Effect of Exercise on Cardiac Output, Left Coronary Flow and Myocardial Metabolism in the Unanesthetized Dog

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Studies of the cardiac response to the normal physiological stress of exercise have been centered around the measurement of cardiac output or left ventricular dimensions. In clinical studies on both normal and pathological subjects, the cardiac output is generally determined by the indicator dilution technique, yielding mean flow values over a period of time.1-4 In animal studies, measurements of the mean cardiac output during exercise have been obtained by the indicator dilution method or the Fick principle.5, 6 In addition, direct measurements of phasic cardiac output during exercise have been made with the ultrasonic flowmeter,7 and various devices on the ventricular wall have permitted the evaluation of ventricular dimensions.8

Hepps et al.9 reported briefly on the direct measurement of coronary blood flow during exercise but phasic flow values are not available. The present report deals with the simultaneous measurement of coronary blood flow during exercise and myocardial oxygen usage in the dog during moderate to relatively severe exercise.

Methods

The preliminary studies in 1959 and 1960 were performed on healthy greyhound dogs weighing 30 to 45 kg, and the later studies on mongrel dogs of 17 to 23 kg body weight. Prior to the surgical procedure, the animals were well-trained and conditioned to run on a treadmill at speeds up to 24 km per hour at an 11° grade. Under pentobarbital anesthesia and positive pressure respiration (Harvard respirator pump), a left thoracotomy was performed at the fifth intercostal space and the precardium opened posteriorly to the left phrenic nerve from the level of the great vessels to that of the inferior vena cava. The main left coronary artery was dissected free of all surrounding tissue and a flow transducer was applied. The main left coronary artery was of sufficient length to accommodate a flow probe in approximately one of three dogs. The left circumflex and anterior descending coronary arteries were dissected as close to their origins as possible, and in a region free from significant side branches, for installation of two pneumatic occlusive devices (fig. 1). Construction details on these cuffs will be published later.

When the main left coronary artery was not long enough to accept a flow probe, the left circumflex coronary artery was dissected close to its origin and a flow transducer installed. A second length of the same artery, 3 to 5 mm distal to the transducer, was prepared to accept a pneumatic occlusive cuff. A natural tissue bridge was maintained between the two dissected areas to keep the transducer and cuff physically separated. When this was not possible, a prosthetic bridge of Ivalon sponge was placed between the transducer and the cuff. A large flow transducer was fitted to the ascending aorta as close to the valves as possible, and a snug ring of Ivalon sponge placed on the central side of the transducer to prevent aortic rupture. A specially prepared indwelling plastic tubing was placed in the coronary sinus to permit sampling of blood.10 For the measurement of central aortic blood pressure, a plastic tubing was threaded down the left common carotid artery into the brachiocephalic artery and positioned with the tip at the level of the aorta. This catheter was constructed by covering a length of 1 mm I.D.
FIGURE 1
Pneumatic occlusive cuff. The device is placed around a blood vessel and held in place by two circumferential sutures. Left view shows the lumen of the deflated cuff. Air injection causes inflation and closure of the lumen (right view).

Surflene tubing* with a soft polyvinyl chloride sheath to prevent kinking. The soft PVC tubing extended 1.5 cm beyond the stiff Surflene at the aortic end. (Soaking the PVC tubing in ethylene dichloride for four to five minutes causes it to swell and slip easily over the Surflene. On drying, the fit is very snug and the two tubes are inseparable.)

The pericardium was then closed with interrupted stitches of 4-0 silk. All cables and tubes were directed posteriorly between the heart and the left lung, looped in place along the inner wall of the left posterior thoracic cavity and brought out through the chest incision. The chest was closed by repairing all layers independently, and any contained air was evacuated. The cables and tubes were directed subcutaneously toward the low neck and shoulder area. The external ends of the blood sampling catheters and occlusive cuffs were terminated by special stainless steel stopcocks (fig. 2) designed for chronic implantation. The transducer connectors and stopcocks were placed above and below the scapular bones. They did not appear to interfere with the animals, and no protective jacket or covering was necessary. Immediately after the injection or withdrawal. The outlet tubing of the coupler, equipped with side holes or "bird's eyes," depresses the ball and maintains the valve open. In use, the stopcock is installed with the skin of the animal between the base and the retaining ring. No special precautions are necessary and the device has remained functional for the duration of the experiments.

*ITT Surpreant Manufacturing Company, Clinton, Massachusetts.

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operation, 300 to 500 ml of saline were given intravenously.

Penicillin and streptomycin were administered at the time of general anesthesia, repeated postoperatively, then daily for five days, at which time the animals appeared to have completely recovered. There was no sign of infection. The blood pressure and coronary sinus catheters were flushed daily with saline, and the dead space filled with heparin. The flow transducers used in these experiments have been described previously. Their small size and low mass made it unnecessary to attach them to surrounding tissues. The method of calibration of the flowmeters has been published. The two flow amplifiers were of different carrier frequencies (400 and 1,000 cycles/sec) to eliminate all possibility of interference. The pneumatic occlusive devices were also very light and did not require attachment to the surrounding structures.

For blood pressure measurements, the central aortic catheter was connected via a three-way stopcock to a Statham P23Db strain gauge taped to the animal at the level of the heart. Arterial blood samples for oxygen determination were obtained by turning off the pressure gauge temporarily. Blood samples from the aorta and the coronary sinus were collected in lubricated heparin. The flow transducers used in these experiments have been described previously. Their small size and low mass made it unnecessary to attach them to surrounding tissues. The method of calibration of the flowmeters has been published. The two flow amplifiers were of different carrier frequencies (400 and 1,000 cycles/sec) to eliminate all possibility of interference. The pneumatic occlusive devices were also very light and did not require attachment to the surrounding structures.

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The data were recorded by an Electronics for Medicine DR-8 recorder. The heart rate was computed from the duration of each cardiac cycle. The left coronary flow per minute and the cardiac output per minute were derived from the integration with a planimeter of the area under the respective curves. Stroke coronary flow and stroke cardiac output were calculated as the respective quotients of the coronary flow per minute and the cardiac output per minute divided by the heart rate. The peripheral resistance was computed as the mean aortic blood pressure in mm Hg divided by the cardiac output in ml/min, and the coronary resistance as the mean aortic blood pressure in mm Hg divided by the coronary flow in ml/min. Myocardial oxygen usage was obtained by multiplying the coronary arteriovenous difference in ml oxygen per ml blood by the coronary flow per minute. This calculation is based on the findings of Olsson et al., that blood obtained from the coronary sinus is of the same chemical composition as that from the great cardiac veins. Left ventricular work was calculated as the product of the cardiac output in liters per minute and of the blood pressure in meters of water.

Exercise experiments generally started six to seven days postoperatively, at which time the dog was capable of effort nearly as intensive as before surgery. During the first ten to twelve postoperative days, however, the intensity of exercise was mild (up to 10 km/hr for 2 to 3 min). All runs on the treadmill were done at an 11° angle and were of two types: a) graded exercise in which the rate was increased in discrete steps, generally 4, 8, 12, 16 km/hr, depending on the tolerance of the dog, and, b) sustained heavy exercise in which the treadmill was brought rapidly to a speed of 12 to 16 km/hr within 10 to 15 seconds, again depending on the dog, and maintained at that speed until the dog appeared ready to stop.

Results

The results reported here are from eleven experiments on five dogs with flow transducers on the left circumflex coronary artery, and seven experiments on four dogs with transducers on the main left coronary artery.

The flow patterns of the main left and left coronary artery branch are not grossly different, and the response to exercise in the two vessels will not be treated separately. The resting patterns are very similar to those obtained previously. Briefly, the coronary flow decreases sharply and often approaches zero following the onset of isometric contraction. It then rises with ventricular ejection and reaches a spike in early systole. It levels briefly at peak systolic pressure and drops mildly but sharply during protodiastole, again to near zero, and, at times, below zero.

With the closure of the aortic valves, the coronary flow goes up rapidly to its maximum rate to decrease gradually with the fall in diastolic pressure.

In this study, the dogs did not perform similarly on the treadmill; even the same animal was not necessarily willing to do the same amount of work on two different days. The response to exercise, however, varied directly with the severity and the duration of the stress. Two representative experiments are selected to illustrate the results. Other experiments yielded the same pattern of response within the given speed and duration. The maximum treadmill speed for both the sustained heavy exercise and the graded exercise was 16 km/hr.

Figure 3 illustrates the continuous response to sustained heavy exercise. The experiment...
was performed on the eleventh postoperative day and flow was measured in the left circumflex coronary artery. Control values were obtained with the dog standing on the treadmill. A rate of exercise of 16 km/hr was reached in 12 seconds. The experiment was timed from the beginning of exercise which lasted 3 min and 25 sec. As exercise begins, the heart rate increases from 96 to 280 beats/min (300%) within 10 sec, then becomes essentially level. It rises slowly to 305 at 2 min, then declines gradually to 280 at 3 min, 20 sec. As the treadmill is stopped, it falls precipitously to 195, then descends gradually to a recovery value of 78 at 20 min. From a control of 110 mm Hg, the mean central aortic blood pressure dips mildly and transiently as exercise begins, then increases to 140 mm Hg at 12 sec. From there it rises slowly to 160 mm Hg at 2 min, and remains relatively stable until the end of exercise. Following the cessation of activity, it falls to 135 mm Hg within 5 sec, to rise again rapidly and fluctuate about 155 mm Hg for 1 min. It then declines gradually to a recovery level of 115 mm Hg.

The cardiac output and left circumflex coronary artery flow respond generally as the heart rate. As exercise begins, the cardiac output increases at a rate slightly slower than the heart rate, and from a control of 3.4 liters/min, reaches nearly 12 liters/min in 25 sec (350% increase). For the remainder of the experiment, the changes in cardiac output are parallel to those in the heart rate. The left circumflex coronary artery flow increases from a control of 26 ml/min to 108 ml/min (400%) within 20 sec of the start of exercise, and remains at this high level until the treadmill is stopped. It declines fairly rapidly during the first minute after exercise to 38 ml/min, then gradually reaches a recovery level of 27 ml/min.

The changes in stroke volume and stroke coronary flow during exercise are similar. The stroke volume decreases from a control of 36 ml to 29 ml (20%) within 8 sec of the start of exercise.
exercise, then increases rapidly to 39 ml at 20 sec (10%) and maintains this level for the duration of the run. When the treadmill is stopped, the stroke volume increases almost immediately to 46 ml (28% above control) then falls gradually. At 6 min, it is 30 ml (17% below control) and at recovery, it is 34 ml. The stroke coronary flow falls from 0.28 ml to 0.16 ml (43%) at 6 sec, then increases to 0.39 ml at 18 sec (39% above control). It remains between 0.36 to 0.39 ml during exercise. Within 8 sec after the end of exercise, it increases to 0.6 ml (66%). At 6 min, it is 0.21 ml (25% below the control), and at recovery, it is 0.28 ml.

Figure 4 shows selected sections of record from the same experiment. The curves are, from top to bottom, mean central aortic blood pressure, flow in the left circumflex coronary artery, and systemic cardiac output. Because of artifacts caused by the violent motion of the running animal, phasic changes of aortic blood pressure are unobtainable during exercise. The basic pattern of the coronary blood flow does not change greatly during exercise except for the disproportionate shortening of systole and diastole as the heart accelerates. The first dip following isometric contraction is elevated considerably while the second dip at protodiastole remains as low as during the control. This second dip is mildly and transiently higher following the end of exercise. Systolic volume flow increases significantly more than diastolic volume flow. The ratio of systolic flow to diastolic flow is 0.22 during the control, and 1.00 during peak exercise. The peak velocity of the stroke output increases to 150% of the control, while the ejection period decreases to 63%, resulting in a rather small increase in stroke volume. At the same time, the diastolic duration shortens to 22% of the control, yielding the large elevation in minute cardiac output.

Figures 5 and 6 illustrate the response to a graded exercise experiment performed on the seventh day postoperative. In this case, the main left coronary artery flow was measured. Again the control values were obtained with the dog standing on the treadmill, and the experiment was timed from the beginning of

**Figures 4**

Sections of record showing the changes in blood pressure, left circumflex coronary artery flow and cardiac output at selected moments during exercise. Vertical lines are 0.1 second time markers.
Graph illustrating the effect of graded exercise on heart rate, blood pressure, main left coronary artery flow, stroke coronary flow, cardiac output and stroke volume.

Sections of record illustrating the changes in blood pressure, main left coronary artery flow and cardiac output during graded exercise. Vertical lines are 0.1 second time markers.
exercise. Except for the degree of response, the changes are similar to those resulting from heavy exercise. Figure 5 shows definite increases of heart rate, central aortic blood pressure, flow in the main left coronary artery, and systemic cardiac output between the control and exercise steps of 4, 8, and 12 km/hr. The stroke coronary flow and stroke cardiac output follow the general pattern illustrated in figure 3 except that the initial changes at the onset of exercise are milder. Following the end of exercise, and during recovery, the changes are generally similar. Figure 6 shows the flow pattern in the main left coronary artery during the same experiment. The initial changes, although less abrupt, parallel those shown in figure 4, and an equilibration seems to be reached at 24 sec for the 4 km/hr step. A section of record at 24 sec is not shown since, at 58 sec, just before increasing the treadmill speed to 8 km/hr, the patterns are still the same. At 1 min, 50 sec, and 2 min, 50 sec, equilibration is reached for 8 and 12 km/hr, respectively. At 3 min, 3 sec, the exercise has just ended, and at 3 min, 50 sec, recovery has begun. At 10 min, there seems to be full return to control values.

The ratio of coronary flow to cardiac output does not change greatly during exercise except for a transient drop immediately after the beginning of exercise, and a slight increase following the end of exercise. In figure 3, the flow in the left circumflex coronary artery is about 1% of the control during the control. As exercise begins, it drops to 0.5% then readjusts rapidly to the control value for the duration of the stress. At the end of exercise, it increases briefly to 1.6% then returns to approximately 1% of the cardiac output. In figure 5, the main left coronary artery flow is 2.5% of the cardiac output throughout, except at the start and end of exercise when it drops to 1.8% and rises to 3.1% of the cardiac output, respectively. The ratios of coronary flow to cardiac output for the other experiments of this study are in accord with the values mentioned above.

**METABOLIC STUDIES**

Simultaneous metabolic studies were performed in nine experiments on five dogs. Blood samples were collected during the control period just prior to exercise, as definite changes in the hemodynamic response became apparent during exercise, and after recovery, generally 10 to 20 min following the end of exercise. The control values vary slightly from day to day in the same animal because it was difficult to control various environmental conditions causing slight excitement. The oxygen usage increases rapidly and considerably during exercise.

Table 1 illustrates the results of a typical graded exercise experiment. The oxygen usage increases progressively with the rate of exercise. From a control of 5.1 ml/min, it rises to 10.6 ml/min for the 3 km/hr exercise rate, 12.9 ml/min for 6 km/hr, 16.2 ml/min for 9 km/hr, and 19.2 ml/min for 12 km/hr. Once equilibration to a given rate of exercise is reached, total time of exercise does not appear to account for further increase in oxygen utilization.

<table>
<thead>
<tr>
<th>Time</th>
<th>Condition</th>
<th>Hematocrit</th>
<th>Coronary sin oxygen</th>
<th>Coronary A-V oxygen</th>
<th>Coronary oxygen usage</th>
<th>Percentage oxygen extraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:0</td>
<td>Control</td>
<td>43</td>
<td>4.97</td>
<td>14.12</td>
<td>5.08</td>
<td>74</td>
</tr>
<tr>
<td>0:45</td>
<td>3 km/hr</td>
<td>44</td>
<td>4.25</td>
<td>15.29</td>
<td>10.60</td>
<td>78</td>
</tr>
<tr>
<td>1:45</td>
<td>3 km/hr</td>
<td>43</td>
<td>4.00</td>
<td>15.31</td>
<td>10.56</td>
<td>79</td>
</tr>
<tr>
<td>4:00</td>
<td>6 km/hr</td>
<td>45</td>
<td>3.90</td>
<td>16.31</td>
<td>12.88</td>
<td>81</td>
</tr>
<tr>
<td>6:00</td>
<td>9 km/hr</td>
<td>46</td>
<td>3.78</td>
<td>16.88</td>
<td>16.20</td>
<td>82</td>
</tr>
<tr>
<td>7:30</td>
<td>12 km/hr</td>
<td>48</td>
<td>3.10</td>
<td>18.24</td>
<td>19.15</td>
<td>85</td>
</tr>
<tr>
<td>11:30</td>
<td>Recovery</td>
<td>45</td>
<td>3.04</td>
<td>17.62</td>
<td>6.94</td>
<td>85</td>
</tr>
<tr>
<td>24:00</td>
<td>Recovery</td>
<td>43</td>
<td>4.37</td>
<td>14.23</td>
<td>4.55</td>
<td>76</td>
</tr>
</tbody>
</table>
No attempt was made to push the dogs to exhaustion. The coronary oxygen usage reaches 10.6 ml/min after 45 sec, at 3 km/hr, and remains unchanged after 1 min, 45 sec, at the same rate. In the sustained stress experiment (figs. 3 and 4), the oxygen usage rises from 3.6 to 15.8 ml/min in approximately 30 sec. As the heavy exercise continues, the oxygen utilized by the myocardium rises further to reach 21 ml/min at 2 min. It oscillates between 21 and 22 ml/min until the end of exercise when it returns gradually to the control value. All experiments yielded a very similar pattern of response except that the degree of exercise influenced the magnitude of change.

Discussion

In the experiments reported here, special precautions were taken to avoid the effects of excitement. The dogs were reasonably well-trained to stand at rest on the treadmill or to run in step with the belt speed. At that time, the heart rate was taken as an index of relative rest. During the experiments, efforts were made to avoid all sudden motions and sharp noises. All the required sensing and recording equipment was readied beforehand in order to shorten the length of time the animal would have to stand on the treadmill before the start of exercise. Although some degree of excitement must have diluted the results, we believe that a fairly good state of rest was obtained, as evidenced by the relatively low heart rate, cardiac output and myocardial oxygen usage during the control. Furthermore, following recovery, the measured parameters returned close to the control values.

At times, a slight drift in the coronary flow pattern occurred generally after the onset of exercise or immediately after the cessation of exercise. This instability appears to be caused by a change in transducer electrode to blood vessel contact, and has no effect on the sensitivity of the flowmeter. It is gradual and the values of coronary flow are correct provided frequent zeros are obtained. Zero flow was determined routinely every minute during the control measurements. The duration of vessel occlusion was only 0.2 to 0.3 sec, and the slight reactive hyperemia disappeared generally within 10 sec. In figures 4 and 6, the coronary flow zero does show a change in position due to this drift. When the flow in the main left coronary artery is measured, occlusion by pneumatic cuffs of the left circumflex and left descendens coronary arteries yields a baseline which is higher than true zero, since flow in the septal artery is intact. The zero thus-obtained is only a point of reference. According to Eckstein et al., and to unpublished observations by Sevelius in this laboratory, this reference zero was lowered by 9 to 16% to yield approximately true zero flow.

Our findings on cardiac output in the exercising dog are in general agreement with data already published. The cardiac output can increase by a factor of 4 or more during strenuous treadmill exercise. This increase is associated with cardio-acceleration; elevation in stroke volume seldom exceeds more than 10 to 15%. The slight transient drop in stroke volume as exercise begins appears to be a mechanical effect caused by the delay in the response of the cardiac output in relation to heart rate. It does not seem associated with systemic vasodilatation although the peripheral resistance decreases by 50% within 8 sec of the onset of exercise. Within the first 4 sec after the end of exercise, the peripheral resistance remains essentially unchanged while the stroke volume increases immediately but transiently, and the heart rate falls precipitously.

In our experience, anticipation of exercise did not produce significant cardiovascular changes. This could be the result of the special effort made to avoid stimulating the dogs during the control period of our experiments. The effects of the nervous system on the circulation have been reported. Stimulation of the sympathetic nerves is known to cause increased cardiac contractility and metabolism, and cardio-acceleration. Smith et al. have obtained responses analogous to those elicited by exercise stimulation of the hypothalamus. Exercise experiments performed on dogs with denervated hearts have
shown the important role of the nervous system in controlling the circulation.

As in the case of the cardiac output, most of the large increase in left myocardial flow during exercise is contributed by the high heart rate. The increase in stroke coronary flow is relatively mild. Figure 3 shows a 440% increase in the left circumflex coronary flow rate per minute during exercise while the stroke coronary flow increases by only 38%. Figure 5 illustrates a 280% increase in main left coronary flow per minute while the stroke coronary flow increases barely by 8%. In most of the experiments, the rise in stroke coronary flow was under 20%. The 38% cited above is the highest observed in these experiments.

The slight reduction of stroke coronary flow during the first 12 sec of exercise appears again to be caused by the lag of the left coronary flow behind the heart rate. At 4 sec of exercise (fig. 3) when the data indicate no change in coronary resistance, the stroke coronary flow is down by about 32%. At the end of exercise, the stroke coronary flow increases transiently by 60% with no significant change in coronary resistance. Concurrently, the heart rate drops from 280 to 180/min while the left coronary artery flow per min decreases by only 5 to 8%.

The extra oxygen used by the myocardium during exercise is supplied by both a widening of the coronary arteriovenous difference and an increase in flow per minute. Table 1 shows that the myocardial oxygen usage increases 275% during exercise. Changes of arteriovenous difference contribute only 30% of this increase; the remaining 245% is supplied by the increase of coronary flow. These values are representative for experiments measuring left circumflex coronary artery flow. In the case of the main left coronary artery, typical values are: 475% increase in myocardial oxygen usage, 25% supplied by increase in arteriovenous difference, 450% contributed by increase in coronary flow.

The percentage of oxygen extraction by the myocardium does not increase greatly during exercise. Table 1 shows an increase from 74 to 85%; the largest change observed in these experiments is from 75 to 89%. The added oxygen resulting in the widening of the arteriovenous difference is made available by an increased hematocrit that appears to be the result of increased red cell concentration rather than fluid losses. Following splenectomy and a two-week recovery period in two animals, the red cell concentration did not vary by more than 2% during exercise and the amount of work the dogs were able to perform appeared lessened. For the same work before splenectomy, the hematocrit increased by 12 to 18%.

The level of oxygen in the coronary sinus blood, while the dog is standing at rest on the treadmill, varies from day to day. Values from 3.5 to 5 volumes per cent have been observed in these experiments. The coronary sinus oxygen content decreases with exercise. In the experiment illustrated in table 1, it decreases from 5 to 3 volumes per cent (40%). This change is representative; other experiments have shown decreases ranging from 38 to 50%.

The relationship between oxygen usage and coronary flow is linear as seen in figure 7 (left), a plot of eight separate experiments on four dogs. Figure 7 (right) shows that oxygen usage is also a linear function of left ventricular work. Here the points follow two separate lines because the calculated oxygen usage is necessarily larger when the main left coronary artery flow is measured. Since heart weights were not always recorded, the results cannot be expressed in terms of a standard mass of myocardium. However, all dogs used in these experiments were roughly of the same weight and stature. In three dogs the heart was weighed at autopsy, the left ventricles weighing 52, 53, and 57 g, respectively.

The close correlation between cardiac work, oxygen usage, and coronary flow indicates strongly that cardiac work is an important determinant of myocardial oxygen usage and that this oxygen demand regulates coronary flow. This is in accord with previous findings in the open-chest dog and in the intact anesthetized animal. The product of the heart rate by the blood pressure has also shown excellent correlation with myocardial
oxygen usage. In the experiments reported here, since the stroke volume is nearly constant, the product of blood pressure by heart rate is analogous to cardiac work.

Summary
Cardiac output, left coronary artery flow, central aortic blood pressure and myocardial metabolism have been studied in the intact unanesthetized dog during exercise. Cardiac output and left coronary artery flow increase 350 to 400% during moderately severe exercise. The primary mechanical determinant of this increase appears to be cardio-acceleration; the stroke volume and stroke coronary flow contribution is relatively mild. Myocardial oxygen usage increases 300% or more with only a small elevation of the percentage of extraction of oxygen. The large increase of coronary flow in the dog and the significant elevation in hematocrit supply the extra oxygen.

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