Effects of Exercise on the Coronary and Collateral Vasculature of Beagles with and without Coronary Occlusion

KONRAD W. SCHEEL, LESLIE A. INGRAM, AND JACK L. WILSON

SUMMARY The purpose of this study was to determine if exercise stimulates coronary collateral vessel growth and if exercise after coronary occlusion can promote additional collateral growth. One group of 10 beagles served as control. The second group consisted of 10 normal beagles exercised at 50% of maximum O₂ consumption 7 days/week for 6 weeks. In the third group, the circumflex was occluded (Ameroid method) in eight beagles for 6 months. In the fourth group, seven beagles were exercised for 8 weeks following 3 months of circumflex occlusion. The coronary and collateral circulation was assessed, using an isolated heart preparation. It was found that exercise did not stimulate collateral growth in normal beagles. However, exercise after coronary occlusion doubled collateral conductance to the impaired vascular bed compared to animals with only coronary occlusion. Our study shows that, in beagles with coronary occlusion, exercise after a 3-month convalescent period promotes epicardial and intramyocardial (septal) collateral growth. Coronary reserve in the trained animals returned to 52% of initial capacity vs. 34% for the untrained animals. Circ Res 48: 523–530, 1981

IN STUDIES of the value and effects of exercise on the coronary and collateral circulation, investigators have recognized that differences in age (Åstrand, 1960; Julius et al., 1967), genetic predisposition (Andersen, 1967; Frick, 1967), sex (Åstrand, 1960), and physical fitness (Frick, 1967; Andersen, 1967; Heiss et al., 1976) should be considered. In a large number of clinical and experimental studies, final interpretation of results has been hampered by one or more of these variables and, consequently, has led to the question of whether exercise benefits or does not benefit (Ferguson et al., 1974; Heaton et al., 1978; Neill and Oxendine, 1979) the coronary or collateral circulation.

Methodological problems also may contribute to the controversy. With coronary occlusion, the blood flow measured with the tracer microsphere technique is determined by the series resistance of the collateral and coronary vasculature, and resistance changes in either vascular bed will affect myocardial perfusion. Yet it would seem desirable to attempt to determine whether exercise affects primarily the collateral, coronary, or both vascular beds. Although our isolated heart preparation may not simulate the in vivo heart in all respects, measurement of the collateral circulation can be separated from that of the coronary circulation (Jones and Scheel, 1980). In addition, our preparation allows rigidly controlled conditions by abolishing vasomotion and by controlling cardiac activity. Both parameters, again, can influence the coronary and collateral circulation independently or simultaneously.

The objectives of this study were: (1) to evaluate quantitatively the effects of exercise on structural changes of the coronary and collateral vasculature in the normal beagle and beagles with chronic circumflex occlusion (reduced coronary reserve), (2) to distinguish between collateral growth due to occlusion only and collateral growth with exercise in the presence of coronary occlusion, and (3) to determine the role of septal collateralization, a manifestation of intramyocardial collateralization, in these models. For this study, animals were selected to be similar with respect to environment, age, sex, physical fitness, and heredity. The study was designed to produce a moderate exercise stress of 50% of maximum oxygen consumption for 45 minutes per day.

Methods

We studied 35 adult male beagles from a closed colony (Marshall Research). Four beagles had the same sire, and seven others had one half-brother in the study. These animals were divided into four groups. Beagles in the control group (10) were caged their entire lives and were 9.1 ± 0.3 (avg. ± SEM) months old at the time the coronary and collateral resistance determinations were performed (termination of the experiment). The second group of 10 beagles (control-exercise group) was 9.4 ± 0.2 months old and not statistically different in age from the first group at termination of the experiment. However, these dogs were exercised for 6 weeks (7 days/week) prior to termination of the experiment.
In the third group of eight beagles (occlusion group), a 2.5 mm i.d. Ameroid occluder (Threepoint Products) was placed surgically on the circumflex artery (Scheel et al., 1976b) at age 9.4 ± 0.2 months. These animals remained caged until termination of the experiment at an age of 14.1 ± 0.2 months. In the fourth group of seven beagles (occlusion-exercise group), an Ameroid occluder of the same size was implanted on the circumflex at age 9.8 ± 0.1 months, and the exercise program was started 3 months post-surgery for 8 weeks (5 days/week). The age of these dogs at the termination of the experiment was 14.7 ± 0.2 months and not statistically different from the age of the beagles with Ameroid occluder but no exposure to exercise. Although there was an age difference between the control and Ameroid groups, male beagles reach growth maturity between 7 and 8 months (Andersen, 1970), and changes in coronary vascular growth due to age were not expected.

Exercise Protocol

The control-exercise and occlusion-exercise groups of beagles were run on a Warren-Collins treadmill. The speed, incline, and duration of exercise were increased gradually over an average of 8 days and then maintained throughout the experiment. Young (1961) has shown that a treadmill speed of 3.6 miles/hr at an incline of 25% (15 degrees) stresses the beagle to 50% of maximum oxygen consumption. The animals ran at this level for 45 minutes per day for a total of 143.0 ± 1.4 kilometers for the control-exercise, and 135.3 ± 1.0 kilometers for the occlusion-exercise groups. Since there is a remarkable similarity of myocardial blood flow between humans and dogs in their response to exercise (Ball et al., 1975), the level of exercise used is comparable to that of man cycling at 5.5 miles per hour or mowing the lawn (Reiff et al., 1967). No electrical or other stimuli were used to induce performance by the animals. In fact, most dogs voluntarily ran from their cages onto the treadmill and were exercised two at a time. No deaths occurred during exercise.

Determination of Coronary and Collateral Resistances

The coronary and collateral circulations were examined during maximum vascular dilation, constant pressure perfusion, and constant afterload (ventricles vented to atmospheric pressure). Therefore, changes in blood flow would be a reflection of structural changes of the coronary and collateral vasculature. The method used has been described in previous publications from this laboratory (Scheel et al., 1976a, 1976b, 1977, 1980).

Briefly, for the isolated heart preparation, the experimental animal’s heart was removed carefully, and the circumflex, left anterior descending, and right coronary arteries were cannulated and perfused with fresh blood. The anterior descending artery was cannulated just distal to the left common bifurcation and origin of the septal artery. The septal artery was perfused via the aorta. Blood flow to each cannulated vessel was measured with electromagnetic flow meters in the beating heart preparation perfused from a constant pressure reservoir (100 mm Hg). A continuous infusion of adenosine (6.7 mg/min) was used for maximal vasodilation, which was confirmed by the absence of a hyperemic response following 30 seconds of coronary occlusion. Cannulation of the vessels was performed proximal to all coronary branches except the septal and, in the dogs with an Ameroid constrictor, just distal to the occlusion. Following determination of all hemodynamic parameters, the flow probes were calibrated, and the heart weight and hematocrit were recorded.

Coronary Resistance Determinations

Coronary vessel resistances were calculated from the late diastolic portion of the coronary flow waveform, and the prevailing monitored pressure was referenced to the A-V valve. Measurements were made at various perfusion pressures, thereby establishing a pressure-flow relationship. All measurements were corrected for pressure losses of the perfusion system, and a linear pressure-flow curve was obtained. The coronary resistances were determined for a pressure of 100 mm Hg and extrapolated to a hematocrit of 40 vol.%. Details of the analysis are shown in previous work from this laboratory (Scheel et al., 1976a).

Coronary Collateral Resistance Determinations

All coronary collateral determinations were made at a pressure of 100 mm Hg. Retrograde flow measurements were performed on each cannulated vessel individually and by simultaneous measurements on combinations of two coronary vessels. In calculating the collateral resistances, we took into account pressure losses of the perfusion system, the resistance of the retrograde flow cannula, blood flow diversion through the coronary vessel on which the retrograde flow was performed, collateral connections to other vessels, and the hematocrit of the blood perfusate (Scheel et al., 1977, 1980). Collateral contributions by the septal artery were estimated by measuring the retrograde flow from the circumflex, anterior descending, and right simultaneously while the septal artery was the only vessel perfusing the heart (Scheel et al., 1980).

Statistical Methods

Nonpaired Student’s t-tests were used for the statistical analyses between groups. An analysis of variance was applied when all groups were tested, followed by a modified t-test (Wallenstein et al., 1980).
**Results**

Table 1 is a summary of some of the baseline variables for all groups of beagles used in this study. The ages of the dogs in the control and control-exercise groups were not significantly different at the time of the isolated heart procedure. No age difference was noted between the occlusion and occlusion-exercise groups. Body weights, heart weights, and ratios of heart weight to body weight showed no statistical differences among the groups. Thus, it can be assumed that the exercise level used in this study did not produce cardiac hypertrophy. The average heart rate of the beagles following the first day of full exercise level was 163 ± 9.3 beats/min and decreased to 152 ± 6.7 beats/min (P = 0.05) on the last day of exercise. The heart rate, calculated from an electrocardiogram, was obtained approximately 1 minute after exercise, and thus may not represent peak rates.

**Coronary Resistances**

The coronary resistances of the vasodilated left anterior descending (A), circumflex (C), and right (R) coronary arteries are listed in Table 2. Although statistically there is no difference in these resistances between the control and control-exercise groups, the average resistances in the control-exercise group all are lower. When the coronary resistances between the beagles with circumflex occlusion are compared to the group with coronary occlusion and exercise, again the difference in resistance is not statistically significant. However, the circumflex coronary resistances of the Ameroid groups are significantly larger compared to the control groups (P < 0.05).

**Collateral and Septal Collateral Resistances**

The method used in these experiments allowed us to determine the collateral resistances, including the septal contribution, and also to calculate separately the septal collateral resistances. First, collateral data including the septal contribution (Table 3) will be reported, and then data for the septal collaterals will be shown separately. The reason we chose to show the septal collateral data separately is that they represent intramyocardial collateralization (Scheel et al., 1980), in contrast to epicardial collateralization.

**Collateral Resistances**

The collateral resistances (Table 3) of the control and control-exercise groups did not differ significantly. However, in the occlusion-exercise group, collateral resistance between the anterior descending and septal to circumflex, R<sub>SA-C</sub>, and the collateral resistance, R<sub>SR-C</sub>, were significantly reduced as compared to the occlusion group. When the collateral resistances between the groups without occlusion are compared to the groups with coronary occlusion, collateral resistances are considerably lower in these beagles and similar to the response we have seen in mongrel dogs (Scheel et al., 1977).

**Septal Collateral Resistances**

The collateral resistances between the septal and right coronary artery, R<sub>S-R</sub>, the septal and anterior

**Table 2 Coronary Resistances**

<table>
<thead>
<tr>
<th>Groups</th>
<th>RA</th>
<th>RC</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.65</td>
<td>0.41</td>
<td>1.55</td>
</tr>
<tr>
<td>(n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control-exercise</td>
<td>0.57</td>
<td>0.36</td>
<td>1.25</td>
</tr>
<tr>
<td>(n = 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion</td>
<td>0.78</td>
<td>0.70</td>
<td>1.26</td>
</tr>
<tr>
<td>(n = 8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion-exercise</td>
<td>0.62</td>
<td>0.56</td>
<td>1.35</td>
</tr>
<tr>
<td>(n = 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are expressed as average ± SEM. Coronary resistances of the anterior descending, RA, circumflex, RC, and right, RR, are expressed in mm Hg/ml/min. Values were corrected for pressure losses of the perfusion system and extrapolated to a hematocrit of 40. An analysis of variance between all four groups showed statistical significance at P < 0.05 for RA. A modified t-test between control groups (control and control-exercise) and occlusion groups showed that RA was larger for the groups with Ameroid occlusion (P < 0.05).

**Table 1 Basic Beagle Data**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age (months)</th>
<th>Hct. (vol.%)</th>
<th>Total running distance (km)</th>
<th>Body wt (kg)</th>
<th>Heart wt (g)</th>
<th>Ratio, heart-to-body wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9.1</td>
<td>46.4</td>
<td>12.04</td>
<td>115.0</td>
<td>0.0096</td>
<td></td>
</tr>
<tr>
<td>(n = 10)</td>
<td>±0.3</td>
<td>±0.9</td>
<td>±0.39</td>
<td>±5.4</td>
<td>±0.0003</td>
<td></td>
</tr>
<tr>
<td>Control-exercise</td>
<td>9.4</td>
<td>47.8</td>
<td>143.0</td>
<td>11.07</td>
<td>0.0101</td>
<td></td>
</tr>
<tr>
<td>(n = 10)</td>
<td>±0.2</td>
<td>±0.8</td>
<td>±1.4</td>
<td>±0.41</td>
<td>±0.0004</td>
<td></td>
</tr>
<tr>
<td>Occlusion</td>
<td>14.1</td>
<td>47.0</td>
<td>13.30</td>
<td>136.1</td>
<td>0.0102</td>
<td></td>
</tr>
<tr>
<td>(n = 8)</td>
<td>±0.2</td>
<td>±0.9</td>
<td>±0.55</td>
<td>±7.9</td>
<td>±0.0003</td>
<td></td>
</tr>
<tr>
<td>Occlusion-exercise</td>
<td>14.7</td>
<td>50.3</td>
<td>135.3</td>
<td>12.97</td>
<td>0.0099</td>
<td></td>
</tr>
<tr>
<td>(n = 7)</td>
<td>±0.2</td>
<td>±1.0</td>
<td>±1.0</td>
<td>±3.6</td>
<td>±0.0004</td>
<td></td>
</tr>
</tbody>
</table>

Results are expressed as average ± SEM. All data at termination date of experiment.
S, A, C, and R represent the septal, anterior descending, circumflex, and right coronary arteries, respectively. The combinations of letters indicate combined collaterals from the designated vessels to the other vascular bed. Resistances include the septal contribution and are expressed in mm Hg/(ml/min).

Table 3: Collateral Resistances (R)

<table>
<thead>
<tr>
<th>Groups</th>
<th>RsA,C</th>
<th>RsC,A</th>
<th>RsC,R</th>
<th>RsR,C</th>
<th>RsC,R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=9)</td>
<td>18.9</td>
<td>17.2</td>
<td>122.2</td>
<td>34.9</td>
<td>187.2</td>
</tr>
<tr>
<td></td>
<td>17.0-21.2</td>
<td>16.3-18.1</td>
<td>104.9-142.2</td>
<td>28.2-43.3</td>
<td>154.3-227.0</td>
</tr>
<tr>
<td></td>
<td>40.6</td>
<td>35.7-46.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control-exercise (n=9)</td>
<td>25.9</td>
<td>19.8</td>
<td>133.0</td>
<td>45.8</td>
<td>185.3</td>
</tr>
<tr>
<td></td>
<td>22.3-30.2</td>
<td>17.9-21.9</td>
<td>112.5-157.3</td>
<td>40.5-51.7</td>
<td>157.7-217.8</td>
</tr>
<tr>
<td></td>
<td>44.3</td>
<td>40.3-48.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion (n=8)</td>
<td>1.6</td>
<td>2.0</td>
<td>3.0</td>
<td>1.3</td>
<td>21.5</td>
</tr>
<tr>
<td></td>
<td>1.3-2.0</td>
<td>1.6-2.5</td>
<td>2.2-4.2</td>
<td>1.2-1.4</td>
<td>16.1-28.8</td>
</tr>
<tr>
<td></td>
<td>17.0</td>
<td>14.0-20.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occlusion-exercise (n=7)</td>
<td>0.7*</td>
<td>1.5</td>
<td>4.3</td>
<td>0.83*</td>
<td>33.1</td>
</tr>
<tr>
<td></td>
<td>0.6-0.9</td>
<td>1.2-1.8</td>
<td>3.0-6.1</td>
<td>0.69-0.99</td>
<td>21.4-51.2</td>
</tr>
<tr>
<td></td>
<td>15.6</td>
<td>12.3-19.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results are expressed, in the first line of each group, as average resistance reconverted from logarithmic to original units; the second line in each group is the average ± 1 SEM reconverted from logarithmic to original units. The statistical analyses were performed on the logarithms of the data. The subscripts S, A, C, and R represent the septal, anterior descending, circumflex, and right coronary arteries, respectively. The combinations of letters indicate combined collaterals from the designated vessels to the other vascular bed. Resistances include the septal contribution and are expressed in mm Hg/(ml/min).

Table 4: Septal Collateral Resistances

<table>
<thead>
<tr>
<th>Groups</th>
<th>RsA</th>
<th>RsC</th>
<th>RsR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=3)</td>
<td>58.2</td>
<td>86.2</td>
<td>415.7</td>
</tr>
<tr>
<td></td>
<td>33.2-102.2</td>
<td>42.8-173.7</td>
<td>363.3-475.8</td>
</tr>
<tr>
<td>Control-exercise (n=3)</td>
<td>69.2</td>
<td>69.2</td>
<td>328.8</td>
</tr>
<tr>
<td></td>
<td>66.2-72.3</td>
<td>62.1-77.2</td>
<td>216.5-499.3</td>
</tr>
<tr>
<td>Occlusion (n=8)</td>
<td>18.2</td>
<td>4.6</td>
<td>40.5</td>
</tr>
<tr>
<td></td>
<td>15.7-21.1</td>
<td>3.4-6.1</td>
<td>33.3-49.9</td>
</tr>
<tr>
<td>Occlusion-exercise (n=7)</td>
<td>13.8</td>
<td>1.9*</td>
<td>47.8</td>
</tr>
<tr>
<td></td>
<td>11.2-17.0</td>
<td>1.5-2.5</td>
<td>26.6-85.9</td>
</tr>
</tbody>
</table>

Results are expressed, in the first line of each group, as average resistance reconverted from logarithmic to original units; the second line in each group is the average ± 1 SEM reconverted from logarithmic to original units. RsA, RsC, and RsR represent the collateral resistances between the septal, S, and anterior descending, circumflex, and right, respectively.

Discussion

Effects of Exercise on the Coronary Vasculature

This study does not show any statistically significant difference in the resistance of the coronary vascular beds between control and control-exercise and between occlusion and occlusion-exercise groups of beagles. Tepperman and Pearlman (1961) used corrosion-cast techniques and demonstrated an increase in coronary arterial tree size in exercised rats. Stevenson et al. (1964) noted an increase in the ratio of coronary cast weight to total heart weight at certain exercise levels. Leon and Bloor (1968) noted an increase in cross-sectional luminal areas of coronary arteries in exercised rats with ventricular hypertrophy; but, in rats not so severely exercised (no hypertrophy), an increased cross-sectional area could not be discerned. Astrand and Rodahl (1970) illustrated an increase in number of capillaries in exercised guinea pig hearts and a further increase in capillary density with total running distance. Similar results were obtained by McElroy et al. (1978) in the rat stressed by swimming exercise. Some of the disparity in the results of the effects of exercise on the coronary vasculature probably are related to the level and duration of exercise stress and differences in the applied techniques, as well as the above-mentioned factors.

In this study, a comparison of circumflex resistance of the control and control-exercise animals with the occlusion and occlusion-exercise groups (Table 2) showed a significantly larger circumflex resistance for the latter two groups. The pressure difference between the aorta and the artery distal to the occlusion often is assumed to be an index of
collateralization (Neill and Oxendine, 1979). However, an increase in the resistance of the occluded vascular bed, even if the collateral resistance does not change, could lead to an increased pressure distal to the occlusion. Consequently, the pressure difference between the aorta and the artery distal to the occlusion would decrease and could erroneously be interpreted as decreased collateral resistance. In this case, the decreased pressure difference would actually be caused by an increased coronary resistance. The above observation points toward the importance of determinations for coronary resistance and collateral resistances. The tracer microsphere technique, as usually applied, does not distinguish between these variables, but reflects their series resistance.

Effects of Exercise on Collateral Resistances

The data of Table 3 indicate no difference in collateral resistances between the control and control-exercise groups. Similar results were obtained by Cohen et al. (1978), who also used beagles (from the same supplier). Their exercise protocol, however, was even more demanding than ours, and the training period lasted 10-12 weeks. Khouri et al. (1965), Ball et al. (1975), Vatner and Pagani (1976), and Barnard et al. (1977) have shown that the coronary vessels have the capacity to increase blood flow 4- to 6-fold with exercise, and Ball et al. (1975) have shown that this increase in flow is distributed evenly from epi- to endocardium. Thus, the metabolic demands of the exercise level used in this study (50% of maximum O2 consumption) should have been met by an increase in coronary flow. That is, coronary reserve was sufficient to prevent the myocardium from becoming ischemic, and, in the absence of ischemia, collateral growth was not stimulated. On the other hand, when the coronary reserve was impaired by circumflex occlusion, the exercise level most likely produced a metabolic demand that exceeded coronary reserve, resulting in ischemia and an additional stimulus for collateral growth. This hypothesis is supported by the observation that the total collateral resistances between the anterior descending and septal artery to the circumflex, RSA-C, and between the septal and right to circumflex, RSRC, were decreased in the occlusion-exercise group as compared to the occlusion group without exercise. The data from Table 4 and Figure 1 indicate that the septal artery, RSA-C, substantially contributed to this collateral growth. Since the septal artery is located deep within the myocardium, its collateral development is a manifestation of intramyocardial collateralization. This study also confirms earlier observations on mongrel dogs (Scheel et al., 1977) that collateral growth appears to develop toward the ischemic myocardium (circumflex), and collaterals from the anterior descending, right, and septal artery show a preferential growth pattern toward the circumflex (RSA-C, RSRC from Table 3 and RSC from Table 4).

There is considerable controversy in the literature on the collateral-promoting ability of exercise in animals. Eckstein's experiments (1957), which in methodology are similar to this study, revealed a significantly better collateralization in exercised dogs with coronary occlusion than in non-running dogs. Studies in pigs suggested collateral improvement with physical training (Schaper et al., 1971). On the other hand, Burt and Jackson (1965), Kaplinsky et al. (1968), Amann et al. (1971), and Schaper et al. (1971) were unable to demonstrate improved collateral development with exercise in dogs. Schaper et al. (1971) suggested that this was due to the fact that dogs develop primarily epicardial collaterals, in comparison to pigs with primarily intramyocardial collaterals. Hence, this study has demonstrated both epicardial and intramyocardial (via septal artery) collateralization.

Inferences on Coronary Reserve

The question of how much blood flow can be supplied optimally to the myocardium of the occluded vessel is of importance not only after acute coronary occlusion, but also after chronic coronary occlusion. The answer to this question following acute occlusion will dictate the amount of remaining viable myocardium (White et al., 1978). The answer to the question in the case of chronic occlusion will dictate the coronary reserve available to the remaining viable myocardium. Since this study deals primarily with the consequences of long-term coronary occlusion and how exercise can alter the coronary vasculature, the question of coronary reserve should be examined in light of this study.

Hoffman (1978) has pointed out that coronary flow is autoregulated to the level of myocardial demand and that the amount of flow available above the demand flow is the coronary reserve. Thus, coronary reserve varies with the basic demand. However, if autoregulation is abolished, as was the case in this study, maximum coronary flow is dictated by the anatomical constraints, such as the radius, length, and number of vessels. From the quantitative data of the coronary and collateral resistances obtained in this study, it is possible to calculate the increase in coronary reserve obtained in dogs with coronary occlusion and exercise above those with only coronary occlusion. Based on the calculations developed in the Appendix, it can be shown that the coronary reserve in beagles with 5 months’ coronary occlusion is about 34% of the reserve of the unoccluded vessel. This value is consistent with observations by Schaper et al. (1976). In the beagles exercised in the presence of coronary occlusion, the coronary reserve increased to 52% of the reserve of the unimpaired vessel. In light of the observation that coronary reserve increases as col-
latterals develop with time and that this reserve is enhanced with exercise, we will discuss recent studies by other investigators.

In their work, Lambert et al. (1977) placed an Ameroid constrictor on dogs for 6–10 months. (The average time post Ameroid placement for our study was 5 months.) They used two levels of exercise: light, defined as running on a treadmill at 4 mph at 4% grade; and moderate, running at 6 mph at 8% grade. The animals with 6–10 months of occlusion (but no exercise training) were exercised to the above levels, tracer microspheres were injected, and then the dogs were killed immediately. They found that these levels of exercise did not produce either subepicardial or subendocardial ischemia. Thus, their studies indicate that collateral growth (even without additional exercise training) provides sufficient coronary reserve to prevent myocardial ischemia at these exercise levels.

The calculations based on our studies suggest that after 5 months of Ameroid occlusion the beagles in the occlusion group were capable of a 2.9-fold increased blood flow. Therefore, the results of Lambert et al. are not incompatible with those of this study.

Neill and Oxendine (1979) also investigated the effects of exercise on collateral formation in dogs. In their preparation, consisting of placement of an Ameroid constrictor on the circumflex, exercise training was instituted only 6 days after Ameroid placement. The exercise protocol consisted of treadmill running at 5 mph and 15% grade for 30 min/day for 5 and 8 weeks. Tracer microspheres were injected at the end of these two training periods, during rest, and two levels of pacing (200/min and 250/min). Pacing at a rate of 200 beats/min did not show any differences in relative perfusion between the circumflex and anterior descending territories in either the 5- or 8-week trained animals. However, when the hearts were paced to a rate of 250 beats/min, the circumflex territory in the 5-week trained animals showed relative underperfusion. Their conclusions are reflected in the title of their work, "Exercise can promote coronary collateral development without improving perfusion of ischemic myocardium." In an attempt to relate their study to our investigation, we must consider several aspects. Previous works from this laboratory (Scheel et al., 1976a, 1980) have shown that collateral growth during the time period of Neill and Oxendine's investigation (1 to 2 months after Ameroid placement) has not reached full maturity. Retrograde flow measurements to the circumflex in our study were about 225 ml/min in the trained dogs (Fig. 1). In comparison, their retrograde flows averaged 35 ml/min in the 8-week Ameroid-occluded and trained animals.

On the other hand, it is encouraging to note that, in the study by Neill and Oxendine (1979), the exercise program, even though started early and ended during the rapid collateral growth period, produced an increased coronary reserve such that the metabolic demands, when raised (200 beats/min), appear to have been met. Thus, it seems that collaterals, following long-term coronary occlusion, can return a limited coronary reserve to the remaining viable myocardium. This coronary reserve also is increased by exercise training. However, a metabolic demand can be found which would require a coronary flow greater than can be met by the limits imposed by the collateral circulation.

In summary, our experiments show that the level...
of exercise used in this study did not significantly stimulate either collateral or coronary vascular growth in the normal beagle. We attribute this observation to the high coronary reserve inherent in the normal dog. Gradual coronary occlusion severely limits coronary reserve. However, some of the coronary reserve capacity was reestablished 3 months after implantation of the constrictor. Institution of an exercise program at that time had the effect of doubling the collateral growth (hence, coronary reserve) compared to the group of animals with occlusion but not exercised. The source of this collateral growth was by epicardial as well as intramyocardial (septal) collateralization. Thus, exercise can cause structural changes in coronary collateral vessels in animals with a reduced coronary reserve. This increased collateralization then could be protective of the collateral-dependent myocardium in times of a limited increase in metabolic demands.

**Appendix**

**Determinations of Coronary Reserve**

The average resting circumflex coronary flow can be related to maximum flow, as determined in this preparation, by dividing the maximum flow by 6.67 (Scheel et al., 1980). Average maximum circumflex flow from Table 2 can be obtained by dividing 100 by 0.41 = 244 ml/min (perfusion pressure = 100 mm Hg). Thus, resting circumflex flow is calculated as 36.6 ml/min (244/6.67). This value is within the range obtained by Cohen et al. (1978) in comparable beagles. The coronary reserve is about 207 ml/min (93.5 ml/min / 244/6.67 = 0.63). Thus, the coronary reserve to this vascular bed, if directly supplied and when supplied via collaterals, indicates that collateralization allows only 34% of the original reserve (46.134.7).

In dogs with occlusion and exercise, the collateral conductance to the circumflex increased to 2.26 (Fig. 1; resistance = 0.44 PRU). The maximum flow via collaterals now is 93.5 ml/min [100/(0.44 + 0.63)], and the coronary reserve 69.5 ml/min (93.5 - 24). This flow now constitutes 51.6% of the unoccluded vessel's coronary reserve (69.5/134.7).

Based on the vascular changes seen, it can be concluded that exercise raised the coronary reserve of the occluded vessel from 34% to almost 52% of its native ability, and that this increased reserve was due to an increase in collateral conductance.

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K W Scheel, L A Ingram and J L Wilson

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