<td></td>
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<tr>
<td>1.</td>
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<tr>
<td>3.</td>
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<td>30min</td>
<td>100</td>
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<tr>
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<td></td>
<td></td>
<td>200</td>
</tr>
<tr>
<td>4.</td>
<td>5.5mph</td>
<td>30min</td>
<td>100</td>
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<tr>
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<tr>
<td>5.</td>
<td>5.0mph</td>
<td>20min</td>
<td>100</td>
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<tr>
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<td>6.</td>
<td>5.2mph</td>
<td>20min</td>
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<td>7.</td>
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<td></td>
<td>213+4</td>
</tr>
</tbody>
</table>

R = RESTING        E = EXERCISE       MEAN ± S.E. = MEAN ± STANDARD ERROR
TABLE 2

PHYSIOLOGICAL DATA

<table>
<thead>
<tr>
<th>EXERCISE GROUP</th>
<th>HEART RATE MEAN BEAT/MIN</th>
<th>BLOOD PRESSURE MEAN mmHg</th>
<th>SUBENDOCARDIAL/SUBEPICARDIAL FLOW RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>E</td>
<td>R</td>
</tr>
<tr>
<td>1. 7.0mph 20min</td>
<td>100</td>
<td>180</td>
<td>95</td>
</tr>
<tr>
<td>2. 7.0mph 20min</td>
<td>90</td>
<td>200</td>
<td>75</td>
</tr>
<tr>
<td>3. 6.7mph 20min</td>
<td>85</td>
<td>195</td>
<td>115</td>
</tr>
<tr>
<td>4. 6.0mph 30min</td>
<td>110</td>
<td>230</td>
<td>75</td>
</tr>
<tr>
<td>5. 6.0mph 30min</td>
<td>72</td>
<td>210</td>
<td>80</td>
</tr>
<tr>
<td>6. 6.0mph 30min</td>
<td>60</td>
<td>190</td>
<td>75</td>
</tr>
<tr>
<td>7. 6.0mph 30min</td>
<td>85</td>
<td>210</td>
<td>75</td>
</tr>
<tr>
<td>MEAN 6.4 + 1.9mph</td>
<td>86+6</td>
<td>202+6</td>
<td>84+6</td>
</tr>
</tbody>
</table>

R = RESTING  E = EXERCISE  MEAN + S.E. = MEAN + STANDARD ERROR
13 mmHg during partial stenosis to 114 ± 11 mmHg with complete occlusion. Arterial diastolic pressure increased from 72 ± 9 mmHg to 79 ± 8 mmHg. Left atrial mean pressure increased from 6.8 ± 1.5 mmHg to 9.6 ± 2.0 mmHg, again from partial to complete coronary occlusion.

**Chronic Sedentary Group:** These animals had heart rates of 143 ± 6 beats/min during partial stenosis, and 140 ± 8 beats/min at total occlusion. Blood pressures were 126 ± 5/76 ± 1 mmHg at partial stenosis, and 118 ± 9/69 ± 5 mmHg at total occlusion. Left atrial pressures increased from 4.0 ± 1 mmHg to 6.0 ± 1 mmHg respectively.

**Chronic Exercise Group:** These animals increased their mean heart rate from 126 ± 8 beats/min at partial stenosis to 139 ± 13 beats/min after total occlusion. This difference, however, was not significant statistically. The aortic pressures were 118 ± 9/78 ± 5 mmHg prior to occlusion, and increased to 121 ± 6/76 ± 5 mmHg after total occlusion. Left atrial pressures were 4.2 ± 1.0 mmHg at partial occlusion, and 4.5 ± 1.0 mmHg at complete occlusion.

As expected, the dogs with left thoracotomy and pentobarbital anesthesia had much faster heart rates than the closed chest conscious dogs.

**B. TRANSMURAL MYOCARDIAL BLOOD FLOW**

**PHASE I**

**Control and Exercise Groups:** Flow for the full thickness of the normal anterior myocardium was similar in control and exercised dogs. Resting flow in the anterior wall averaged 0.94 ± 0.06 ml/min/gm. With
exercise this increased to 2.43 ± 0.19 ml/min/gm in the control dogs, and 2.37 ± 0.12 ml/min/gm in the exercised dogs. Full thickness resting flow to the posterior (ischemic) myocardium was similar to anterior myocardial flow in both control and exercise dogs, averaging 0.93 ± 0.15 ml/min/gm and 0.90 ± 0.10 ml/min/gm respectively (p > .05). During exercise the posterior myocardial flow averaged 2.27 ± 0.13 ml/min/gm and was slightly less than anterior flow. In the exercised dogs posterior flow during exercise was essentially the same as anterior flow, averaging 2.43 ± 0.16 ml/min/gm. Thus, mean values for full thickness posterior myocardial flow during exercise were not significantly different in control and exercised dogs.

PHASE II

Acute Coronary Group (Table 3): With partial stenosis, myocardial blood flow was 1.05 ± 0.18 ml/min/gm in the anterior wall, and 0.78 ± 0.11 ml/min/gm in the posterior wall. Thus, the stenotic circumflex artery carried about four-fifths of the normal flow. At total occlusion of the circumflex artery, anterior myocardial blood flow increased to 1.24 ± 0.23 ml/min/gm, while flow to the posterior myocardium decreased to 0.16 ± 0.04 ml/min/gm. The reduction in the posterior myocardium ongoing from partial to total occlusion of the circumflex artery was highly significant (p < 0.001), and there appeared to be very little collateral blood flow to the posterior wall.

Chronic Sedentary Group (Table 4): Blood flow to the posterior wall supplied by the constricted circumflex artery was 1.06 ± 0.08 ml/min/gm, and anterior wall blood 1.28 ± 0.18 ml/min/gm. Although the absolute myocardial flow to the posterior wall was not different from that of the acute coronary
<table>
<thead>
<tr>
<th></th>
<th>PARTIAL STENOSIS</th>
<th>TOTAL OCCLUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANTERIOR</td>
<td>POSTERIOR</td>
</tr>
<tr>
<td>TRANSMURAL</td>
<td>1.05±0.18</td>
<td>0.78±0.11</td>
</tr>
<tr>
<td>SUBEP.</td>
<td>1.05±0.20</td>
<td>0.83±0.07</td>
</tr>
<tr>
<td>MIDMYO.</td>
<td>1.04±0.16</td>
<td>0.78±0.16</td>
</tr>
<tr>
<td>SUBENDO.</td>
<td>1.08±0.16</td>
<td>0.74±0.20</td>
</tr>
</tbody>
</table>

**MEAN ± 1 STANDARD ERROR**

**SUBEP.** = **SUBEPICARDIAL LAYER**

**MIDMYO.** = **MIDMYOCARDIAL LAYER**

**SUBENDO.** = **SUBENDOCARDIAL LAYER**
TABLE 4

MYOCARDIAL BLOOD FLOW ml/min/gm
CHRONIC SEDENTARY GROUP (8)
(OPEN CHEST)

<table>
<thead>
<tr>
<th></th>
<th>PARTIAL STENOSIS</th>
<th>TOTAL OCCLUSION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANTERIOR</td>
<td>POSTERIOR</td>
</tr>
<tr>
<td>TRANSMURAL</td>
<td>1.28±0.18</td>
<td>1.06±0.08</td>
</tr>
<tr>
<td>SUBEPI.</td>
<td>1.16±0.16</td>
<td>1.13±0.08</td>
</tr>
<tr>
<td>MIDMYO.</td>
<td>1.36±0.18</td>
<td>1.02±0.11</td>
</tr>
<tr>
<td>SUBENDO.</td>
<td>1.31±0.17</td>
<td>0.94±0.12</td>
</tr>
</tbody>
</table>

MEAN ± 1 STANDARD ERROR

SUBEPI. = SUBEPICARDIAL LAYER
MIDMYO. = MIDMYOCARDIAL LAYER
SUBENDO. = SUBENDOCARDIAL LAYER
group, the blood flow to the anterior myocardium was definitely greater than in the acute coronary group. Thus, underperfusion of the posterior myocardium appeared to result in hyperperfusion of the anterior myocardium. At total occlusion of the circumflex artery, the blood flow to the anterior wall remained at $1.29 \pm 0.14$ ml/min/gm, while posterior myocardial flow decreased to $0.77 \pm 0.08$ ml/min/gm. Following total occlusion of the previously constricted circumflex artery, posterior myocardial flow declined only 27%.

Chronic Exercise Group (Table 5): The anterior and posterior walls of this group had similar blood flow of $0.91 \pm 0.09$ ml/min/gm and $0.96 \pm 0.09$ ml/min/gm during partial occlusion. This showed there was no underperfusion or hyperperfusion comparing the myocardium supplied by normal left anterior descending with that supplied by constricted circumflex artery. During total occlusion of the previously constricted circumflex artery, the anterior myocardium maintained blood flow of $0.96 \pm 0.06$ ml/min/gm, while blood flow to the posterior myocardium decreased to $0.48 \pm 0.15$ ml/min/gm. The magnitude of decrease in myocardial blood flow to the posterior myocardium was significant statistically with $p < 0.05$.

The posterior myocardium which was supplied by the constricted circumflex artery had a decrease in blood flow after total occlusion. The decline was dramatic and significant in the acute group and in the chronic exercised group, but much less dramatic and not significant in the chronic sedentary group of dogs.

C. REGIONAL MYOCARDIAL BLOOD FLOW:

PHASE I

Control and Exercise Groups: Regional myocardial blood flow to the subepicardial, midmyocardial, and subepicardial layers of the anterior and posterior left ventricular myocardium at rest and during exercise in both
### TABLE 5

**MYOCARDIAL BLOOD FLOW** ml/min/gm  
**CHRONIC EXERCISE GROUP (8)**  
**OPEN CHEST**

<table>
<thead>
<tr>
<th></th>
<th>PARTIAL STENOSIS</th>
<th></th>
<th>TOTAL OCCLUSION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANTERIOR</td>
<td>POSTERIOR</td>
<td>ANTERIOR</td>
<td>POSTERIOR</td>
</tr>
<tr>
<td>TRANSMURAL</td>
<td>0.91±0.09</td>
<td>0.96±0.09</td>
<td>0.96±0.06</td>
<td>0.48±0.11</td>
</tr>
<tr>
<td>SUBEPI.</td>
<td>0.91±0.09</td>
<td>0.94±0.12</td>
<td>0.92±0.07</td>
<td>0.54±0.15</td>
</tr>
<tr>
<td>MIDMYO.</td>
<td>0.90±0.10</td>
<td>1.03±0.16</td>
<td>0.83±0.06</td>
<td>0.46±0.15</td>
</tr>
<tr>
<td>SUBENDO.</td>
<td>0.93±0.11</td>
<td>0.95±0.15</td>
<td>1.00±0.05</td>
<td>0.38±0.15</td>
</tr>
</tbody>
</table>

**MEAN ± 1 STANDARD ERROR**

**SUBEPI.** = SUBEPICARDIAL LAYER  
**MIDMYO.** = MIDMYOCARDIAL LAYER  
**SUBENDO.** = SUBENDOCARDIAL LAYER
groups of animals is shown in Table 6.

In the control animals, the myocardium supplied by the left anterior descending artery had subepicardial and subendocardial blood flows of $0.86 \pm 0.06 \text{ ml/min/gm}$ and $0.97 \pm 0.07 \text{ ml/min/gm}$ respectively at rest, and these flows increased to $2.35 \pm 0.19$ and $2.47 \pm 0.17 \text{ ml/min/gm}$ during exercise. In the exercised animals subepicardial and subendocardial flows were $0.80 \pm 0.09 \text{ ml/min/gm}$ and $0.97 \pm 0.11 \text{ ml/min/gm}$ respectively at rest, and increased to $2.24 \pm 0.11$ and $2.43 \pm 0.12 \text{ ml/min/gm}$ during exercise. In the anterior myocardium of both the control and exercised dogs' blood flows to the subendocardium were greater than that to the subepicardium both at rest and during exercise. Differences between the two layers and the two groups of animals were not significant statistically ($p > .05$).

In the posterior wall supplied by the constricted left circumflex artery, the subepicardial and subendocardial blood flows in the control dogs were $0.87 \pm 0.06 \text{ ml/min/gm}$ and $0.97 \pm 0.05 \text{ ml/min/gm}$ respectively at rest, and increased to $2.47 \pm 0.17 \text{ ml/min/gm}$ and $1.86 \pm 0.11 \text{ ml/min/gm}$ during exercise. In the exercised dogs, subepicardial and subendocardial blood flows were $0.83 \pm 0.10 \text{ ml/min/gm}$ and $0.94 \pm 0.09 \text{ ml/min/gm}$ at rest, and increased to $2.33 \pm 0.16 \text{ ml/min/gm}$ and $2.49 \pm 0.17 \text{ ml/min/gm}$ respectively during exercise.

Thus, the exercise group had similar anterior and posterior myocardial flows both at rest and during exercise with subendocardial flow slightly exceeding subepicardial flows in both areas; whereas the control sedentary dogs had less increase in posterior subendocardial blood flow during exercise. The subendocardial flow in the posterior wall of these sedentary dogs was significantly less than subepicardial flow. When compared to the exercised
Table 6.

Regional myocardial blood flow - ml/minute/gm of myocardium

<table>
<thead>
<tr>
<th></th>
<th>Anterior Wall</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Rest</td>
<td>0.86 ± 0.06</td>
<td>0.99 ± 0.06</td>
<td>0.97 ± 0.07</td>
<td>0.87 ± 0.06</td>
<td>1.00 ± 0.06</td>
<td>0.97 ± 0.05</td>
</tr>
<tr>
<td>Group Exercise</td>
<td>2.35 ± 0.19</td>
<td>2.55 ± 0.23</td>
<td>2.47 ± 0.17</td>
<td>2.47 ± 0.17</td>
<td>2.38 ± 0.16</td>
<td>1.86 ± 0.11</td>
</tr>
<tr>
<td>Exercise Rest</td>
<td>0.80 ± 0.09</td>
<td>0.96 ± 0.10</td>
<td>0.97 ± 0.11</td>
<td>0.83 ± 0.10</td>
<td>0.97 ± 0.10</td>
<td>0.94 ± 0.09</td>
</tr>
<tr>
<td>Group Exercise</td>
<td>2.24 ± 0.11</td>
<td>2.49 ± 0.11</td>
<td>2.43 ± 0.12</td>
<td>2.33 ± 0.16</td>
<td>2.52 ± 0.14</td>
<td>2.49 ± 0.17</td>
</tr>
</tbody>
</table>

Mean ± 1 standard error

Subepi = Subepicardial layer
Midmyo = Midmyocardial layer
Subendo = Subendocardial layer
animals, there was diminished subendocardial flow in the posterior wall (Figure 4).

When the ratio of subendocardial flow to subepicardial flow is examined, the effect of chronic exercise becomes more apparent. At rest, both control and exercised dogs had higher subendocardial than subepicardial flow to the anterior and posterior myocardium with ratios of $1.16 \pm 0.04$ and $1.23 \pm 0.04$ respectively for anterior myocardium, and $1.13 \pm 0.03$ and $1.17 \pm 0.06$ respectively for posterior myocardium. During exercise the ratio was reduced in the anterior myocardium but remained above 1.0, averaging $1.06 \pm 0.03$ for control dogs, and $1.06 \pm 0.01$ for exercised dogs. In contrast, the subendocardial to subepicardial flow ratio in the posterior myocardium fell to $0.77 \pm 0.05$ in control dogs during exercise, but was maintained at $1.07 \pm 0.03$ in the exercised dogs. This difference between the two groups in posterior subendocardial to subepicardial flow ratio during exercise was significant ($p < 0.001$) (Table 7).

**PHASE II**

**Acute Coronary, Chronic Sedentary and Chronic Exercise Groups:**
Myocardial blood flow to the subepicardial, midmyocardial and subendocardial layers of the anterior and posterior wall during partial stenosis and total occlusion of the left circumflex artery are shown in Tables 4,5, and 6. In the acute coronary group, the myocardium supplied by the left anterior descending artery had subepicardial and subendocardial blood flows of $1.05 \pm 0.20$ ml/min/gm and $1.08 \pm 0.16$ ml/min/gm at partial stenosis, and $1.14 \pm 0.22$ ml/min/gm and $1.22 \pm 0.21$ ml/min/gm at total occlusion. The myocardium of the posterior wall supplied by the stenosed circumflex artery had subepicardial and subendocardial blood flows of $0.83 \pm 0.07$ ml/min/gm and $0.74 \pm 0.20$ ml/min/gm respectively at partial stenosis, and this decreased to $0.20 \pm 0.04$ ml/min/gm and $0.10 \pm 0.04$ ml/min/gm after total occlusion. In the open-chested,
FIGURE 4

MYOCARDIAL BLOOD FLOW DISTRIBUTION

EXERCISE GROUP (EXERCISE)  CONTROL GROUP (EXERCISE)

- - - = ANTENOR WALL WITH S.E.
- - - = POSTERIOR WALL WITH S.E.

(REST)  (REST)

MYOCARDIAL BLOOD FLOW ML/GM/MIN

SUBEPI MIDMYO SUBENDO SUBEPI MIDMYO SUBENDO

REGIONAL MYOCARDIUM

SUBEPI = SUBEPICARDIAL LAYER
MIDMYO = MIDMYOCARDIAL LAYER
SUBENDO = SUBENDOCARDIAL LAYER
TABLE 7.

COMPARISON OF THE FLOW RATIO OF SUBENDOCARDIAL TO SUBEPICARDIAL LAYER BETWEEN THE ANTERIOR AND POSTERIOR WALL

<table>
<thead>
<tr>
<th></th>
<th>CONTROL GROUP</th>
<th>EXERCISE GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REST</td>
<td>EXERCISE</td>
</tr>
<tr>
<td>ANTERIOR WALL</td>
<td>1.16 ± 0.04</td>
<td>1.06 ± 0.03</td>
</tr>
<tr>
<td>POSTERIOR WALL</td>
<td>1.13 ± 0.03</td>
<td>0.77 ± 0.05</td>
</tr>
<tr>
<td>“P”</td>
<td>N.S.</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

“P” - P VALUE; N.S. - NO SIGNIFICANCE
pentobarbital anesthetized preparation, the heart rate was 140 beats/min. and the stenotic circumflex flow was 80% of normal anterior wall. The subendocardial and subepicardial flow ratio was reversed as compared to the anterior myocardium. Following total occlusion of the circumflex artery, the retrograde collateral flow was minimal in these animals at $0.20 \pm 0.04$ ml/min/gm and $0.10 \pm 0.04$ ml/min/gm respectively.

In the chronic animals that had been sedentary after partial stenosis, the subepicardial and subendocardial flows to the anterior wall were $1.16 \pm 0.16$ ml/min/cm and $1.31 \pm 0.17$ ml/min/gm respectively at partial stenosis, and $1.03 \pm 0.10$ ml/min/gm and $1.46 \pm 0.19$ ml/min/gm at total occlusion. Flows to the posterior subepicardium and subendocardium were $1.13 \pm 0.08$ ml/min/gm and $0.94 \pm 0.12$ ml/min/gm respectively with partial occlusion, and $0.96 \pm 0.06$ ml/min/gm and $0.64 \pm 0.11$ ml/min/gm after total occlusion. Although the absolute regional flow values to the posterior wall at partial stenosis were in the normal range, the transmural flow distribution in the posterior myocardium was reversed (subepicardial > subendocardium layer), and the subendocardial flow in the posterior wall was reduced to 80% of that of the anterior wall.

These results indicate underperfusion of the posterior myocardium, and especially the subendocardium, with the chest open and with moderate tachycardia of 140 beats/min. Total occlusion of the circumflex did not affect myocardial flow in the anterior myocardium as we expected. However, the posterior myocardium supplied by the circumflex artery showed 10-30% decrease in blood flow after total occlusion. The retrograde collateral flow was about 70-90% as great as the stenotic flow in these chronic sedentary animals.

In the chronic exercised group of animals with partial circumflex stenosis, the subepicardial and subendocardial flow in the anterior and posterior myocardium
were similar and measured 0.91 to 0.95 ml/min/gm. Transmural distribution was normal (subendocardial > subepicardial layer). There was no underperfusion in the open chested, anesthetized, tachycardic animals who had been exercised for 4 to 6 weeks after partial circumflex constriction. At total occlusion of the circumflex artery, subepicardial and subendocardial flow to the anterior myocardium was maintained at 0.92 ± 0.07 ml/min/gm and 1.00 ± 0.05 ml/min/gm. However, these flows were only 0.54 ± 0.15 ml/min/gm and 0.38 ± 0.15 ml/min/gm respectively in the posterior myocardium.

When we compared subendocardial flow in the posterior wall during partial stenosis to the flow during total occlusion, the difference was significant at p < 0.001 in the acute coronary group and p < 0.01 in the chronic exercise group. The change was not significant (p > 0.05) in the chronic sedentary group (Figure 5).

D. POSTMORTEM CORONARY ANGIOGRAMS (PHASE II):

Coronary angiograms done post-mortem showed 87.5 ± 2%, 89.0 ± 2%, and 87.0 ± 3% cross-sectional narrowing of the circumflex artery in acute coronary, chronic sedentary, and chronic exercised groups respectively. There was no difference in the degree of narrowing between any group of dogs.

E. THIOFLAVIN-S FLUORESCENT DATA (PHASE II):

The Thioflavin-S fluorescence of the myocardium revealed two patterns. One pattern showed areas of non-fluorescence in the myocardium, mostly in the subendocardium. The other showed diffuse homogenous decreased intensity of fluorescence in the posterior wall as compared to that of the anterior wall. Nearly all the acute and chronic sedentary dogs had the first pattern, while
FIGURE 5

Regional Myocardial Flow
Posterior Wall  ml/min/gm

Subepicardial layer  Subendocardial layer
S = Stenosis  O = Occlusion

p < .001  p > .05  p < .01

ml/min/gm

0.25

0.50

0.75

1.00

1.25

S  O

Acute Coronary G.  Chronic Sedentary G.  Chronic Exercise G.
the chronic exercised dogs all had a diffuse pattern. The average areas of fluorescence in the posterior myocardium after total left circumflex were 22%, 76 ± 8%, and 61.0 ± 7% for acute coronary, chronic sedentary, and chronic exercised dogs respectively. Retrograde flow to the posterior wall after total left circumflex occlusion was in decreasing order: the chronic sedentary; chronic exercised; and acute coronary groups. These results are consistent with the data from the microsphere myocardial flow measurement.


DISCUSSION

The purpose of our study was to examine the effects of daily exercise on myocardial blood flow, both at rest and during exercise, in a region of viable myocardium to which the blood supply had been limited by prior coronary constriction. A control group of animals that had not undergone exercise showed a reduction in subendocardial blood flow in the area supplied by the constricted circumflex artery during acute exercise. In contrast, a group of animals exercised daily after circumflex constriction had no reduction of subendocardial blood flow in the posterior myocardium with subsequent acute exercise. Although there were hemodynamic differences between the two groups of animals, the differences were not of great magnitude. The lower heart rate and higher mean arterial pressure, both at rest and during exercise, in the exercised animals probably represents a conditioning effect.\textsuperscript{17-20} Similarly, the increased treadmill duration in these animals was due to conditioning. Although myocardial oxygen consumption was not measured, we first believe that the two groups of animals achieved similar increases in total myocardial oxygen consumption during exercise since the double product of heart rate and mean arterial pressure\textsuperscript{37,38} were essentially the same for both groups of animals at the time exercise blood flow measurements were made. Secondly, total and regional blood flow to the anterior (normally perfused) myocardium did not differ between the two groups of dogs either at rest or during exercise. Under conditions where flow is not limited by coronary constriction, it is reasonable to assume that increases in blood flow reflect increases in oxygen requirements.

Our results demonstrate that daily exercise augments myocardial blood flow to the ischemic myocardium, especially in the subendocardial area. This could
come from augmentation of flow through collateral vessels. Several experiments done in animals with normal coronary arteries have demonstrated that there was no effect of daily exercise on retrograde coronary flow or myocardial flow, and this is consistent with our findings in the anterior myocardium. Tepperman showed increased heart/body weight ratios and coronary artery cast weight/heart weight ratios in a group of exercised animals. Cobb was unable to demonstrate a decrease in infarct size or incidence of arrhythmias after total left anterior descending artery occlusion in a group of animals that had been trained for 6 weeks following partial occlusion of this vessel. Kaplinsky et al and Lambert et al studied dogs with total occlusion of one coronary artery sufficiently proximal to produce myocardial ischemia at rest, and were unable to show a significant exercise effect. However, since ischemia is the major stimulus for collateral formation, it is probably difficult to demonstrate an additional effect of exercise in such animals.

Our results are consistent with those of Eckstein and Heaton et al in suggesting that daily exercise increased collateral formation in dogs with partial or total coronary constriction. In Eckstein's study, measurements of collateral flow were by retrograde coronary blood flow in open chest anesthetized animals. This method did not measure regional myocardial flow during exercise or rest, and differs from our methods in that pre-existing epicardial collaterals between the left anterior descending and circumflex arteries were not ligated. The dogs had extensive epicardial collaterals, but without ligation of these vessels it is difficult to attribute improved blood flow to enlargement of intramyocardial collaterals. In Heaton's study, the source of collateral blood flow to the ischemic myocardium was from normal diagonal or partially constricted (60-90%) left circumflex arteries. At baseline blood flow study, they
found the endocardial flow of the collateral area to be 83% of the normal area at rest and 69% at exercise with reversal of transmural myocardial distribution. Six weeks later they found improved subendocardial perfusion at rest and during exercise in the collateral dependent zone with normal transmural myocardial distribution in both groups of animals. The exercised animals had lower baseline exercise myocardial flow and higher followup exercise myocardial flow. The control sedentary animals had higher baseline flow and lower followup flow. Therefore, there was a significant difference in the exercising endocardial flow comparing baseline and followup studies only in the exercised animals. In the exercise group, these investigators disregarded the physical conditioning response (slower heart rate) to treadmill exercise. The Ameroid constrictor used in these experiments produces a total occlusion that is different from our partial constriction of the coronary artery.

In addition to enhancing collateralization of ischemic myocardium, daily exercise may have important effects on the autonomic nervous system, both with regard to systemic hemodynamic as well as coronary vasomotor tone.\textsuperscript{17,20,42} Our exercised dogs had slightly less tachycardia and slightly higher mean arterial pressures during submaximal exercise than did our control dogs, and the combined effect of these hemodynamic differences could have enhanced antegrade flow beyond the point of constriction\textsuperscript{43} as well as flow through collateral vessels.\textsuperscript{21,26}

To answer the question of enhanced antegrade flow versus increased collateral flow, three additional groups of animals were studied: an acute coronary group, in which total occlusion followed a short period of partial constriction at the same operation; and 2 chronic groups, in which total occlusion followed 6 weeks of either rest or programmed exercise.
The degree of constriction of the left circumflex artery was proven to be 80-90% of cross-sectional diameter by postmortem coronary angiogram. This same degree of coronary constriction did not produce posterior myocardial underperfusion in conscious, quiet, Phase I dogs with slow heart rates of 80-100 beats/min or in experiments by prior investigators. However, the acute coronary artery group showed slight underperfusion of the posterior wall, particularly in the subendocardial layer at heart rates of 140 beats/min and pentobarbital anesthesia. This observation of myocardial ischemia during tachycardia with proximal coronary constriction was similar to the observations of Ball and Neil. In the chronic sedentary group, the absolute flow to the posterior wall from the partial constricting circumflex was in the normal range of 0.9-1.1 ml/min/gm, but was only 80% of the anterior wall myocardial flow, and had reversal of the transmural myocardial flow ratio (subendocardial flow < subepicardial flow). This posterior wall underperfusion was accompanied by compensatory vasodilatation to the remaining left ventricle as seen in the slight hyperperfusion of the anterior myocardium. In the chronic exercised group, myocardial flow in the anterior myocardium was similar to the posterior myocardium despite slight tachycardia (130 beats/min) and the conditions of anesthesia. This beneficial effect of exercise could be from the slower heart rate and decreased post-stenotic vascular resistance resulting in increased antegrade flow or from retrograde flow through developing collaterals. The myocardial flow measurement following total occlusion of the circumflex artery showed there was little myocardial flow to the posterior wall in the acute coronary group. The posterior wall maintained about 70-90% of the stenotic flow following total occlusion in the chronic sedentary group. The chronic exercised group had a decline in posterior myocardial flow to 40-50% of the stenotic flow following total occlusion. It appears, therefore, that
when total occlusion followed a period of partial occlusion the collateral vessels could carry much more retrograde flow to the posterior wall in the chronic sedentary group than in the chronic exercised group. This is good evidence against attributing the subendocardial flow found in the posterior myocardium of the exercised dogs during treadmill exercise to retrograde collateral flow. Total occlusion should have caused sufficient vasodilatation to maximize retrograde flow, and yet the chronic exercised group had less retrograde collateral myocardial blood flow to the posterior wall than did the chronic sedentary dogs.

Thioflavin-S staining of the posterior wall following total occlusion of the circumflex artery verified little myocardial flow to the posterior wall in the acute coronary group. The higher percentage of fluorescent staining in the posterior wall in the chronic sedentary dogs compared to the chronic exercised dogs was consistent with the greater flow to the posterior myocardium as demonstrated by microsphere flow measurements. However, the chronic sedentary dogs showed punched out areas of nonfluorescent staining in the subendocardial layer, while the chronic exercised dogs had lighter but more evenly distributed staining. This demonstrated that after total occlusion of the circumflex artery the chronic sedentary dogs had marked subendocardial underperfusion, while the chronic exercised dogs had only diffuse posterior myocardial underperfusion.

Although ischemia is considered a potent stimulus for coronary vasodilatation, recent studies by Gould et al have shown that additional coronary vasodilatation in an ischemic zone can be achieved with potent coronary vasodilator agents such as dipyridamole. It is possible, therefore, that daily exercise could influence distribution of flow to an ischemic area during
subsequent exercise by modification of autonomic mechanisms acting directly on coronary vasomotor tone and/or autoregulatory resistance.

Another explanation of increased antegrade myocardial flow would be a lesser degree of constriction produced in the main circumflex artery in the exercised group due to the stimulus of exercise causing gradual expansion of the constricted area. However, this hypothesis could not be proven by post-mortem angiograms in comparing the constriction in the acute coronary, chronic sedentary, and chronic exercise groups. All groups showed rather uniform cross-sectional constriction of 85-90%. Using two occlusions applied in succession, as in our model, Levin et al demonstrated that only a small difference in degree of occlusion in the second ligature could drastically decrease the resting flow across the area of constriction. However, in our model the narrowing rendered no decrease in resting flow and only moderately limited the increase in flow during tachycardia. Berne has shown 66-85% of coronary perfusion to occur during diastole. Since the exercised group had slower heart rates at rest and at any given stage of exercise, the increased antegrade flow through the constricted circumflex might be related to the longer diastolic period. It was for this reason our flow determinations during exercise in both the control and exercised groups were made at a given target heart rate for more than 200 beats/min, rather than a given exercise load.

In conclusion, our studies demonstrate that a training period of daily exercise improves subendocardial blood flow to the myocardium rendered ischemic by prior coronary constriction. We could not prove that enhanced collateral flow was the mechanism to explain the beneficial effects of exercise. There was convincing evidence that daily exercise increased antegrade flow to the
posterior myocardium supplied by the constricted circumflex artery. Additional studies will be needed to understand the mechanisms of this enhanced antegrade flow. We suggest that these studies be directed toward modulation of vaso-motor tone in the post-constricted vessel, and correlated with exercise modification of autonomic sympathetic responses.
The effect of exercise on regional myocardial flow was studied in 15 dogs with proximal circumflex coronary arterial constriction. Using pentobarbital anesthesia and aseptic surgical technique, 80-90% occlusion of the proximal circumflex coronary was created by ligature, and epicardial collaterals between the left anterior descending and circumflex coronary arteries were obliterated by sutures. Chronic cannulation of the left atrial appendage and of the aorta were then performed. After recovery from surgery, the animals were divided into exercise and control groups (7 and 8 animals respectively). Animals in the exercise group ran on a treadmill for 45 minutes a day, 5 days a week, at 4-6 mph, on a 10% incline. The control group of animals rested. After 4-6 weeks microsphere regional myocardial flow measurements were performed at rest and during treadmill exercise to a heart rate of 200 beats/min in both groups. At rest, blood flow to anterior and posterior left ventricular walls was normal in both exercise and control animals. The transmural distribution of flow was likewise normal (more flow to the subendocardial myocardium) in both groups. The dogs who were exercised regularly after coronary narrowing had normal subendocardial flow to the posterior wall with normal distribution during exercise. Control dogs, however, had less subendocardial flow to the posterior wall than to the anterior wall with reverse transmural distribution (less flow to subendocardial myocardium) during exercise (1.86 ± 0.11 ml/min/g vs 2.47 ± 0.17 ml/min/g; p < 0.05).

To determine the mechanism for improved subendocardial blood flow during treadmill in the exercise dogs, collateral blood flow was studied by completely occluding the previously constricted circumflex coronary arteries. In 6 dogs (acute coronary group) total coronary occlusion followed shortly after partial
constriction during the first thoracotomy. Sixteen dogs (8 chronic exercise and 8 chronic sedentary) underwent a 4-6 week interval of either programmed exercise or rest. Collateral flow was then performed at a second thoracotomy. Collateral flow to the posterior wall (flow after complete coronary occlusion) was highest in the chronic sedentary dogs, less in the chronic exercise dogs, and least in the animals studied acutely (0.77 ± 0.08 ml/min/gm vs 0.48 ± 0.11 ml/min/gm vs 0.16 ± 0.04 ml/min/gm). When we compared subendocardial flow in the posterior wall during partial stenosis to flow during total occlusion, the difference was significant at p < 0.001 in the acute coronary group and p < 0.01 in the chronic exercise group. The change was not significant (p > 0.05) in the chronic sedentary group. This suggests that the improved exercise subendocardial flow in the exercise dogs resulted not from increased collateral flow, but from increased antegrade flow across the constriction. Such an increase in antegrade flow may have resulted from a decrease in resistance of the coronary vascular bed beyond the constriction.
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The thesis is, therefore, accepted in partial fulfillment of the requirements for the degree of Master of Science.

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