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EXPERIMENTAL STUDIES

Myocardial Oxygen Consumption During Exercise in the Presence of Left Ventricular Hypertrophy Secondary to Supravalvular Aortic Stenosis

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The hypothesis that abnormally increased myocardial oxygen demands may contribute to increased vulnerability to ischemia during exercise in the chronically pressure-overloaded hypertrophied left ventricle was tested. Myocardial oxygen consumption was measured during a five stage graded treadmill exercise protocol in eight normal dogs and nine adult dogs in which a 90% increase in left ventricular mass was produced by banding the ascending aorta at 8 weeks of age. Heart rate increased progressively during exercise in both groups of dogs, but was significantly faster than normal in the group with aortic banding. Coronary blood flow increased progressively with exercise in both groups, but was significantly greater than normal in dogs with aortic banding during each exercise stage. Coronary sinus oxygen tension decreased significantly and similarly during exercise in normal and hypertrophied hearts.

In dogs with hypertrophy, oxygen consumption per gram of myocardium averaged 52% greater than normal during exercise. This excess myocardial oxygen consumption in dogs with aortic banding resulted from an abnormally large increase in oxygen consumption per beat during exercise and from the faster heart rate in this group of dogs. Measurements of myocardial blood flow with microspheres demonstrated a lower subendocardial/subepicardial blood flow ratio in dogs with hypertrophy; this ratio decreased significantly during exercise in dogs with hypertrophy, but not in normal dogs.

These data are consistent with the hypothesis that increased vulnerability to ischemia in the pressure-overloaded hypertrophied left ventricle is the result of both increased myocardial oxygen demands during exercise and abnormalities of myocardial perfusion.

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The chronically pressure-overloaded hypertrophied left ventricle may exhibit increased vulnerability to ischemia during periods of increased cardiac work. Thus, patients with left ventricular hypertrophy may experience angina pectoris and develop electrocardiographic (ECG) changes suggestive of subendocardial ischemia during exercise despite angiographically normal coronary artery anatomy (1,2). Exercise-induced ischemia in the hypertrophied heart could result from abnormalities of myocardial perfusion, excessive increases in oxygen demands during stress or a combination of both. Previous studies from this laboratory (3–6) have demonstrated abnormalities of subendocardial blood flow during pacing-induced tachycardia or treadmill exercise in experimental animals with left ventricular hypertrophy secondary to banding of the ascending aorta or valvular aortic stenosis. This perfusion abnormality was sufficient to cause myocardial ischemia, as demonstrated by production of lactate into coronary venous blood during pacing-induced tachycardia (7). The vulnerability of the hypertrophied subendocardium to ischemia may be modified by coronary perfusion pressure. Thus, when left ventricular hypertrophy was produced by perinephritic hypertension, the increased coronary perfusion pressure during diastole was able to partially correct the exercise-induced subendocardial perfusion abnormality (8).

In addition to abnormalities of myocardial perfusion, excessive myocardial oxygen demands in the hypertrophied heart could contribute to development of ischemia during exercise. In the setting of valvular or supravalvular aortic stenosis, as well as of arterial hypertension, left ventricular systolic pressure has been reported (4,6,8) to undergo supra-

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normal increases during exercise. Augmented increases in systolic wall stress could contribute to the development of ischemia by causing exaggerated increases in myocardial oxygen demand during exercise. Consequently, this study was conducted to test the hypothesis that myocardial oxygen consumption during exercise is abnormally increased in the chronically pressure-overloaded hypertrophied left ventricle.

Methods

Production of ventricular hypertrophy. Studies were performed in accordance with the "Position of the American Heart Association on Research Animal Use" adopted November 11, 1984. Studies were performed in nine adult mongrel dogs in which left ventricular hypertrophy was produced by banding the ascending aorta at age 8 weeks, as well as in eight normal adult mongrel dogs that served as a control group. To produce hypertrophy, dogs were anesthetized with sodium pentobarbital (25 to 30 mg/kg intravenously), intubated and ventilated with a respirator. A right thoracotomy was performed in the third intercostal space. The ascending aorta was dissected from the surrounding fat pad and encircled with a polyethylene band 3.0 mm in width. While left ventricular and aortic pressure were measured distal to the constriction, the band was tightened until a peak systolic pressure gradient of 20 to 30 mm Hg was achieved. The thoracotomy incision was repaired, and the dog was allowed to recover. At approximately 3 months of age the dog was trained to run on a motor-driven treadmill.

Surgical preparation. Surgery for long-term instrumentation was performed when the dogs were 11 ± 2 months of age. Dogs were anesthetized with sodium pentobarbital (30 to 35 mg/kg intravenously), intubated and ventilated with a respirator. A left thoracotomy was performed in the fifth intercostal space, and the heart was suspended in a pericardial cradle. A polyvinyl chloride catheter, 3 mm outer diameter, was introduced into the left internal thoracic artery and advanced into the ascending aorta distal to the constricting band. A similar catheter was introduced into the left atrial cavity through the atrial appendage. A third catheter was inserted into the left ventricle through the apical dimple. A final catheter was introduced into the right atrium through the atrial appendage, manipulated into the coronary sinus, advanced until the tip could be palpated 2 to 3 cm beyond the coronary sinus ostium and secured with a purse-string suture. The proximal 2.5 cm of the left circumflex coronary artery was dissected free, and an electromagnetic flowmeter probe (Howell Instruments) was snugly fitted around the artery. A hydraulic occluder constructed of polyvinyl chloride tubing, 2.7 mm outer diameter was placed around the vessel distal to the flow meter probe. The pericardium was loosely closed, and the catheters and electrical leads were tunneled subcutaneously to exit at the base of the neck. The chest was closed in layers, the left hemithorax evacuated of air with a chest tube and the dog allowed to recover. Catheters were flushed daily with heparin-saline solution and were protected with a nylon vest. An identical surgical procedure was performed in eight normal dogs that served as a control group. Dogs were studied 9 to 15 days after surgery; at the time of study, they were active and fully recovered from the effects of surgery.

Experimental protocol. Aortic, left atrial and left ventricular pressures were measured with a Statham P23ID pressure transducer at mid-chest level. Left circumflex coronary artery blood flow was measured with a Statham SP2202 electromagnetic flow meter. The zero flow baseline was established with 2 to 3 s total occlusions of the coronary artery. All pressure and coronary blood flow measurements were recorded continuously throughout the study on an eight channel direct-writing oscillograph (model 8800, Hewlett Packard). Before beginning the study, the dogs underwent a 5 min period of warm-up exercise, during which the rate of exercise was gradually increased to 6.4 km/h at a 10% grade. A 30 min rest period was allowed after this warm-up period; hemodynamic variables were recorded continuously to ensure that all measurements had returned to the control steady state before the exercise protocol was started. Coronary sinus and aortic blood samples (1.0 ml each) were then withdrawn anaerobically for determination of myocardial oxygen consumption during rest conditions.

Immediately thereafter, a five stage graded exercise treadmill protocol was begun: stage 1 = 4.8 km/h at 5% grade; stage 2 = 6.4 km/h at 5% grade; stage 3 = 6.4 km/h at 10% grade; stage 4 = 6.4 km/h at 15% grade; and stage 5 = 6.4 km/h at 20% grade. Each exercise stage was 3 min in duration, except for stages 2 and 4, which were extended to 4.5 min to allow for the administration of radioactive microspheres. Coronary sinus and aortic blood samples were withdrawn during the third minute of each exercise stage. During exercise stages 2 and 4, blood sampling was immediately followed by left atrial injection of radioactive microspheres for determination of regional myocardial blood flow. At the conclusion of the fifth stage of exercise, a 2 to 3 s coronary artery occlusion was again performed to ensure that the flow meter baseline measurement had remained stable throughout exercise.

Determination of myocardial oxygen consumption. Arterial and coronary sinus blood specimens were kept in iced syringes until the conclusion of exercise. Oxygen tension (Po_2), carbon dioxide tension (Pco_2) and pH were then measured with a blood gas analyzer (model 113, Instrumentation Laboratory) calibrated with known gas mixtures. Hemoglobin content was determined by the cyanmethemoglobin method. Coronary sinus and aortic oxyhemoglobin saturation values were calculated from the blood Po_2, pH and temperature by using the oxygen dissociation curve for dog blood (9). Blood oxygen content was calculated as

Table 1. Hemodynamic Data in Eight Normal Control Dogs and Nine Dogs in Which Left Ventricular Hypertrophy Was Produced by Banding the Ascending Aorta

	Heart Rate (beats/min)		Aortic Pressure (mm Hg)		Mean Aortic Pressure (mm Hg)		LV Systolic Pressure (mm Hg)		LV End-Diastolic Pressure (mm Hg)	
	Normal	LVH	Normal	LVH	Normal	LVH	Normal	LVH	Normal	LVH
Rest	124 ± 5	151 ± 10	118/74 ± 5/4	118/80 ± 3/3	99 ± 4	96 ± 4	126 ± 5	230 ± 8*	2 ± 1	13 ± 2*
Ex 1	177 ± 4	196 ± 12	137/75 ± 6/6	121/70 ± 7/5	103 ± 5	89 ± 6*	146 ± 3	269 ± 15*	5 ± 1	16 ± 1*
Ex 2	197 ± 5	227 ± 8*	150/72 ± 5/6	119/60 ± 4/6*	110 ± 5	87 ± 5*	157 ± 4	300 ± 14*	8 ± 1	20 ± 3*
Ex 3	214 ± 4	240 ± 6*	163/76 ± 5/5	121/60 ± 3/4*	113 ± 5	87 ± 4*	168 ± 4	321 ± 13*	9 ± 2	24 ± 4*
Ex 4	228 ± 5	254 ± 5*	172/75 ± 4/4	128/63 ± 5/3*	116 ± 4	91 ± 4*	176 ± 4	349 ± 14*	10 ± 2	27 ± 4*
Ex 5	245 ± 5	264 ± 7*	181/87 ± 5/2	135/80 ± 9/4*	120 ± 3	104 ± 6*	188 ± 7	358 ± 15*	10 ± 2	28 ± 4*

*$p < 0.05$ vs. normal. Values are mean values ± SEM. Ex = exercise stage; LV = left ventricular; LVH = left ventricular hypertrophy.

hemoglobin × 1.34 × percent oxygen saturation + (0.0031 × Po_2). Myocardial oxygen consumption was computed as the product of flow measured in the left circumflex coronary artery and the difference in oxygen content between aortic and coronary sinus blood.

Measurement of myocardial blood flow. Regional blood flow was measured with left atrial injections of microspheres, 15 μm in diameter, labeled with gamma emitting radionuclides iodine-125, cobalt-57, strontium-85, niobium-95 or scandium-46 (NEN Company and 3M Company). Microspheres were obtained as 1 μCi of each radionuclide in 10 ml of 10% dextran. Microspheres were agitated for at least 15 min in an ultrasonic bath before injection. During each injection, 3×10^6 microspheres were administered into the left atrial catheter over a 15 s interval, and the catheter was flushed with 10 ml of isotonic saline solution. Beginning 5 s before each injection and continuing for 90 s, a reference sample of arterial blood was withdrawn at a rate of 15 ml/min with a peristaltic pump. Microsphere injections resulted in no detectable hemodynamic change.

Tissue preparation and determination of radioactivity. At the conclusion of study, the dog was anesthetized with sodium pentobarbital (30 to 35 mg/kg intravenously), and a left thoracotomy was performed in the fifth intercostal space. The left circumflex coronary artery was isolated at the level of the flow meter probe, and 10 ml of Evans blue dye was injected into the artery to stain the myocardium perfused by the left circumflex coronary artery. The heart was then arrested with potassium chloride, removed and fixed in 10% buffered formalin. After fixation, the heart was sectioned into four rings of equal thickness parallel to the mitral valve ring. The first three rings were divided into six circumferential regions corresponding to the anterior free wall, interventricular septum, posterior free wall, posterior papillary muscle region, lateral wall and anterior papillary muscle. These specimens were then divided into four transmural layers of equal thickness from epicardium to endocardium, weighed and placed into vials for counting.

Myocardial and blood specimens were counted in a gamma spectrometer with a multichannel analyzer (model 5912, Packard Instrument Company) at window settings corresponding to the peak energies of each radionuclide. The activities recorded in each energy window and the sample weights were entered into a digital computer programmed to correct for overlapping counts between radionuclides and background activity and compute the corrected counts/min per g of myocardium. Blood flow (Q_m) was computed with the formula: $Q_m = Q_r \cdot C_m / C_r$, where Q_r = reference blood flow rate (ml/min), C_m = counts/min of the myocardial specimen and C_r = counts/minute of the reference blood specimen.

Data analysis. Heart rate, the coronary flow meter signal and all pressures were measured directly from the strip chart recordings. The coronary artery flow meter signal was calibrated by using the measurements of tissue flow obtained with microspheres at rest and during exercise stages 2 and 4. A least squares fit was obtained between the flow meter signal and simultaneous microsphere measurements from the left ventricular wall perfused by the left circumflex coronary artery; this relation was then used to convert flow meter signals to absolute blood flow for the remaining exercise stages. Mean left ventricular blood flow for each intervention was determined by averaging the flow to all left ventricular samples for each dog. Hemodynamic and blood flow data were compared with use of analysis of variance for repeated measures. A value of $p < 0.05$ was required for statistical significance. When significant differences were found, pairwise comparisons were performed to determine where significant differences existed. Probability values were adjusted by using the Bonferonni method, which corrects for performing multiple tests on correlated data (10).

Results

Left ventricular mass. Mean left ventricular weight for the eight normal dogs was 102.8 ± 6.1 g, and mean body weight was 24.9 ± 1.1 kg; the respective values for the nine dogs with aortic banding were 143.4 ± 10.1 g and 18.4 ± 0.9

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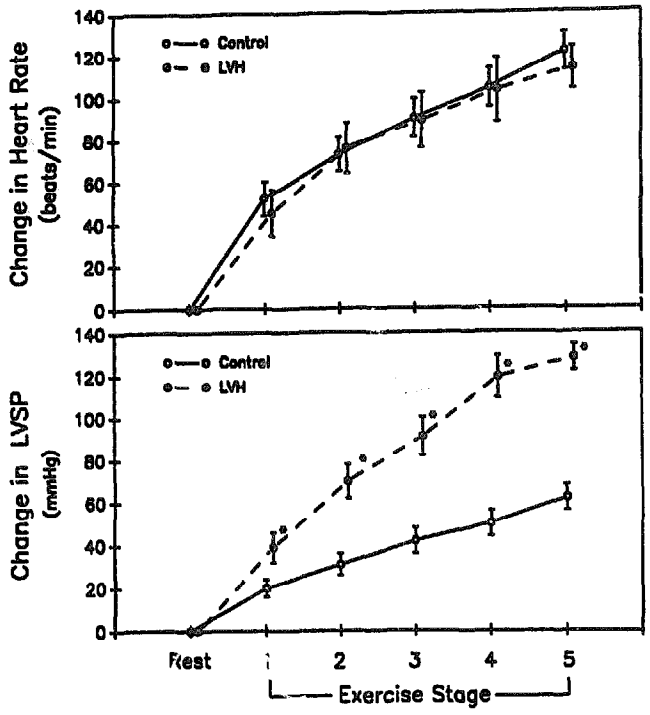

Figure 1. Increases in heart rate and left ventricular systolic pressure (LVSP) during graded treadmill exercise in eight normal control dogs and nine dogs in which left ventricular hypertrophy (LVH) was produced by banding the ascending aorta. *$p < 0.05$ versus control.

kg. The left ventricular/body weight ratio of 4.12 ± 0.13 in the normal dogs was increased to 7.83 ± 0.49 g/kg in dogs with aortic banding ($p < 0.01$).

Hemodynamic data (Table 1). Heart rate in the normal dogs increased progressively from 124 ± 5 beats/min at rest to 245 ± 5 beats/min during the highest level of exercise. Heart rate tended to be faster in dogs with aortic banding than in normal dogs during standing on the treadmill at rest, although this difference was not statistically significant. Heart rate was significantly faster in dogs with aortic banding than in normal dogs during exercise stages 2 to 5. The increase in heart rate from rest to exercise stage 5 was similar in normal dogs (mean increase 121 ± 9 beats/min) and dogs with aortic banding (mean increase 113 ± 10 beats/min) (Fig. 1). Aortic systolic, diastolic and mean pressures increased progressively with increasing exercise intensity in normal dogs. During rest conditions, aortic pressure distal to the aortic band was not significantly different from normal in dogs with hypertrophy. However, in dogs with hypertrophy, aortic pressure decreased below the rest value during the first three exercise stages ($p < 0.05$) and was not significantly different from the rest value during exercise stages 4 and 5. Consequently, aortic pressures were significantly less in dogs with aortic banding than in normal dogs during each exercise stage.

Left ventricular pressures (Table 1). Left ventricular systolic pressure increased progressively with exercise from 126 ± 5 mm Hg at rest to 188 ± 7 during the highest level of exercise in normal dogs. In dogs with aortic banding, left ventricular systolic pressure was increased at rest and underwent a substantially greater than normal increase during exercise (Fig. 1). Left ventricular end-diastolic pressure was significantly greater than normal in dogs with aortic stenosis both at rest and during exercise. The heart rate-systolic left ventricular pressure product was significantly increased in dogs with hypertrophy at rest and during all exercise stages.

Myocardial oxygen consumption and coronary blood flow (Table 2). In normal dogs, coronary blood flow increased from 1.39 ± 0.21 ml/min per g at rest to 3.24 ± 0.39 during the highest level of exercise (mean increase 1.85 ± 0.29; $p < 0.01$). In dogs with aortic banding, coronary blood flow underwent a significantly greater increase, from 1.71 ± 0.12 ml/min per g at rest to 4.94 ± 0.46 ml/min per g during the highest level of exercise (mean increase 3.23 ± 0.37; $p < 0.05$ in comparison with normal). During each exercise stage, blood flow per gram of myocardium was significantly greater in dogs with aortic banding than in normal dogs ($p < 0.05$). Coronary sinus oxygen tension was 20.8 ± 1.8 torr in the normal dogs during rest conditions; oxygen tension decreased significantly during exercise ($p < 0.05$). In dogs with aortic banding, coronary sinus oxygen tension also underwent a significant decrease from rest to exercise ($p <$

Table 2. Coronary Blood Flow, Coronary Sinus Oxygen Tension and Myocardial Oxygen Consumption

	Coronary Blood Flow (ml/min per g)		Coronary Sinus Po_2 (torr)		Myocardial O_2 Consumption (ml/min per g)	
	Normal	LVH	Normal	LVH	Normal	LVH
Rest	1.39 ± 0.21	1.71 ± 0.12	20.8 ± 1.8	18.0 ± 1.3	0.158 ± 0.027	0.215 ± 0.018
Ex 1	1.83 ± 0.23	2.56 ± 0.24*	16.5 ± 1.0	15.3 ± 0.8	0.223 ± 0.030	0.328 ± 0.038*
Ex 2	2.21 ± 0.21	3.26 ± 0.16*	15.1 ± 1.2	14.5 ± 0.9	0.278 ± 0.020	0.427 ± 0.029*
Ex 3	2.59 ± 0.26	3.85 ± 0.24*	14.3 ± 1.4	14.0 ± 1.0	0.332 ± 0.030	0.495 ± 0.019*
Ex 4	3.01 ± 0.29	4.64 ± 0.32*	13.5 ± 1.3	13.5 ± 0.8	0.395 ± 0.034	0.598 ± 0.033*
Ex 5	3.24 ± 0.39	4.94 ± 0.46*	12.6 ± 1.1	13.3 ± 1.3	0.438 ± 0.040	0.656 ± 0.034*

*$p < 0.05$ vs. normal. Values are mean ± SEM. Blood flow and oxygen consumption are expressed per gram of myocardium. Po_2 = oxygen tension; other abbreviations as in Table 1.

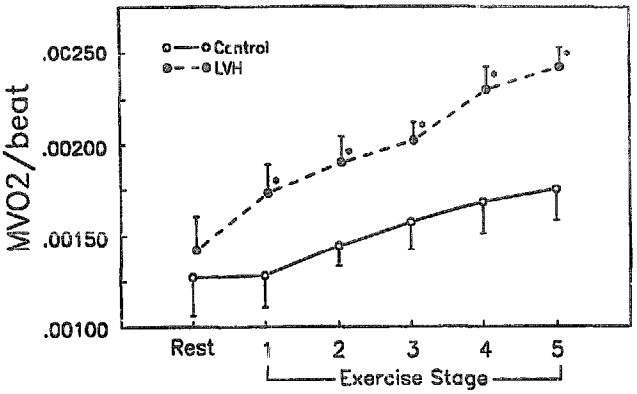

Figure 2. Myocardial oxygen consumption (ml/min per g) (MVO2) per beat at rest and during graded treadmill exercise in eight normal control dogs and nine dogs in which left ventricular hypertrophy (LVH) was produced by banding the ascending aorta. *p < 0.05 versus control.

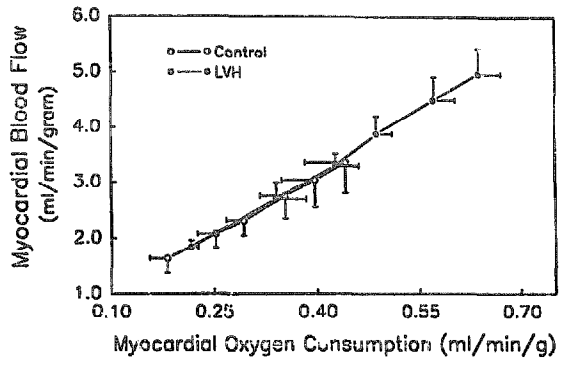

Figure 3. Relation between myocardial blood flow and myocardial oxygen consumption at rest and during graded treadmill exercise in eight normal control dogs and nine dogs in which left ventricular hypertrophy (LVH) was produced by banding the ascending aorta.

0.01). There was no significant difference in coronary sinus oxygen tension between normal and hypertrophied hearts at rest or during any exercise stage.

In normal dogs, oxygen consumption per gram of myocardium increased from 0.158 ± 0.027 ml/min per g at rest to 0.438 ± 0.040 ml/min per g during exercise stage 5 (mean increase 0.280 ± 0.032; $p < 0.01$). The increase in myocardial oxygen consumption during exercise was significantly greater in dogs with aortic banding, from 0.215 ± 0.018 ml/min per g at rest to 0.656 ± 0.034 during exercise stage 5 (mean increase 0.441 ± 0.032; $p < 0.05$ in comparison with normal). In dogs with aortic banding, myocardial oxygen consumption was significantly greater than normal during each exercise stage (each $p < 0.05$), although not at rest.

Myocardial oxygen consumption normalized for heart rate (Fig. 2). In the normal dogs, oxygen consumption was 0.00124 ± 0.00021 ml/min per g per beat during rest conditions. Myocardial oxygen consumption per beat tended to increase during the higher levels of exercise and was significantly greater during exercise stages 4 and 5 than at rest or during exercise stage 1 in the normal dogs ($p < 0.05$). In dogs with hypertrophy, myocardial oxygen consumption per beat was not different from normal during rest conditions; however, it increased significantly from rest to exercise stage 2 ($p < 0.05$) and then underwent further progressive increases with each exercise stage. Myocardial oxygen consumption per beat was significantly greater than normal in dogs with aortic banding during exercise stages 2 to 5 ($p < 0.05$). In addition, at similar heart rates, myocardial oxygen consumption per beat was significantly greater in hypertrophied than in normal hearts ($p < 0.05$).

To determine whether the response of the coronary vessels to increased myocardial oxygen consumption during exercise was similar in normal dogs and in dogs with aortic banding, coronary blood flow was plotted as a function of myocardial oxygen consumption (Fig. 3). There was no difference in the relation between coronary blood flow and myocardial oxygen consumption in normal dogs and dogs with aortic banding.

Transmural myocardial blood flow (Table 3). Myocardial blood flow was measured with microspheres at rest and during exercise stages 2 and 4, and the ratio of subendocardial/subepicardial flow was determined. Myocardial blood flow was significantly greater than normal in dogs with aortic banding during both exercise levels, but not at rest. The ratio of subendocardial/subepicardial flow was significantly decreased in dogs with aortic banding at rest and during each exercise stage (each $p < 0.05$). To determine whether the difference in subendocardial/subepicardial flow ratios was the result of the differences in heart rate between the two groups, subendocardial/subepicardial flow ratios were plotted as a function of heart rate (Fig. 4). Over the range of overlapping heart rates, subendocardial/subepicardial flow ratios were significantly lower in dogs with hypertrophy than in normal dogs ($p < 0.05$).

Discussion

The most important finding of this study was that during exercise at identical external work loads, oxygen consump-

Table 3. Myocardial Blood Flow and the Subendocardial/Subepicardial Flow Measured With Microspheres at Rest and During Exercise Stages 1 and 4

	Myocardial Blood Flow (ml/min per g)		Endo/Epi Flow	
	Normal	LVH	Normal	LVH
Rest	1.38 ± 0.22	1.69 ± 0.14	1.27 ± 0.08	1.09 ± 0.08*
Ex 1	2.05 ± 0.20	3.34 ± 0.35*	1.42 ± 0.04	1.02 ± 0.09*
Ex 4	3.04 ± 0.48	4.44 ± 0.40*	1.19 ± 0.09	0.80 ± 0.08*

*p < 0.05 compared with normal. Endo/Epi = subendocardial/subepicardial; other abbreviations as in Table 1.

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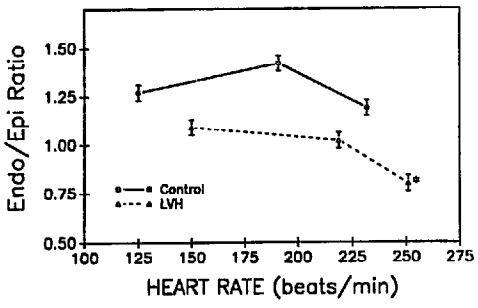

Figure 4. Ratio of subendocardial/subepicardial (Endo/Epi) blood flow measured with microspheres at rest and during light (6.4 km/h at 5% grade) and heavy (6.4 km/h at 15% grade) exercise in eight normal dogs and nine dogs in which left ventricular hypertrophy (LVH) was produced by banding the ascending aorta. The subendocardial/subepicardial flow ratio is shown relative to heart rates observed during the three experimental conditions to correct for direct effects of heart rate on the transmural distribution of blood flow. *$p < 0.05$ versus control.

tion per gram of myocardium was significantly greater in dogs with aortic banding than in normal control dogs. This finding indicates that increased oxygen demands could contribute to increased vulnerability to ischemia during exercise in the chronically pressure-overloaded hypertrophied left ventricle. The increased myocardial oxygen consumption in dogs with hypertrophy was the result of both a significantly increased oxygen consumption per beat as well as the faster heart rates during exercise in this group of animals.

Myocardial oxygen consumption during rest conditions. Several investigators have measured oxygen consumption in pressure-overloaded hypertrophied myocardium. Using feline right ventricular papillary muscles in which hypertrophy was produced by pulmonary artery banding to cause an abrupt increase in right ventricular systolic pressure, Cooper et al. (11) observed an increase in oxygen consumption relative to isometric tension development. In contrast, when hypertrophy was produced by gradual progressive pressure overload after pulmonary artery banding in young growing cats, papillary muscle oxygen consumption was decreased relative to that in normal muscles at similar levels of tension development (12). Similarly, Breisch et al. (13) found that total heat production during contraction in the pressure-overloaded hypertrophied feline left ventricle was significantly reduced when compared with normal at all levels of mechanical performance. In contrast to these in vitro studies, in the present study during rest conditions, there was no significant difference in oxygen consumption per gram of myocardium expressed directly or per beat in normal and hypertrophied hearts. In the intact heart, oxygen consumption is importantly influenced by the magnitude of systolic wall stress (14). In response to elevated systolic pressure, myocardial hypertrophy occurs to distribute the increased systolic load over a larger cross-sectional area, thereby decreasing systolic wall stress toward normal (15). In patients with diverse causes of left ventricular hypertrophy, Strauer (16,17) reported that myocardial oxygen consumption was variable, but was significantly correlated with computed systolic wall stress. Although systolic wall stress was not determined in the present study, the findings support the concept that hypertrophy occurred to restore systolic wall stress toward normal during rest conditions, with normalization of myocardial oxygen consumption.

Myocardial oxygen consumption during exercise. Although there was no significant difference in myocardial oxygen consumption between the two groups of dogs during rest conditions, the increase in oxygen consumption during exercise was greater than normal in the dogs with hypertrophy. Part of the greater oxygen consumption in dogs with hypertrophy could be attributed to the faster heart rates in this group. As in previous studies (4,6) in which left ventricular hypertrophy was produced by banding the ascending aorta or by creating valvular aortic stenosis, heart rate during rest conditions tended to be faster in hypertrophied than in normal hearts, but this difference was not statistically significant. Although the mean difference in heart rate between normal dogs and dogs with aortic banding was not greater during exercise than at rest, this difference became statistically significant during exercise stages 2 to 5. This occurred because heart rates were more variable at rest and during light exercise than during higher levels of exercise, so that confidence limits were smaller during higher levels of exercise. Although cardiac failure may be associated with an increased heart rate at rest (18,19), none of the dogs included in this study had left ventricular dilation or pulmonary congestion and all had excellent exercise tolerance. In addition, cardiac failure is commonly associated with a subnormal increase in heart rate during exercise (18,19), whereas in the present study, the increase in heart rate during exercise was similar in both groups of dogs. Thus, the mechanism for the faster heart rates in dogs with aortic banding is unclear.

After normalization for heart rate, oxygen consumption per beat was still significantly greater in dogs with aortic banding than in normal dogs during moderate and heavy levels of exercise. This indicates that factors other than heart rate must have contributed to the abnormally increased oxygen consumption during exercise in dogs with hypertrophy. A prominent difference between the two groups of dogs was the exaggerated increase in left ventricular systolic pressure during exercise in dogs with aortic banding. Although the degree of myocardial hypertrophy may have been appropriate to normalize systolic wall stress during rest conditions (15,16), this exaggerated increase in left ventricular systolic pressure during exercise in the presence of a fixed left ventricular outflow obstruction would be expected to result in abnormally increased systolic wall stress during exercise. Because systolic wall stress is a fundamental

determinant of myocardial oxygen demand (14), a supranormal increase in systolic wall stress during exercise could explain the increased myocardial oxygen consumption per beat in the dogs with aortic banding.

Coronary blood flow. In the normal heart, coronary blood flow is regulated in response to changing myocardial oxygen needs. The increase in coronary blood flow during exercise in the normal dogs was slightly less than required to maintain a constant level of arteriovenous oxygen extraction, so that coronary sinus oxygen tension decreased significantly during exercise. In normal dogs, this decrease in coronary venous oxygen saturation during exercise is at least in part the result of sympathetic coronary vasoconstriction, which opposes the increase in coronary blood flow. Bache et al. (20) demonstrated that the decrease in coronary sinus oxygen tension that normally occurs during exercise was antagonized by selective alpha$_1$-adrenergic blockage with prazosin or nonselective alpha-adrenergic blockade with phentolamine. In the present study, a similar decrease in coronary sinus oxygen tension occurred in response to treadmill exercise in dogs with aortic banding. These findings demonstrate that the response of the coronary resistance vessels that occurs during the increased myocardial oxygen demands during exercise is normal in dogs with chronic left ventricular hypertrophy secondary to supravalvular aortic stenosis.

An important problem that must be considered in interpretation of these results is whether inadequate coronary blood flow limited the increase in myocardial oxygen consumption that occurred during exercise in dogs with hypertrophy. Thus, if coronary blood flow could not increase adequately, myocardial oxygen consumption would have been limited by the perfusion abnormality. If this occurred, the increase in myocardial oxygen demands in the hypertrophied hearts would have been underestimated. However, several lines of evidence fail to support this possibility. First, if coronary perfusion had been the limiting factor in preventing myocardial oxygen consumption from increasing in proportion to the increased oxygen demands during exercise, myocardial blood flow should have increased to its maximal value, and then been unable to increase further with increasing exercise intensity. This did not occur; with each successive exercise stage, coronary blood flow underwent a further significant increase, indicating that at least into exercise stage 4, a further increase in coronary blood flow was possible. In addition, if maximal coronary vasodilation had been achieved, increasing exercise intensity should have produced a further decrease in coronary venous oxygen tension below that observed in normal dogs. However, coronary venous oxygen tension was similar in both normal and hypertrophied hearts. These data fail to support the concept that myocardial oxygen consumption was limited by complete loss of coronary vasodilator reserve in dogs with hypertrophy.

Ventricular diastolic function. In dogs with hypertrophy, left ventricular end-diastolic pressure was abnormally increased at rest, with a further substantial increase during exercise. This is in agreement with previous studies both in patients (21) and in experimental animals (4,8) with hypertrophy secondary to chronic left ventricular pressure overload. Because mechanical function was not examined in detail, it is not possible to assess the relative contributions of abnormalities of left ventricular chamber stiffness and intrinsic myocardial stiffness to the increased diastolic pressures. However, if the combination of augmented oxygen demands and relative subendocardial underperfusion resulted in myocardial ischemia during exercise, this would be expected to increase diastolic myocardial stiffness as the result of impaired relaxation or increased diastolic tone (22,23). Such ischemia-induced decreases in diastolic compliance could lead to further impairment of myocardial perfusion in the hypertrophied heart (24).

Aortic blood pressure. In the normal dogs, aortic pressure increased progressively with exercise. In contrast, in the dogs with aortic banding, aortic pressure failed to increase during exercise and actually decreased slightly during exercise of intermediate intensity. Lack of a normal increase in atrial pressure during exercise may be the result of activation of left ventricular baroreceptors in response to the exaggerated increase in left ventricular systolic and diastolic pressure that occurs during exercise in the presence of left ventricular outflow obstruction (25). These reflex changes have been implicated in the inappropriate systemic vasodilation that can occur during exercise in patients with severe valvular aortic stenosis (22).

Clinical implications. Although the experimental model of ascending aorta banding used in this study produces marked left ventricular hypertrophy, it differs in several aspects from valvular aortic stenosis and arterial hypertension, which are more common clinical causes of left ventricular systolic overload. With ascending aorta banding, the pressure in the proximal aortic segment from which the coronary arteries arise is equal to left ventricular pressure during systole. At the end of ejection, pressure equilibrates nearly instantaneously across the area of aortic narrowing, so that coronary perfusion pressure in diastole is equal to distal aortic pressure (4). Despite this difference in coronary perfusion dynamics, myocardial blood flow during rest conditions and pacing-induced tachycardia is similar in experimental models of valvular aortic stenosis and ascending aorta banding (3–6). This similarity of myocardial perfusion with subcoronary and supracoronary aortic stenosis probably exists because coronary perfusion occurs principally during diastole, so that the increased systolic coronary perfusion pressure in aortic banding does not produce substantial alteration of the distribution of myocardial blood flow. Unlike valvular aortic stenosis or ascending aorta banding, arterial hypertension is associated with increased

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coronary perfusion pressure during diastole. This increase in aortic diastolic pressure has been shown (8) to counteract, at least in part, the subendocardial perfusion abnormality during stress in the hypertrophied left ventricle.

In the present study, the abnormally increased myocardial oxygen demands during exercise appeared to be related to the exaggerated increase in left ventricular systolic pressure in dogs with aortic banding. The increase in left ventricular systolic pressure during exercise would likely be similar whether the left ventricular outflow obstruction is located at the valvular or supravalvular level. Thus, the exaggerated increase in myocardial oxygen consumption during exercise in the experimental model of ascending aorta banding would be also expected to occur with valvular aortic stenosis. Although findings from the experimental laboratory must be applied with caution in the clinical setting, these data suggest that the increased vulnerability of the chronically pressure-overloaded hypertrophied left ventricle to exercise-induced ischemia may be related to both abnormally increased myocardial oxygen demands during exercise and abnormalities of myocardial perfusion.

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