Blood flow to respiratory, cardiac, and limb muscles in dogs during graded exercise

DAVID E. FIXLER, JAMES M. ATKINS, JERE H. MITCHELL, AND LAWRENCE D. HORWITZ
Pauline and Adolph Weinberger Laboratory for Cardiopulmonary Research, Department of Internal Medicine and Department of Pediatrics, University of Texas Health Science Center, Southwestern Medical School, Dallas, 75235, and Department of Medicine, University of Texas Health Science Center, San Antonio, Texas 78284

MATERIALS AND METHODS

Animal preparation. Fourteen dogs, weighing 17-23 kg, were trained to run on a level treadmill. Each dog underwent a sterile thoracotomy under sodium pentobarbital anesthesia. An electromagnetic flow probe was placed around the ascending aorta. A solid-state pressure transducer (Konigsberg P18) was implanted within the left ventricle through a stab incision in the left anterior free wall. All catheters and wires were exteriorized at the back of the neck. The dogs were allowed 3 wk for recovery; none had arrhythmias or infections, and all could exercise at their preoperative levels when studies were performed. In two dogs, an additional catheter was inserted into the proximal aorta through the left carotid artery a few days before the experiments began. Left atrial pressures were measured through the implanted catheters with Statham P23 Db manometers. A zero reference for the solid-state left ventricular pressure transducers was obtained by assuming that left ventricular end-diastolic pressure was equal to the mean left atrial pressure at rest (12). Aortic flow was measured with a Zepeda EDP2 electromagnetic flowmeter; it was assumed that there was zero flow at end-diastole. Pressure and flow transducers were calibrated in vitro prior to and after implantation (12). In vivo calibrations of both pressure and flow transducers correlated closely with in vitro calibrations. Signals were recorded using a Beckman RM oscillograph.

Control measurements were obtained while the dogs stood quietly on the treadmill prior to the initial exercise period. Dogs ran for 3-4 min at preselected levels of mild and moderate exercise (11) on the level treadmill (0° grade). Mild exercise ranged from 3 to 4 mph and moderate exercise from 6 to 8 mph. Between exercise periods the dogs were allowed 5 min of rest.

Blood flow determinations. To measure organ blood flows, left atrial injections of radioactive microspheres (25 μm in diameter) labeled with 125I, 141Ce, 85Sr, and 46Sc were performed. These microspheres are mixed with the blood in the heart and are distributed in proportion to flow. Therefore, the amount of radioactivity entering an organ is proportional to its blood flow at the

with dynamic exercise, greater demands are made on a variety of muscles; limb musculature to increase locomotion, cardiac muscle to increase systemic and pulmonary flows, and respiratory musculature to increase ventilation. During very strenuous exercise, the metabolic costs of ventilation may demand up to 20% of the oxygen-transporting capacity and hence may be one of the factors limiting performance (3). Previous exercise studies have measured blood flow through coronary and limb vessels, but none has described flow changes in respiratory muscles (6, 9, 17, 18, 22). Therefore, the distribution of cardiac output among the various muscle groups during exercise is not known.

The purpose of this study was to simultaneously measure blood flow in many organs at rest and during two exercise levels using the radioactive microsphere technique (2, 7, 21). In this manner we were able to place in perspective the changes in flow to various muscle groups and organs at a series of exercise loads.

fixler, david e., james m. atkins, jere h. Mitchell, and lawrence d. horwitz. Blood flow to respiratory, cardiac, and limb muscles in dogs during graded exercise. Am. J. Physiol. 231(5): 1515-1519. 1976. — the distribution of cardiac output was analyzed in six dogs, with the animals at rest and running on a level treadmill for 3 min at 3-4 mph (mild exercise) and 3 min at 6-8 mph (moderate exercise). Organ flows were measured using 25-μm-diam radioactive microspheres. Cardiac output averaged 2.5, 4.6, and 5.7 liters/min, for rest, mild exercise, and moderate exercise, respectively. The greatest change was in diaphragmatic flow which increased by 216% with mild exercise and 500% with moderate exercise. Flow to intercostal muscles increased by 180 and 198%, to the exercising gastrocnemius muscle by 139 and 224%, and to cardiac muscle by 57 and 100% during mild and moderate exercise, respectively. Renal and cerebral flows did not change significantly. Significant decreases in flow occurred in the small and large intestines during moderate exercise. It is concluded that the increase in cardiac output during submaximal exercise was redistributed in a manner which limited flow to the brain, intestines, and kidneys and increased flow to the diaphragm, heart, and limb muscles.

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time of the microsphere injection (7, 21). To accurately measure organ flow, the microspheres must not pass through the capillary bed. To validate that this did not occur, two additional animals were anesthetized and catheters were placed in the jugular, renal, femoral, hepatic, and mesenteric veins. Blood was withdrawn from these catheters during microsphere injections. Injections were performed during basal conditions, hypoxia (\( \text{Po}_2 \) less than 45 mmHg), hypercarbia (\( \text{Pco}_2 \) greater than 60 mmHg), and isoproterenol infusion (0.5 \( \mu \text{g/kg per min} \)). The fraction of microspheres leaking through an individual organ was calculated by obtaining venous and arterial reference blood samples, as described by Archie and co-workers (2). Less than 1% of the microspheres entering an individual capillary bed leaked into the venous drainage. The only exception was a 4% leakage fraction under hypercarbic conditions for the region draining via the jugular vein; however, hypercarbia was not present in any of the exercise studies.

Blood flows were measured during the third minute of exercise when heart rate and cardiac output had stabilized in each of the animals. We injected approximately 500,000 microspheres into the left atrium from a small vial and flushed them in with 15 ml of warm saline over a period of 20 s. These numbers of microspheres resulted in at least 1,000 microspheres of each nuclide being present in the smallest tissue sample, with skin being the only exception. Although previous studies have documented satisfactory mixing of the microspheres with left atrial injections, we compared blood flows in the right and left kidneys to be certain adequate mixing had occurred (7). The animals reported here had less than a 15% difference in flows between the two kidneys. In those animals with aortic catheters, absolute organ flow was measured by the reference sample method (2, 7). Blood was withdrawn with a Holter pump from the aorta at a rate of 11 ml/min beginning just before the microspheres were injected and continuing for 90 s thereafter. Reference flow was measured directly from these timed volume collections. Since the microspheres are distributed to all arteries in proportion to flow, organ flow was determined from the equation: organ flow (ml/min) = [arterial reference flow (ml/min) \( \times \) organ nuclide activity]/[arterial reference nuclide activity].

In those animals in which an arterial reference sample was not obtained, we measured organ flow by determining the total amount of radioactivity injected and the proportion of radioactivity in the organ, according to the equation: organ blood flow (ml/min) = [cardiac output (ml/min) \( \times \) organ nuclide activity]/[injected nuclidic activity]. Organ flows are expressed in terms of flow per 100 g of tissue. Cardiac output was measured by the aortic flow probe and the electromagnetic flowmeter. To quantitate the radioactivity injected, the filled glass injector vials were counted with a gamma-well scintillation counter. The residual radioactivity in the vials was counted after each injection and subtracted from that present before the injection to determine the amount of radioactive nuclide injected. At the end of the experiment, each animal was killed and the organs of interest were removed. The organs were cleaned and weighed after removal of superficial fat. Organs of small volume, such as the heart, individual skeletal muscles, spleen, and adrenals were counted in their entirety. Larger organs such as the kidneys, intestines, liver, and brain were homogenized, and three 6- to 10- \( \mu \)g tissue samples from each organ were counted. The concentration of each nuclide in the three tissue samples did not differ by more than 10%, assuring satisfactory homogenization. The radioactivity emitted by each nuclide was determined by the method of Rudolph and Heymann (21), modified by changes in the constants used for differential spectrometry after calibration of the counting equipment. Because of the small number of animals, statistical comparisons were made by nonparametric analyses (two-tailed sign tests) (24).

**Estimation of vascular resistance.** In the dogs reported, mean arterial pressures were not measured because of difficulties in maintaining patency of small arterial catheters without altering flows in organs distal to the catheters. We subsequently measured mean arterial pressures in an additional seven dogs running according to the same exercise protocol and similarly instrumented. The mean arterial pressures in this group of animals were used to estimate resistances in the animals having measurements of organ flows. Resistance was calculated by dividing the average mean aortic pressure of the second group of animals by the average organ flow (ml/min per 100 g) of the flow study animals during rest and moderate exercise.

**RESULTS**

Of the 14 animals studied, 2 dogs had apparent cerebrovascular accidents during the microsphere injections, 2 had evidence of poor microsphere mixing, and 4 failed to complete the exercise protocol on the day of study. Therefore, the results presented here are from the six dogs completing the protocol and not having methodological problems. The mean hemodynamic measurements at various exercise levels are shown in Table 1. Heart rate increased from an average resting value of 111 ± 13 beats/min at 0.5 min at 3-4 mph to 177 ± 10 beats/min at 3-4 mph, 196 ± 9 beats/min at 6-8 mph. Cardiac output increased from 2.5 ± 0.3 liters/min to 4.6 ± 0.7 liters/min at 0.5 min at 3-4 mph, 5.7 ± 0.8 liters/min at 3-4 mph, and 5.7 ± 0.8 liters/min at 6-8 mph. Stroke volume increased from 27 ± 3 ml to 31 ± 3 ml at 0.5 min at 3-4 mph, 33 ± 4 ml at 3-4 mph, 55 ± 4 ml at 0.5 min at 3-4 mph, and 55 ± 4 ml at 3-4 mph. Systolic pressure increased from 113 ± 4 mmHg to 137 ± 3 mmHg at 0.5 min at 3-4 mph, 156 ± 6 mmHg at 3-4 mph, and 156 ± 6 mmHg at 6-8 mph. Diastolic pressure increased from 5 ± 1 mmHg to 5 ± 1 mmHg at 0.5 min at 3-4 mph, 7 ± 1 mmHg at 3-4 mph, and 7 ± 1 mmHg at 0.5 min at 3-4 mph.

**Table 1. Hemodynamic findings at different exercise levels**

<table>
<thead>
<tr>
<th>No. of measurements</th>
<th>Rest</th>
<th>Mild (0.5 min at 3-4 mph)</th>
<th>Moderate (3.5 min at 6-8 mph)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>111 ± 13</td>
<td>177 ± 10</td>
<td>196 ± 9</td>
</tr>
<tr>
<td>Cardiac output, liters/min</td>
<td>2.5 ± 0.3</td>
<td>4.6 ± 0.7*</td>
<td>5.7 ± 0.8*</td>
</tr>
<tr>
<td>Stroke vol, ml</td>
<td>27 ± 3</td>
<td>31 ± 3</td>
<td>33 ± 4*</td>
</tr>
<tr>
<td>LV systolic pressure, mmHg</td>
<td>113 ± 4</td>
<td>137 ± 3*</td>
<td>156 ± 6*</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mmHg</td>
<td>5 ± 1</td>
<td>5 ± 1</td>
<td>7 ± 1</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 (significant change from rest value).
value of 111 ± 13 (SE) to 177 ± 10 beats/min with mild exercise and to 196 ± 9 beats/min with moderate exercise. Cardiac output rose from 2.5 ± 0.3 to 4.6 ± 0.7 and 5.7 ± 0.8 liters/min with mild and moderate exercise, representing increases of 86 and 129%, respectively. This increase in cardiac output was accomplished primarily by increasing heart rate; stroke volume increased 16 and 25% with mild and moderate exercise, respectively. Left ventricular systolic pressure increased at both levels. Mean aortic pressures measured in the second group of animals exercised according to the same protocol increased from 98.4 ± 6.1 mmHg at rest to 121 ± 7.0 mmHg with moderate exercise.

Average organ blood flows at the various exercise levels are shown in Table 2. The greatest changes were seen in those muscle groups whose work loads were increased with exercise; that is, respiratory, limb, and cardiac musculature (Fig. 1). With mild and moderate exercise, flow to the diaphragm increased by 275 and 500%, respectively, and flow to the intercostal musculature increased by 160 and 186%. Total coronary flow increased 16 and 25% with mild and moderate exercise, flow to the right ventricular myocardium increased by 71 and 121% compared to 71 and 115% increases to the left ventricular myocardium. Flow to the gastrocnemius muscle increased by 153 and 224% with mild and moderate exertion. Figure 2 shows changes in blood flows to many organs at moderate exercise expressed as percent change from each animal's own resting value. The only organs where flow fell significantly were the small and large intestines during moderate exercise. Cerebral and renal flows remained near control values at both levels of exercise.

Estimated systemic vascular resistance (mmHg/liter per min) decreased from 39.4 at rest to 21.3 with moderate exercise. Figure 3 shows the overall changes which occurred in vascular resistances of the individual organs during moderate exercise. Resistance fell substantially in the exercising muscle groups, i.e., heart, diaphragm, intercostal and gastrocnemius musculature and tended to increase in the cerebral, renal, and intestinal vasculatures.

**Table 2. Flows**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Rest</th>
<th>Mild</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>77 ± 10</td>
<td>121 ± 15*</td>
<td>161 ± 26*</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>16 ± 3</td>
<td>60 ± 6*</td>
<td>96 ± 18*</td>
</tr>
<tr>
<td>Intercostal muscle</td>
<td>15 ± 4</td>
<td>39 ± 5*</td>
<td>43 ± 8*</td>
</tr>
<tr>
<td>Gastrocnemius muscle</td>
<td>17 ± 3</td>
<td>43 ± 9*</td>
<td>55 ± 14*</td>
</tr>
<tr>
<td>Brain</td>
<td>62 ± 3</td>
<td>61 ± 6*</td>
<td>58 ± 3</td>
</tr>
<tr>
<td>Renal</td>
<td>347 ± 54</td>
<td>286 ± 35</td>
<td>313 ± 69</td>
</tr>
<tr>
<td>Small intestine</td>
<td>46 ± 7</td>
<td>33 ± 4</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>Large intestine</td>
<td>68 ± 15</td>
<td>36 ± 4</td>
<td>41 ± 10*</td>
</tr>
<tr>
<td>Spleen</td>
<td>122 ± 29</td>
<td>103 ± 48</td>
<td>128 ± 14</td>
</tr>
<tr>
<td>Liver (via hepatic artery)</td>
<td>21 ± 11</td>
<td>16 ± 2</td>
<td>24 ± 9</td>
</tr>
<tr>
<td>Adrenals</td>
<td>218 ± 32</td>
<td>251 ± 24</td>
<td>268 ± 27*</td>
</tr>
<tr>
<td>Tongue</td>
<td>29 ± 17</td>
<td>43 ± 13</td>
<td>53 ± 8</td>
</tr>
<tr>
<td>Skin</td>
<td>10 ± 2</td>
<td>7 ± 2</td>
<td>8 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < 0.05 (significant change from rest value).

**DISCUSSION**

The purpose of this study was to measure changes in blood flow to respiratory, limb, and cardiac muscle, and other individual organs during graded exercise stress. There is ample evidence that local metabolic factors induce vasodilatation in the exercising muscle (10, 13, 14, 22, 26), which is not overridden by sympathetic vasoconstriction (18, 23). In addition, several investigators have concluded that sympathetic nervous system stimulation causes vasoconstriction during exercise in the gastrointestinal tract (28), kidneys (16, 29), and inactive skeletal muscle (6, 17). Because our methodology permitted simultaneous measurement of regional flow throughout the body, we have been able to provide a comprehensive description of the manner in which cardiac output is redistributed during submaximal exercise.

Although it is well known that the vascular beds of limb and cardiac muscle may regulate flow in accordance with their workloads, little information is available describing blood flow changes in respiratory muscles. Recently, Rochester (19) measured diaphragmatic blood flow in anesthetized dogs by the Kety-Schmidt technique using intravenous infusion of krypton 85. Diaphragmatic blood flow averaged 20 ml/min per 100 g during quiet breathing. During CO2-induced hyperventilation, a 100% increase in minute ventilation was associated with only a 13% increase in diaphragmatic...
blood flow, but a 40% increase in diaphragmatic oxygen consumption, indicating that as the diaphragmatic workload increases, oxygen delivery is augmented by both greater blood flow and oxygen extraction.

The greatest increase in organ perfusion during exercise occurred in muscles involved with respiration, the diaphragm, and intercostals. In the present study of conscious dogs, resting diaphragmatic flow averaged 16 ml/min per 100 g and increased by 500% during moderate exercise. Presumably this indicates a large increase in oxygen delivery to the diaphragm. Although the absolute changes in flow to the diaphragm were small (from 11 ml/min at rest to 67 ml/min during moderate exercise), the relative increase in diaphragmatic flow was substantially larger than those in the exercising gastrocnemius or cardiac muscles (Fig. 1). Flow changes to the intercostal musculature paralleled those seen in limb muscle. These data indicate that with submaximal exercise the increased work of breathing distributed a greater fraction of respiratory muscle flow to the diaphragm.

Although flow was redistributed toward respiratory, limb, and cardiac musculature, there were no changes or minimal changes in flow to the brain, kidney, spleen, liver (hepatic artery), and skin. Only in the intestines did significant decreases in flow occur. Flow to the tongue increased over 90%, which may reflect this organ's thermoregulatory role in the dog (1).

Under basal conditions, the distribution of cardiac output reflects the integrated response of vascular resistances in various organs. With exercise, cardiac output increases significantly, and regional perfusion is determined by adjustment of the vascular resistances. In this study we were unable to measure mean arterial pressures in the animals having organ flow determinations because multiple arterial catheterizations interfere with distal organ flows. Therefore, we used the mean arterial pressure values from a separate group of animals performing an identical exercise protocol to estimate gross changes in organ vascular resistances. Mean arterial pressure increased from 98 ± 6 mmHg at rest to 121 ± 7 mmHg with moderate exercise. These changes are similar to those reported by others (15, 27). In our study, during moderate exercise resistance apparently fell substantially in the respiratory, locomotor, and cardiac musculature. The fall in resistances to active muscle can be attributed to local metabolic effects (10). Resistance apparently rose in the brain, kidney, and intestines. Our results showing that renal vascular resistance increases during exercise is in agreement with other investigators (4, 16). The results showing significant falls in intestinal flows are at variance with measurements of mesenteric arterial flow recorded with ultrasonic flowmeters (25) but agree with dye-dilution determinations of intestinal flow in humans (28). We observed an apparent rise in resistance in the skin during exercise: in species which use the skin for heat dissipation, such as man, there may be a difference in cutaneous flow patterns.

Because our methodology permitted simultaneous measurement of regional flow throughout the body, we have been able to provide a comprehensive description of the manner in which cardiac output is redistributed during submaximal exercise. The effect of the heterogeneous alterations in organ resistances is to redistribute the cardiac output. During running, large quantities of blood were directed toward the respiratory and locomotor musculature and away from such organs as the intestines, kidneys, brain, and skin. The largest increase in flow occurred in respiratory musculature, confirming the high workload associated with ventilation during exercise.

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