Regulation of Myocardial Blood Flow by Oxygen Consumption Is Maintained in the Failing Heart During Exercise

Jay H. Traverse, Peter Melchert, Gordon L. Pierpont, Bryan Jones, Melanie Crampton, Robert J. Bache

Abstract—The hemodynamic abnormalities and neurohumoral activation that accompany congestive heart failure (CHF) might be expected to impair the increase in coronary blood flow that occurs during exercise. This study was performed to determine the effects of CHF on myocardial oxygen consumption and coronary blood flow during exercise. Coronary blood flow was measured in chronically instrumented dogs at rest, during 2 stages of graded treadmill exercise under control conditions (n=10), and after the development of CHF produced by 3 weeks of rapid ventricular pacing (n=9). In the normal dogs, coronary blood flow increased during exercise in proportion to the increase in the heart rate×the left ventricular systolic blood pressure product (RPP). After the development of CHF, resting myocardial blood flow was 25% lower than normal (P<0.05). Myocardial blood flow increased during the first stage of exercise, but then failed to increase further during the second stage of exercise despite an additional increase in the RPP. Myocardial oxygen consumption during exercise was significantly lower in animals with CHF and paralleled coronary flow. Despite the lower values for coronary blood flow in animals with CHF, there was no evidence for myocardial ischemia. Thus, even during the second level of exercise when coronary flow failed to increase, myocardial lactate consumption continued and coronary venous pH did not fall. In addition, the failure of coronary flow to increase as the exercise level was increased from stage 1 to stage 2 was not associated with a further increase in myocardial oxygen extraction. Thus, cardiac failure was associated with decreased myocardial oxygen consumption and failure of oxygen consumption to increase with an increase in the level of exercise. This abnormality did not appear to result from inadequate oxygen availability, but more likely represented a reduction of myocardial oxygen usage with a secondary decrease in metabolic coronary vasodilation. (Circ Res. 1999;84:401-408.)

Key Words: heart failure ■ exercise ■ blood flow ■ oxygen consumption

Congestive heart failure (CHF) is associated with neurohumoral and hemodynamic alterations that might impair the response of the coronary circulation to exercise. For example, in the normal heart, activation of the sympathetic nervous system during exercise acts to limit the increase in coronary blood flow by opposing metabolic vasodilation.1,2 This effect could be of greater importance in CHF because of the generalized increase in adrenergic vasoconstrictor activity.3,4 Coronary vasodilation might also be impaired by the elevated levels of angiotensin II and endothelin-1 that exist in CHF.5 Hemodynamic alterations that accompany CHF could also impair the ability to increase coronary blood flow during exercise. Thus, the decrease in aortic pressure and increase in left ventricular diastolic pressure in CHF result in a decrease in perfusion pressure across the coronary vascular bed. Finally, there is evidence that endothelium-dependent vasodilation is impaired in CHF.6,7

Failure of coronary blood flow to increase adequately during exercise could limit myocardial oxygen availability, thereby impairing cardiac performance. However, studies of myocardium isolated from failing ventricles have demonstrated reductions of energy expenditure that might result in decreased myocardial oxygen demands during exercise.8,9 Consequently, this study was performed to determine the effect of CHF on coronary blood flow and myocardial oxygen consumption during exercise. Measurements were obtained in chronically instrumented dogs during control conditions and after the development of pacing-induced cardiac failure.

Materials and Methods

Studies were carried out in 13 adult mongrel dogs weighing 25 to 30 kg trained to run on a motor-driven treadmill. All studies were performed in accordance with the “Position of the American Heart Association on Research Animal Use” and were approved by the Animal Care Committee of the University of Minnesota.

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Measurements were repeated and the treadmill was stopped. Then increased to 6.4 km/h at 0% grade. Three minutes later all coronary venous blood samples obtained. The treadmill speed was begun at 3.2 km/h at 0% grade. Three minutes after the onset of exercise, they were allowed to rest for 1 hour before the second exercise stage was performed. The dogs were then exercised at a speed of 6.4 km/h at 0% grade, and hemodynamics measurements, blood gases, and myocardial blood flow were repeated as described above.

**Surgical Preparation**

Animals were premedicated with acepromazine (10 mg IM), anesthetized with sodium pentobarbital (30 to 35 mg/kg IV), intubated, and ventilated with room air supplemented with oxygen to maintain arterial blood gases in the physiological range. A left thoracotomy was performed in the fifth intercostal space. A heparin-filled polyvinyl chloride catheter (3.0 mm OD) was introduced into the left thoracic artery and advanced until the tip was positioned in the ascending aorta. The pericardium was opened, and the heart was suspended in a pericardial cradle. A second catheter was placed into the left atrium through the atrial appendage and secured with a purse-string suture. A similar catheter was introduced into the right atrium, manipulated into the coronary sinus ostium, and advanced until the catheter tip could be palpated in the great cardiac vein at the origin of the anterior interventricular vein to permit venous blood sampling from the myocardial region perfused by the left anterior descending coronary artery (LAD). A fluid-filled catheter and a high-fidelity Konigsberg micromanometer were placed in the left ventricle at the apex and secured in place. The proximal LAD was dissected free, and a Doppler velocity probe (Craig Hartley) was placed around the vessel. A heparin-filled silicone rubber catheter (0.3 mm ID) was introduced into the artery distal to the occluder. Finally, a unipolar epicardial pacing lead (Medtronic Inc) was screwed into the right ventricle, and the pericardium was then loosely closed. All catheters and electrical leads were tunneled subcutaneously to exit at the base of the neck. The thoracotomy was closed in layers and evacuated of air. A programmable pacing generator modified to allow rapid pacing (Medtronic 5385) was placed in a subcutaneous pocket in the lateral chest wall and connected to the pacing lead. Catheters were flushed daily with heparin to maintain patency and were protected with a nylon vest.

**Experimental Protocol**

**Exercise Responses in the Normal Heart**

After allowing 7 to 10 days for recovery from surgery, the animals were returned to the laboratory for control measurements. The aortic and left ventricular pressures were measured with pressure transducers (Spectramed model TNF-R) at midchested level. The Konigsberg micromanometer was calibrated to the fluid-filled left ventricular catheter. Pressure was recorded at normal and high gain for measurement of left ventricular end-diastolic pressure (LVEDP) and left ventricular (LV) dP/dt. Data were recorded on an 8-channel direct writing recorder (Coulbourn Instruments). The at rest hemodynamic and coronary blood flow control measurements were recorded with the dog standing quietly on the treadmill. For determination of myocardial oxygen consumption, aortic and coronary venous blood samples (2 mL each) were withdrawn anaerobically and maintained in iced syringes for blood gas analysis. Treadmill exercise was then begun at 3.2 km/h at 0% grade. Three minutes after the onset of exercise, hemodynamic measurements were obtained and aortic and coronary venous blood samples obtained. The treadmill speed was then increased to 6.4 km/h at 0% grade. Three minutes later all measurements were repeated and the treadmill was stopped.

**Production of CHF**

CHF was produced by rapid ventricular pacing. The day after completion of the baseline exercise studies, the pacemaker was activated and pacing was started at 220 beats per minute; pacing was continued at that rate or adjusted upward to a maximum of 250 beats per minute based on the progression of heart failure. Weekly assessments of hemodynamics and coronary blood flow were obtained with the dogs standing quietly in a sling in normal sinus rhythm 1 hour after the pacemaker had been deactivated. CHF was deemed to have developed when the resting LVEDP was >25 mm Hg or when the visual estimation of ejection fraction by 2-dimensional echocardiography was <25%.

**Exercise Responses in CHF**

On the day of study the pacemaker was deactivated, and 2 hours later the dogs were placed on the treadmill. Resting hemodynamic measurements were obtained, and aortic and coronary blood specimens were withdrawn for blood gas determination. In 6 of the animals, radioactive microspheres were administered into the left atrium for determination of myocardial blood flow. Exercise was then begun at 3.2 km/h. Hemodynamic data were recorded continuously, and 3 minutes after the onset of exercise, blood gases were obtained. A second injection of radioactive microspheres was administered into the left atrium, and exercise was continued for 2 more minutes. Because the animals appeared fatigued after the first stage of exercise, they were allowed to rest for 1 hour before the second exercise stage was performed. The dogs were then exercised at a speed of 6.4 km/h at 0% grade, and hemodynamics measurements, blood gases, and myocardial blood flow were repeated as described above.

**Measurement of Myocardial Blood Flow**

Myocardial blood flow was measured after the development of heart failure with the use of 15 μm-diameter microspheres labeled with 141Ce, 85Sr, 85Sr, 51Cr, 95Nb, or 46Sc (NEN Co). For each measurement, 3 × 106 microspheres were injected into the left atrium and flushed with normal saline. Microspheres were selected in order that the isotopes could be evenly distributed between interventions. A reference sample of arterial blood was obtained from the aortic catheter at a constant rate of 15 mL/min with a peristaltic pump beginning at the time of microsphere injection and continuing for 90 seconds. After completion of the exercise protocols, the animals were euthanized with an overdose of pentobarbital, and the heart was removed and fixed in 10% buffered formalin. After fixation, the left ventricle was separated from the atrium and right ventricle, and the epicardial vessels and fat were trimmed away. The left ventricle was then divided into 5 rings from base to apex. Each ring was subdivided into 6 anatomical regions with the use of a standard template. On the basis of previous staining of the LAD region, the anterior and septal regions were taken as the LAD perfusion territory. The weight of this region was used to calculate the Doppler flow measurements on a per gram basis. Specimens from LAD and non-LAD perfused regions were divided into epicardial and endocardial halves, weighed, and placed into vials for counting. Myocardial and blood reference specimens were counted in a gamma

**TABLE 1. Hemodynamics and Coronary Blood Flow in Normal and CHF Dogs**

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>CHF</th>
<th>Normal</th>
<th>CHF</th>
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<th>CHF</th>
<th>Normal</th>
<th>CHF</th>
<th>Normal</th>
<th>CHF</th>
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<tbody>
<tr>
<td><strong>Pressure</strong>, mm Hg</td>
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<tr>
<td><strong>LV Systolic</strong></td>
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<tr>
<td><strong>LV dP/dt, mm Hg/s</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Normal</strong></td>
<td>102±5</td>
<td>65±4</td>
<td>116±4</td>
<td>140±5</td>
<td>120±5</td>
<td>105±5</td>
<td>8±1</td>
<td>28±2</td>
<td>2260±120</td>
<td>1520±150‡</td>
</tr>
<tr>
<td><strong>EX-1 (3.2 km/h)</strong></td>
<td>116±4†</td>
<td>89±4†</td>
<td>161±6†</td>
<td>167±7†</td>
<td>141±4†</td>
<td>112±5†</td>
<td>11±1†</td>
<td>32±2†</td>
<td>3260±200†</td>
<td>1830±120†</td>
</tr>
<tr>
<td><strong>EX-2 (6.4 km/h)</strong></td>
<td>128±4†‡</td>
<td>99±3*†‡</td>
<td>194±8‡‡</td>
<td>185±5‡‡</td>
<td>156±3‡‡</td>
<td>122±3‡‡</td>
<td>15±1*†</td>
<td>33±1*†</td>
<td>3860±210‡‡</td>
<td>2080±110*†</td>
</tr>
</tbody>
</table>

Normal group (n=10). CHF indicates heart failure group (n=9).

*P<0.05 vs Normal.

†P<0.05 vs Normal.

‡P<0.05 vs EX-1.
TABLE 1. Continued

<table>
<thead>
<tr>
<th>Coronary Blood Flow, mL/min</th>
<th>Triple Product×10⁶</th>
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<tbody>
<tr>
<td>Normal</td>
<td>CHF</td>
</tr>
<tr>
<td>48±4</td>
<td>28±2*</td>
</tr>
<tr>
<td>72±6†</td>
<td>36±4†</td>
</tr>
<tr>
<td>91±8‡</td>
<td>38±3†</td>
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spectrometer (Packard Instrument Co) at window settings corresponding to the peak energies of each radionuclide. The activity in each energy window was corrected for background and overlapping counts between isotopes. Blood flow to each myocardial specimen (Qm) was computed using the formula Qm = Qr × Cm/Cr, where Qr is the reference blood flow rate (mL/min), Cm is the counts per minute of the myocardial specimen, and Cr is counts per minute of the reference blood specimen. Coronary blood flow (mL/min) in the LAD was determined as the sum of blood flow in all regions identified in the LAD perfusion bed divided by the weight of the LAD perfusion area.

Determination of Myocardial Oxygen Consumption

Blood samples from the aorta and anterior interventricular vein were analyzed for oxygen content with a blood gas analyzer (Instrumentation Laboratory Model 113). Blood samples were maintained on ice in heparinized syringes until completion of the exercise study. Blood oxygen content (mL/100 mL) was calculated as (0.0136 hemoglobin×%O₂ saturation)+(P0₂×0.0031). Oxygen consumption on a per gram basis in the LAD myocardial region (MVo₂) was calculated as myocardial blood flow multiplied by the arteriovenous difference in oxygen content.

Measurement of Lactate

Coronary artery and venous lactate levels were measured in 4 dogs before and after the development of CHF at rest and during each stage of exercise. Blood was collected (2 mL) in tubes containing 2 mol/L perchloric acid and processed according to the method of Hohorst.11

Data Analysis

Heart rate, pressures, and coronary velocity were measured directly from the strip chart recordings. The triple product was defined as heart rate×left ventricular systolic pressure×LV dP/dt. Coronary blood flow in the LAD was calculated from the Doppler frequency shift (kHz) with the equation q=2.5×d²×f, where q is coronary blood flow in mL/min, d is the internal diameter of the artery in mm, and f is the Doppler frequency shift measured in kHz.12 Because the velocity probe is tightly adherent to the coronary artery in chronically instrumented animals, the external diameter of the artery is fixed and equal to the internal diameter of the flow probe. The internal diameter of the artery was taken as 80% of the probe diameter.12 Coronary vascular resistance was calculated as (mean aortic pressure−LVEDP)/myocardial blood flow (MBF). Resistance units were expressed as mm Hg·mL⁻¹·min⁻¹·g⁻¹ of myocardium. Data were compared within and between normal and CHF groups by ANOVA for repeated measures; a value of P<0.05 was required for statistical significance. When a statistically significant result was found, individual comparisons were performed using the Wilcoxon signed-rank test. Data are expressed as mean±SEM.

Results

Hemodynamic Measurements

Hemodynamic data at rest and during exercise in 10 animals during baseline conditions are shown in Table 1. During resting conditions, the mean heart rate was 116±4 beats/min, mean aortic pressure was 102±5 mm Hg, left ventricular systolic pressure was 120±5 mm Hg, and left ventricular end diastolic pressure (LVEDP) was 8±1 mm Hg. Heart rate, aortic pressure, left ventricular systolic pressure, and LV dP/dt increased from rest to the first stage of exercise, with an additional increase during the second exercise stage (each P<0.05). LVEDP increased from rest to the first exercise stage with no further change during stage 2 exercise.

Hemodynamic data of 9 animals with CHF at rest and during exercise are shown in Table 1. Six of these animals were included in the normal group before pacing. After the development of CHF, the resting heart rate during sinus rhythm was significantly faster than during control conditions, while mean aortic pressure, left ventricular systolic pressure, and LV dP/dt were significantly <control (each P<0.05). LVEDP at rest increased from 8±1 mm Hg during control conditions to 28±2 mm Hg after the development of CHF (P<0.01). In response to exercise, heart rates increased to values that were not significantly different from control exercise. Mean aortic pressure increased significantly in response to exercise, but remained less than during control conditions (P<0.05). Similarly, left ventricular systolic pressure and LV dP/dt during exercise were significantly less after the development of CHF. As a result, the triple product was less during exercise after the development of CHF (P<0.05).

![Figure 1](http://circres.ahajournals.org/content/403/3/403/F1.large.jpg)

**Figure 1.** Analog recordings of hemodynamics in 1 dog standing on the treadmill and during 2 stages of exercise before and after the development of CHF. AoP indicates mean aortic pressure; LVP, left ventricular pressure; and CBF, phasic and mean coronary blood flow measured in the LAD artery using a Doppler velocity probe. During control conditions, there was a significant increase in CBF in response to increasing levels of treadmill exercise. After the development of CHF, CBF failed to increase from EX-1 to EX-2 despite an increase in the product of the heart rate and left ventricular systolic pressure.
Coronary Blood Flow

Blood flow measurements obtained with the coronary Doppler probe at rest and during exercise under control conditions and after the development of CHF are shown in Table 1. During control conditions, mean blood flow at rest was 48.2 ± 4 mL/min at a double product of 13.9 ± 0.6 × 10² and a triple product of 31.6 ± 2.3 × 10⁵. Blood flow increased linearly with respect to the double and triple products during exercise to a maximum of 91 ± 8 mL/min at a double product of 30.4 ± 1.8 × 10⁵ and a triple product of 118.1 ± 10.1 × 10⁶.

After the development of CHF, coronary blood flow was significantly less than control at rest and during each stage of exercise (Table 1, Figure 1). Blood flow at rest was 28 ± 2 mL/min and increased significantly during the first stage of exercise to 36 ± 4 mL/min. Despite significant increases in heart rate and the triple product during the second stage of exercise, blood flow was unchanged compared with the first stage of exercise (38 ± 3 mL/min).

Distribution of Myocardial Blood Flow in CHF

Radioactive microspheres were administered for determination of myocardial blood flow after the development of CHF in 6 dogs (Table 2). Myocardial blood flow in the subendocardium and subepicardium increased significantly from rest to exercise stage 1 but then failed to increase further during exercise stage 2. The ratio of subendocardial/subepicardial (ENDO/EPI) flow was not different from unity at rest (1.04 ± 0.04) and did not change significantly during exercise. Both resting and exercise END/EPI values were significantly less than previously reported from this laboratory in normal dogs at rest and during similar levels of exercise.¹³

LV Weight and Echocardiographic Dimensions

The total heart weight was 185 ± 10 g. The left ventricular weight was 101 ± 5 g while the left ventricular weight to body weight ratio was 5.2 ± 0.3 g/kg. Echocardiographic dimensions were obtained in 4 dogs with CHF while in normal sinus rhythm. The left ventricular end-diastolic diameter was 4.4 ± 0.1 cm, and the end-systolic diameter was 3.7 ± 0.1 cm. Posterior wall thickness was 0.9 ± 0.1 cm.

Coronary Vascular Resistance

During resting conditions, coronary vascular resistance in normal dogs was 69 ± 6 mm Hg · mL⁻¹ · min⁻¹ · g⁻¹ and decreased linearly as a function of heart rate with exercise to a minimum of 44 ± 3 mm Hg · mL⁻¹ · min⁻¹ · g⁻¹ during the second stage of exercise (P<0.05). In dogs with CHF, coronary vascular resistance at rest was significantly less than normal (60 ± 9 mm Hg · mL⁻¹ · min⁻¹ · g⁻¹; P<0.05). Coronary resistance decreased significantly during the first stage of exercise in dogs with CHF to 46 ± 7 mm Hg · mL⁻¹ · min⁻¹ · g⁻¹ but failed to decrease further when the level of exercise was increased to stage 2 (48 ± 5 mm Hg · mL⁻¹ · min⁻¹ · g⁻¹). Coronary resistance values were not significantly different between normal and CHF measurements during either level of exercise.

Myocardial Oxygen Consumption

Myocardial oxygen consumption (MV̇O₂) determined in the same 6 animals during control conditions and after the development of CHF is shown in Table 3. Under control conditions, MV̇O₂ increased linearly as a function of the triple product from 136 ± 16 at rest to a maximum 316 ± 34 μL O₂ · min⁻¹ · g⁻¹ during the heaviest level of exercise. The increase in oxygen consumption resulted from both the increase in coronary blood flow as well as an increase in myocardial oxygen extraction, with a decrease in coronary venous PO₂ from 22 mm Hg at rest to 16 mm Hg during exercise (P<0.05). After the development of CHF, myocardial oxygen consumption was significantly reduced compared with control at rest and during both levels of exercise (Table 3, each P<0.05). In addition, although MV̇O₂ increased significantly from rest to the first stage of exercise (P<0.05), there was no further increase as the level of exercise was increased to stage 2 (Figures 2 and 3).

Baseline hemoglobin at rest in the normal animals was 11.0 ± 0.7 g · dL⁻¹ and was not significantly different in CHF. During exercise, there was a small nonsignificant increase in hemoglobin in normal animals and after the development of heart failure. Coronary venous PO₂ was similar in normal and CHF hearts during resting conditions (Table 3). Coronary venous PO₂ tended to decrease less in response to exercise in hearts with CHF than in normal hearts, but this was associated with a smaller increment in oxygen consumption in the failing hearts. After the development of CHF, oxygen consumption during both stages of exercise was similar to the resting value in control hearts. At this similar level of O₂ consumption, coronary sinus PO₂ was lower in the failing hearts than in normal hearts (P<0.05; Figure 2). However, coronary venous PO₂ during exercise in CHF remained higher than the values in the normal hearts during exercise. To determine whether CHF altered the coupling between MV̇O₂ and coronary vasomotor activity, coronary blood flow was plotted against MV̇O₂. As shown in Figure 3, the relationship between coronary blood flow and MV̇O₂ was not altered by CHF.

Myocardial Lactate Uptake and Coronary Venous pH

Coronary arterial and venous lactate levels are shown in Table 4 and percent lactate extraction in Figure 2B. In normal animals, aortic lactate concentration increased in response to exercise, and lactate extraction occurred across the heart both at rest and during exercise. After the development of CHF, aortic lactate tended to increase more than normal during the second exercise stage, although this did not achieve statistical significance. Net lactate extraction by the heart occurred both

<table>
<thead>
<tr>
<th>TABLE 2. Subendocardial (ENDO) and Subepicardial (EPI) Blood Flow in CHF Dogs Measured With Radioactive Microspheres (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional Myocardial Blood Flow, mL · min⁻¹ · g⁻¹</td>
</tr>
<tr>
<td>Subendocardial</td>
</tr>
<tr>
<td>Rest</td>
</tr>
<tr>
<td>EX-1 (3.2 km/h)</td>
</tr>
<tr>
<td>EX-2 (6.4 km/h)</td>
</tr>
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</table>

*P<0.05 vs Rest.
at rest and during exercise after the development of CHF. Net lactate production was not observed in any animal during exercise after the development of CHF. Coronary venous pH was 7.38±0.01 in normal animals at rest and did not change significantly during exercise. Coronary venous pH was not significantly different from normal, either at rest or during exercise after the development of CHF.

**Discussion**

This study demonstrates that in the failing hearts both myocardial oxygen consumption during resting conditions and the response of oxygen consumption to exercise were substantially less than in normal hearts. The decrease in oxygen consumption was matched by a decrease in coronary blood flow with no change in oxygen extraction by the heart. The decreased coronary flow in the failing hearts did not result in evidence of myocardial ischemia during exercise, but rather appeared to be the result of a downward adjustment of myocardial oxygen demands. The implications and possible mechanisms for these differences between the normal and failing hearts are discussed below.

**Myocardial Blood Flow and Oxygen Consumption During Resting Conditions**

Past investigators have reported variable alterations of myocardial blood flow in human subjects and in animals with heart failure. Nitenberg et al. reported similar values for coronary blood flow in patients with dilated cardiomyopathy and in normal control subjects (1.0 versus 1.06 mL/min·g⁻¹ of myocardium). Coronary vascular resistance was significantly lower in the heart failure group while left ventricular end-diastolic pressure was higher; heart rate, mean arterial pressure, and myocardial oxygen consumption were not different between the groups. Similarly, Opherk et al. found no difference in the resting myocardial blood flow between patients with CHF and control subjects by use of the argon washout technique. In contrast, when the radiolabeled albumin microspheres were administered to patients with end-stage dilated cardiomyopathy undergoing cardiac transplantation, Parodi et al. reported a mean value for myocardial blood flow of 0.49 mL/min·g⁻¹. Although these measurements were made under general anesthesia, which might decrease MVO₂, the observed values are markedly less than measurements obtained in normal human subjects with the use of the inert-gas washout technique, positron emission tomography, or coronary-sinus thermodilution, which have consistently yielded values for myocardial blood flow greater than 0.8 mL/min·g⁻¹.

In contrast to these studies in which heart failure was associated with a decrease in coronary blood flow, Wilson et al. reported that MVO₂ was significantly increased in dogs with pacing-induced heart failure. This was a result of an increase in coronary blood flow compared with control with no change in myocardial oxygen extraction. However, that study used the coronary-sinus–thermodilution technique to measure blood flow. Results obtained with the thermodilution technique are critically dependent on the position of the catheter within the coronary vein. Although a stable catheter position can be maintained during several measurements in a single individual, measurements between individuals are fraught with difficulty.

In the present study, myocardial blood flow during resting conditions was lower after the development of CHF than normal. The response of oxygen consumption to exercise were also decreased. The implications and possible mechanisms for these differences between the normal and failing hearts are discussed below.

**Figure 2.** A. Coronary sinus PO₂ plotted as a function of myocardial oxygen consumption (MVO₂) at rest and during 2 stages of exercise (EX-1, EX-2) in the same 6 dogs before and after the development of CHF. There was no significant difference in resting coronary venous PO₂ between the control and CHF groups. Coronary venous PO₂ tended to decrease less in the CHF group compared with the control group during exercise. B. Percent lactate extraction plotted as a function of myocardial oxygen consumption (MVO₂) at rest and during 2 stages of exercise in the same 4 dogs before and after the development of CHF. Lactate extraction by the heart continued during exercise in the failing heart. Values are mean±SEM.
The onset of rapid ventricular pacing is associated with an increase in myocardial blood flow that, however, may not be sufficient to meet the increased metabolic demand produced by the increased heart rate, especially in the subendocardium. Thus, Helmer et al.²⁴ found a lesser increase of subendocardial blood flow in the ventricular region near the pacing site, and this was the region that demonstrated persistent dysfunction when the pacing was discontinued. In addition, morphological studies have demonstrated structural changes similar to those associated with ischemia, including interstitial edema and disruption of collagen fibers in the subendocardium.²⁵ In a preliminary study, Lozano et al.²⁶ reported that the increases in myocardial blood flow and oxygen consumption persist for 7 to 14 days after the onset of rapid pacing. However, within 24 hours after the onset of pacing they observed a beginning decline in contractility that progressed over time. This finding implies that the deterioration of left ventricular function precedes the fall in myocardial blood flow. An important observation in the present study was that the decrease in coronary blood flow appeared to be secondary to the decrease in myocardial oxygen consumption, as the relationship between coronary flow and oxygen consumption was not altered. This suggests that the mechanisms that regulate coronary vasomotor tone in response to myocardial oxygen demands are intact in this model of CHF.

Previous studies of molecular alterations that could affect ATP synthesis or utilization in the failing heart are conflicting. O’Brien et al.²⁷ found that the capacity for fatty acid uptake and oxidation by the Krebs cycle was increased in dogs with pacing-induced heart failure. In a subsequent study, these investigators reported a reduction in mRNA and activity of enzymes involved in oxidative phosphorylation and sarcoplasmic reticulum \( \text{Ca}^{2+} \)-ATPase activity in pacing-induced heart failure.⁸ Studies of isolated muscle strips from failing human hearts showed a reduction in heat liberation by both tension-dependent (actin-myosin cross bridging) and tension-independent (calcium cycling during contraction-relaxation) mechanisms, which suggest a downregulation of energy using processes compared with normal hearts.⁹ Montgomery et al.²⁸ found significant ATP depletion and increased ADP levels in dogs with CHF produced by 4 to 6 weeks of rapid ventricular pacing. Although an increase in ADP would be expected to stimulate mitochondrial respiration (and therefore \( \text{MV}_2 \)), this relationship is complex and dependent on substrate availability. More recent studies have suggested that changes in myocardial [ADP] in vivo are not regularly related to rates of oxidative phosphorylation.³⁰ However, these studies were...
performed in the normal heart and may not be applicable to energy metabolism in the failing heart.

**Myocardial Oxygen Consumption During Exercise**

Although coronary blood flow increased significantly from rest to the first stage of exercise in the failing hearts, a further increase in exercise level (associated with additional increases in heart rate, left ventricular systolic pressure and LV dP/dt) resulted in no further increase in coronary flow. The failure of myocardial oxygen consumption to increase between the first and second levels of exercise did not appear to result from insufficient oxygen availability, since oxygen extraction by the heart did not increase during the second level of exercise. Furthermore, there was no net myocardial lactate production which would be expected if the subnormal coronary blood flow had resulted in ischemia and increased anaerobic glycolysis. In addition, the pH of coronary venous blood did not fall during the second stage of exercise in the failing hearts. These findings suggest that the regulation of coronary blood flow relative to oxygen consumption during exercise is intact, but that the utilization of oxygen is limited in the failing heart.

Although the response of coronary blood flow and myocardial oxygen consumption during exercise has not been previously reported in the setting of CHF, several investigators have examined the response to increased metabolic demands produced by rapid atrial pacing. Shannon et al. demonstrated that during atrial pacing at 170 beats/min myocardial blood flow was less in dogs with pacing-induced heart failure (1.22 mL·min⁻¹·g⁻¹) than in normal animals (1.48 mL·min⁻¹·g⁻¹). The disparity between normal and CHF animals during pacing was most pronounced in the subendocardium as evidenced by a decrease of the ENDO/EPI boundary flow ratio from 1.14 during sinus rhythm to 0.94 during pacing. Spinale et al. observed that atrial pacing at 240 beats/min caused a more dramatic disparity in myocardial blood flow between swine with pacing-induced CHF and normal animals. In normal swine, pacing caused an increase of myocardial blood flow from 1.6 to 3.1 mL·min⁻¹·g⁻¹, while in animals with heart failure, blood flow increased only from 0.75 to 1.25 mL·min⁻¹·g⁻¹. The difference in blood flow rates between these studies likely reflects differences in species and pacing rates, but both demonstrate that the response of myocardial blood flow to the increased metabolic demands produced by rapid atrial pacing is impaired in the failing heart.

**Methodological Limitations**

An important finding in our study was the decreased response of coronary blood flow to exercise in the failing hearts compared with normal hearts. Because control and heart failure measurements were made 3 to 4 weeks apart, it is critical that our Doppler flow velocity measurements remained stable over this period of time. The Doppler probes were rezeroed and calibrated before each study. Computation of blood flow involves multiplying the velocity signal by the cross-sectional area of the artery in order that changes in arterial diameter would affect computed flow. Wang et al. reported a small but significant increase in left circumflex coronary artery diameter measured with sonomicrometer crystals from 4.27 to 4.53 mm after 4 weeks of rapid ventricular pacing. However, in the present study, the region of vessel in which velocity was measured was surrounded by a rigid cuff containing the piezoelectric crystal so that no increase in artery diameter could occur. It is possible that scarring could have caused an increase in arterial wall thickness between the early and late measurements, which would have resulted in an increase in blood velocity through the flow probe. However, this would have led to higher computed flow rates after the development of CHF, which is opposite to what was observed. In other studies in chronically instrumented normal dogs in which repeated measurements of blood flow were made over 3 to 4 weeks, we have observed no systematic change in the blood flow response during exercise.

Resting myocardial blood flow during control conditions was higher than in a previous study that compared coronary flow in dogs before and after pacing-induced heart failure. This probably occurred because in the present study measurements of coronary flow were made with the dogs standing on the treadmill in anticipation of exercise. Our values for resting flow during control conditions are similar to historical controls in our laboratory (1.28±0.14 mL·min⁻¹·g⁻¹) when myocardial blood flow was measured with dogs standing on the treadmill. Likewise, previous measurements from our laboratory obtained from normal dogs lying quietly on a table (0.96±0.8 mL·min⁻¹·g⁻¹) are in close agreement with the resting flow rates reported by Shannon et al. The higher flow rates during control conditions at rest would decrease the increment in flow between rest and the first exercise stage, but should not alter the response to a subsequent increase in exercise level. We did not administer microspheres during the control studies because of the potential for loss of radioactivity due to leaching of the isotopes over the 4-week interval between studies. Consequently, resting flow values were calculated from the Doppler probe and converted to a per gram basis with a standard template to estimate the territory of myocardium (weight) perfused by the LAD. Although this may have resulted in a small underestimation or overestimation of the true tissue blood flow, this error would affect all measurements equally since the heart failure animals served as their own controls. Additional support for the validity of the Doppler measurements is demonstrated by the microsphere measurements taken in 6 dogs with heart failure (Table 2) that also showed that myocardial blood flow did not increase with increasing levels of exercise.

Under control conditions exercise was performed as 2 continuous stages, although after the development of heart failure the 2 exercise stages were separated by a rest period. This was a practical necessity since animals with heart failure had marked exercise intolerance and could not complete the 2 exercise stages without an interruption. However, systemic hemodynamics and coronary blood flow reach steady state levels within 30 to 60 records after the onset of exercise or change in exercise stage in order that the preceding condition (rest or an earlier exercise level) does not appreciably affect the steady state response. Moreover, in 2 additional normal dogs in which the continuous 2-stage exercise protocol was compared with the same 2 exercise stages separated by a 1-hour rest period, there was no difference in the hemodynamic or coronary flow responses between the 2 protocols (data not shown). A final methodological concern relates to the sensitivity for detection of ischemia in the heart failure group during exercise. During the second exercise stage, we observed continued lactate extraction by the
heart and no decrease in the coronary venous blood pH. Nevertheless, although there was net lactate extraction by the entire heart, it is possible that lactate production confined to the subendocardial region might not have been detected.22 No decrease of the ENDO/EPFL flow ratio occurred during the second exercise stage, but we cannot exclude hyperperfusion of a thin layer of the subendocardium that might not have been detected with the microsphere measurements, because the left ventricular wall was divided into only 2 transmural layers.

Conclusions
The development of cardiac failure was associated with decreased myocardial oxygen consumption and failure of oxygen consumption to increase during progressive levels of treadmill exercise. This abnormality did not appear to result from inadequate oxygen availability, but rather appeared to represent an impairment of myocardial oxygen use with a secondary decrease in metabolic coronary vasodilatation. The results suggest that impaired cardiac performance during exercise in the failing heart is accompanied by reduced myocardial oxygen consumption that is appropriately matched by coronary blood flow.

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References
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