Myocardial Blood Flow Distribution in Concentric Left Ventricular Hypertrophy

JUDITH C. REMBERT, LEONARD H. KLEINMAN, JOHN M. FEDOR, ANDREW S. WECHSLER, and JOSEPH C. GREENFIELD, JR., *Departments of Medicine (Cardiology) and Surgery, Veterans Administration Hospital, Durham, North Carolina 27705, and Duke University Medical Center, Durham, North Carolina 27710*

ABSTRACT Regional myocardial blood flow during both control conditions and ischemia-induced vasodilatation was studied in eight chronically instrumented awake dogs. Seven of these animals had coarctation-banding of the ascending aorta performed at 6 wk of age, and the other dog had congenital subvalvular aortic stenosis. The mean left ventricular weight for the group was 157±7.6 g, and the left ventricular body weight ratio was 8.76±0.47 g/kg. None of the animals exhibited signs of congestive heart failure.

During the control state, the mean left ventricular systolic pressure was 249±12 mm Hg and the left ventricular end-diastolic pressure was 11.5±0.5 mm Hg. The aortic diastolic pressure was 74±6 mm Hg. Mean left circumflex coronary artery blood flow was 71±6 cm^3/min. In the animals with coarctation-banding, 52±6% of the flow occurred during systole. In the dog with congenital subvalvular aortic stenosis, 5% of the coronary flow was systolic. Mean transmural blood flow during resting conditions was 0.97±0.08 cm^3/min per g, and the ratio of endocardial to epicardial flow (endo/epi) was 0.88±0.07. During reactive hyperemia, the mean transmural blood flow increased to 3.5±0.30 cm^3/min per g; however, the endo/epi decreased to 0.52±0.06.

These studies document a difference in transmural blood flow distribution between the normal and the hypertrophied left ventricle: during resting conditions, in the normal ventricle, the highest flow occurs in the endocardial layer, whereas in the hypertrophied ventricle, the highest flow is in the middle layers with the endocardial flow less than the epicardial flow. During ischemia-induced vasodilatation, the abnormal endo/epi becomes accentuated markedly. These data demonstrate that, in situations requiring high flow, the endocardial layer of a heart with marked concentric left ventricular hypertrophy may not be perfused adequately.

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INTRODUCTION

In the absence of coronary artery disease, myocardial perfusion appears to be adequate to maintain the metabolic needs of the normal heart during a wide variety of stressful situations. It is well recognized, however, that in patients with marked concentric left ventricular hypertrophy, especially in patients with aortic stenosis, subendocardial underperfusion occurs manifested by angina pectoris and electrocardiographic ST-T wave changes (1, 2). Studies of myocardial blood flow in experimental animals (3–5) and in patients (6–8) with left ventricular hypertrophy have, in general, demonstrated that flow per gram of tissue and(or) oxygen delivery is within normal limits during resting conditions. However, data are minimal concerning the transmural distribution of flow both at rest and during conditions requiring increased levels of blood flow. Marcus et al. (9) reported that in dogs with renal vascular hypertension resulting in an increase in left ventricular mass the endocardial/epicardial flow ratios (endo/epi)[1] were not different from normal animals. However, after adenosine infusion, the coronary vascular resistance to flow was increased. Einzig et al. (10), using animals in whom left ventricular hypertrophy had been produced by aortic banding, found that in the anesthetized state the endo/epi was reduced significantly when compared to normal dogs. From these data and from the observations described above in patients, it seems

[1] *Abbreviation used in this paper*: endo/epi, endocardial/epicardial flow ratios.

reasonable to conclude that subendocardial underperfusion may occur secondary to severe concentric left ventricular hypertrophy.

One of the primary problems involved in obtaining myocardial perfusion data has been the difficulty encountered in developing a suitable large animal model of concentric left ventricular hypertrophy. Recently, a technique has been developed in our laboratory to produce left ventricular hypertrophy by coarctation-banding of the aorta in puppies at 6 wk of age (11). The study reported herein describes the transmural blood flow distribution during control conditions and after ischemia-induced vasodilatation in these dogs studied at 1 yr of age in the awake state. In addition, one dog with congenital subvalvular aortic stenosis was studied in a similar manner.

METHODS

Surgical coarctation of the ascending aorta was carried out in healthy 7-wk-old mongrel puppies from three litters utilizing a technique recently developed in our laboratory. This method has been described in detail elsewhere and will be summarized briefly (11). After the induction of anesthesia with 25 mg/kg thiamylal sodium, the puppies were intubated and maintained on a respirator. Utilizing sterile techniques, a right thoracotomy was performed in the fourth intercostal space, the pericardium incised, and a pericardial cradle fashioned. The ascending aorta was mobilized and surrounded with two strands of umbilical tape at a point equidistant between the aortic valve and the innominate artery. A vascular clamp was applied longitudinally to incorporate the ends of the umbilical tape and a portion of the aorta. The aorta was incised longitudinally for 8–10 mm, and a suture line incorporating the umbilical tape was fashioned. After removal of the clamp the presence of an aortic thrill indicated that a sufficient decrease in the size of the lumen had been accomplished. The pericardium was approximated and the animal allowed to recover. The dogs were maintained on an animal farm until they reached ≅12 mo of age. One litter mate puppy not operated upon served as a normal for the anatomic studies. In addition, an adult mongrel dog having subvalvular aortic stenosis was obtained by serendipity. At the time of instrumentation, all animals appeared to be healthy, and there was no evidence of congestive heart failure.

The dogs were anesthetized with 30–40 mg/kg thiamylal sodium, intubated, and maintained with a modified Emerson respirator (J. H. Emerson, Cambridge, Mass.). A left thoracotomy was performed at the fourth intercostal space. Polyvinyl chloride catheters with a 3-mm outer diameter were inserted into the left subclavian artery, left ventricle, and left atrium. A 2.5- to 3.5-mm Howell ST-type electromagnetic flowmeter probe (Howell Instruments, Camarillo, Calif.) and a pneumatic occluder were positioned on the proximal left circumflex coronary artery (12). The proximal end of the catheters, the occluder, and the leads to the electromagnetic flowmeter probe were tunneled to the base of the neck and placed in a subcutaneous pouch. The chest was closed and the animals allowed to recover. 10–14 days later, all animals were afebrile and appeared to be in good health. The mean hematocrit was 45±2% with a range of 35–52%.

On the day of study the animals were brought to the laboratory and while resting quietly, were studied in the awake state without restraints or sedation. The electromagnetic flowmeter probe wires, the ends of the occluder, and the catheters were exteriorized from the subcutaneous pouch using 2% lidocaine local infiltration anesthesia. Standard lead II of the electrocardiogram was recorded. A no. 6 Sones USCI catheter (U. S. Catheter & Instrument Co., Glens Falls, N. Y.) was positioned into the ascending aorta proximal to the coarctation via the femoral artery using 2% lidocaine local anesthesia. All pressure catheters were connected to Statham P23Db pressure transducers (Statham Instruments, Inc., Oxnard, Calif.) using the level of the right atrium as the zero pressure reference. The flowmeter leads were connected to a Statham model M4000 electromagnetic flowmeter (Statham Instruments, Inc.). The probes had been calibrated previously by allowing measured amounts of physiologic saline to flow through them in a known period of time. The linearity was tested by using different flow rates. The probe calibrations were found to have a ±4% SD and were linear, ±2%, for the range of the flows encountered in this study. All data were recorded on an eight-channel direct-writing oscillograph (model 8800), and eight-channel FM magnetic tape recorder (model 3917 from Hewlett-Packard Co., Medical Electronics Div., Waltham, Mass.).

After all instruments were in place, the animal was allowed to rest and become accustomed to the laboratory environment for at least a 30-min period. Continuous measurements of all hemodynamic parameters were carried out. Throughout the studies the laboratory was kept dimly illuminated, and stimuli which might excite the animal were avoided. The studies were begun after a steady state had been achieved in all the measured physiologic parameters. To determine myocardial blood flow, randomly selected radioactive microspheres were injected into the left atrium. These carbonized microspheres (8–10 μm in diameter, 3M Co., 3M Center, St. Paul, Minn.) were labeled with one of the following gamma-emitting nuclides, ^{125}I, ^{141}Ce, ^{51}Cr, ^{85}Sr, or ^{46}Sc. Each microsphere was obtained as 1.0 mCi in 10 ml of 10% dextran and 0.05% polysorbate-80. This stock solution was diluted in 10% dextran so that 1 ml, the volume injected, contained ≅3 million microspheres. This quantity has been found not to produce any measurable changes in hemodynamic indices. Tween 80 was not added in our laboratory. Before each injection, the microspheres were mixed by alternate agitation for at least 15 min in an ultrasonic bath (3M Co., 3M Center) and a Vortex agitator (Scientific Products Div., American Hospital Supply Corp., McGaw Park, Ill.). The desired volume of microsphere mixture was injected over a 3-s period into the left atrium and immediately flushed with ≅10 ml 0.9% sodium chloride. Beginning simultaneously with each injection, reference samples of arterial blood were withdrawn through the aortic catheter at an average rate of 15.5 cm^3/min using a Harvard withdrawal pump (Harvard Apparatus Co., Inc., Millis, Mass.). Transmural distribution of flow was measured using radioactive microspheres during the control state. After a 5-min period had elapsed, a 45-s total occlusion of the left circumflex coronary artery was carried out and microspheres were injected again beginning 5 s after the release of the occlusion. After a 30-min period, a 20-s occlusion was carried out and the reactive hyperemic response evaluated in triplicate. At least 5 min elapsed between each of these three responses.

At the completion of the study, the dogs were anesthetized with intravenous thiamylal sodium and sacrificed with a lethal dose of intravenous potassium chloride. The heart and great vessels were removed from the thorax and submerged in a bath of phosphate-buffered formalin. The hearts were fixed for a 48-h period during retrograde perfusion with phosphate-buffered formalin through the aorta and pulmonary artery at pressures of 80 and 20 mm Hg, respectively (11). The atria

and great vessles were removed from the ventricles at the atrio-ventricular groove. The cardiac valves and epicardial coronary vessels were dissected free and removed. The right ventricle was dissected from the left ventricle and the septum. The left and right ventricles were weighed, and the left ventricle was sectioned into four equal sections from base to apex as described previously (13). The middle two rings were sectioned into six anatomic regions consisting of the septum, anterior, anterior, anterior papillary, lateral, posterior papillary, and posterior. Each of these sections was cut into six transmural layers. The resulting tissue samples had a mean weight of 1.50±0.23 g. Multiple sections of the heart were also obtained for histologic examination. The diameters of the muscle cells in multiple longitudinal sections of the left ventricle were measured (11). The gamma activity of the individual tissue samples was measured with a gamma spectrometer (model 16776, Beckman Instruments, Inc., Fullerton, Calif.). The counting windows were set to include the peak energies emitted by each nuclide. The data representing the activity of each nuclide in each tissue sample along with the corresponding tissue weights were processed by a computer program which corrected the activity values for channel background activity and cross-channel spillover contaminant activity. The amount of flow per gram of tissue for each sample (Q_m) was computed using the relation:

$$Q_m = Q_r \cdot C_m/C_r,$$

where Q_r is the rate of withdrawal of the reference sample, C_m is the activity per gram of tissue sample, and C_r is the activity of the reference sample.

In evaluating the data, the blood pressures and heart rates were read directly from the oscillographic recordings. The phasic left circumflex coronary flow was obtained from the electromagnetic flowmeter recordings, and the percent of the total flow which occurred during systole was obtained by planimetric integration. For the remainder of this report, the phrase "coronary blood flow" will denote flow in the left circumflex coronary artery. The 20-s reactive hyperemic response was evaluated by computing the flow debt, the percent flow debt repayment, and the peak flow during the reactive hyperemic response as described by Coffman and Gregg (14). The diastolic pressure time index per tension time index was computed according to the method of Buckberg et al. (15) during the control state and during the initial part of the reactive hyperemic response to the 45-s occlusion. Standard statistical techniques were utilized throughout to evaluate the data.

RESULTS

The anatomic data defining the degree of concentric left ventricular hypertrophy are provided in Table I. The mean left ventricular weight for the eight dogs was 157±7.6 g, and the left ventricular body weight ratio was 8.76±0.47 g/kg. In the normal litter mate, the left ventricle weighed 96 g, and this ratio was 4.40 g/kg. The mean muscle cell diameter in the hypertrophied left ventricle was 19.5±3.5 μm and appeared to be greater than found in the normal litter mate, 14.7±2.7 μm. There were no differences between the cell diameters in the six layers of the heart. The mean left ventricular wall thickness was measured in five dogs in the anterior free wall near the equator and ranged from 25.5 to 28 mm, as compared to 13.5 mm in the normal dog. Minimal fibrosis was present, but appeared to be recent and may have been related to the second operative procedure necessary for instrumentation. In no case was confluent myocardial infarction noted, and the degree of fibrosis was <5% in all samples. It did not appear to be more prevalent in any specific region of the heart, but was confined primarily to the three endocardial layers.

Hemodynamic data recorded during the control state in seven dogs are presented in Table II. The average heart rate was 86±3 beats/min. The mean left ventricular systolic pressure was 249±12 mm Hg with an average left ventricular end-diastolic pressure of 11.5±0.5 mm Hg. Aortic diastolic pressure measured in the ascending aorta proximal to the coarctation had an average

TABLE I
Anatomic Data

Dog	Age	Body wt	LV wt	LV/ body wt	RV wt	RV/ body wt
	mo	*kg*	*g*	*g/kg*	*g*	*g/kg*
1	13	19.0	165	8.68	38	2.00
2	14	20.5	163	7.95	43	2.10
3	13	19.1	173	9.06	41	2.15
4	12	16.8	154	9.17	48	2.91
5	14	20.5	190	9.27	46	2.24
6	14	13.2	140	10.61	37	2.80
7	09	12.7	119	9.37	35	2.76
8	—	25.0	150	6.00	37	1.48
Mean	13	18.4	157	8.76	41	2.30
±SEM	0.5	1.4	7.6	0.47	1.7	0.17

Dogs 1–7 had surgical coarctation banding as a puppy and dog 8 had congenital subvalvular aortic stenosis. Abbreviations used: LV, left ventricle; RV, right ventricle.

TABLE II
Control Hemodynamic Data

Dog	Heart rate	Systolic left ventricular pressure	LVED pressure	Diastolic aortic pressure	Left circumflex coronary blood flow
	beats/min	*mm Hg*	*mm Hg*	*mm Hg*	*cm³/min*
1	93	264	13	90	68
2	80	224	8	60	64
4	78	216	13	90	58
5	95	288	11	56	94
6	96	288	12	68	61
7	75	216	12	66	—
8	84	248	12	90	82
Mean	86	249	11.5	74	71
±SEM	3	12	0.5	6	6

Dogs are numbered the same as in Table I. Abbreviation used: LVED, left ventricular end-diastolic pressure.

value of 74±6 mm Hg. Mean coronary blood flow was 71±6 cm³/min. For the six dogs with coarctation-banding, 52±6% of the coronary flow occurred during systole (Fig. 1), whereas in the dog with congenital subvalvular stenosis, only 5% of the flow occurred during systole. The reactive hyperemic response after a 20-s complete occlusion was studied in six dogs. The peak flow was 302±72 cm³/min, and the mean duration of the response was 66±7 s. The flow debt repayment had a mean value of 437±104%. The diastolic pressure time index per tension time index was computed for the control state and 5 s after the beginning of the reactive hyperemic response (15). During control, the mean index was 1.06±0.18, which decreased significantly ($P < 0.05$) to 0.80±0.11 during reactive hyperemia.

Flow to the six layers of the myocardium, obtained during control conditions in seven dogs, is given in Fig. 2A. Average transmural flow was 0.97±0.08 cm³/min. Flow distribution data revealed that the highest flows occurred in layers 2, 3, and 4, with flows in epicardial layer 1 and endocardial layer 6 being significantly less than flows in these three layers ($P < 0.05$). The average endo/epi was 0.88±0.07. In Fig. 2B, myocardial flow data are given for 32 dogs studied in our laboratory, during the control state, using a similar protocol. In these dogs, the mean left ventricular weight was 115±2 g, the left ventricular body weight ratio 4.3±0.1 g/kg, and the left ventricular wall thickness was 14.5±0.25 mm. The mean arterial pressure had an

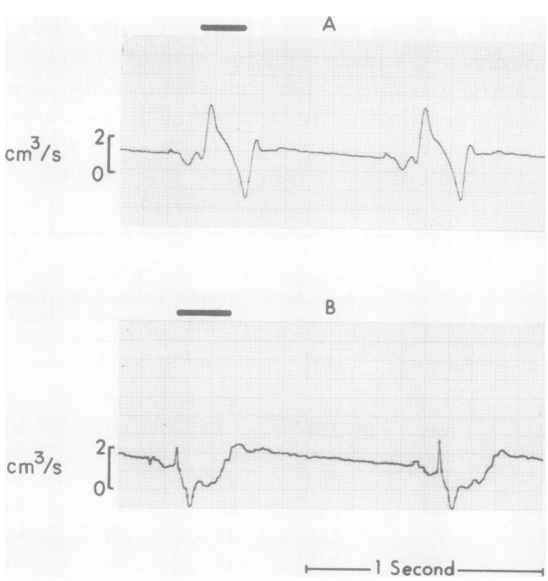

FIGURE 1 Phasic recording of flow in the left circumflex coronary artery from a dog with coarctation banding (A) and the dog with congenital subvalvular stenosis (B). The blank bars represent the period of ejection (systole). Note the marked difference in the contour of phasic flow during systole (see text).

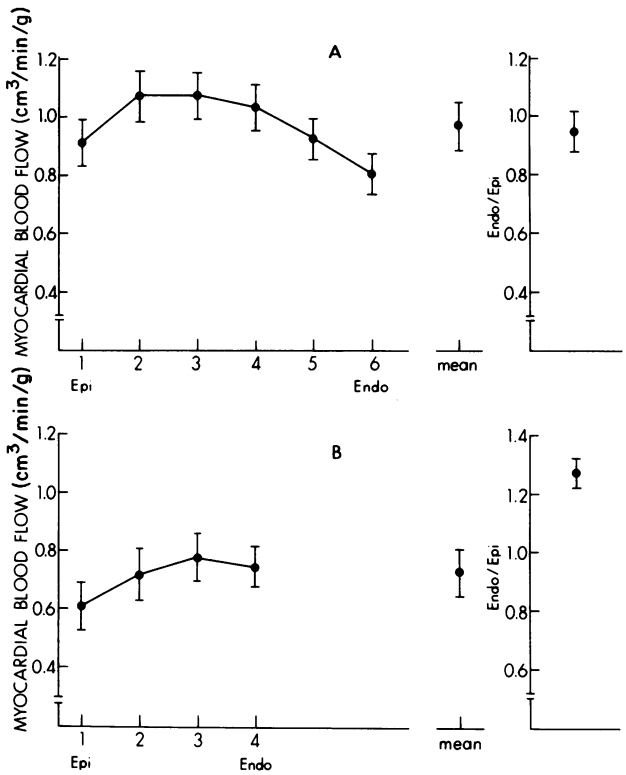

FIGURE 2 (A) Transmural blood flow distribution during resting conditions in seven dogs with concentric left ventricular hypertrophy. Flow for the six transmural layers are illustrated with one being the most epicardial and six the most endocardial. The mean transmural blood flow and the ratio of endocardial to epicardial flow also are given. The mean values (circles) and standard errors of the mean (bars) are illustrated for each entry. (B) Transmural blood flow distribution during resting conditions in 32 normal dogs. The hearts were sectioned into four transmural layers.

average value of 94±3 mm Hg, and the heart rate was 72±7 beats/min. These hearts were sectioned only into four transmural layers. Average transmural flow was 0.73±0.08 cm³/min per g, with endocardial flow being significantly higher ($P < 0.01$) than epicardial flow, endo/epi was 1.27±0.05. In the dogs with hypertrophy, the mean transmural blood flow is significantly higher ($P < 0.05$) and the endo/epi significantly less ($P < 0.05$) than in the normal dogs. Endocardial flow, however, is not significantly different ($P > 0.10$). Mean transmural right ventricular flow in the dogs with hypertrophy was 0.68±0.12 cm³/min per g and the endo/epi was 1.60±0.09.

In six dogs, transmural blood flow was measured 5 s after the onset of reactive hyperemia after a 45-s occlusion (Fig. 3). At this time, the heart rate had increased from a control value of 84±4 to 108±9 beats/min. Mean transmural blood flow in the region of the heart which was not made ischemic increased to 1.48±0.13 cm³/min and the endo/epi was 0.90±0.06. Mean transmural

flow in the ischemic area increased to 3.5±0.30 cm^3/min per g. Layers 1–4 increased proportionally greater than layers 5 and 6, so that the endo/epi fell to 0.52±0.06. In one dog (no. 4, Table I) adenosine, 1 mg/kg per min, was infused intravenously, and transmural myocardial blood flow was measured 5 min after a steady state had been achieved. Mean transmural flow was 3.37 cm^3/min per g and endo/epi was 0.38 for the entire left ventricle. This was associated with an increase in heart rate from 80 to 160 beats/min and no change in the diastolic pressure of 90 mm Hg. In this dog, flow in the right ventricle increased to 3.63 cm^3/min per g with an endo/epi of 1.32.

DISCUSSION

It is apparent, from the data provided in Table I, that all dogs exhibited marked concentric left ventricular hypertrophy. The left ventricular wall was thickened markedly and was sectioned easily into six transmural layers. In addition, the diameters of the muscle cells in the left ventricle were greater than in the normal dog (11). However, the interpretation of the cell diameter data are open to question because the distention of the ventricle during fixation with 80 mm Hg intracoronary pressure may be different in the hypertrophic ventricle and hence make comparisons with the ventricle of normal weight somewhat tenuous. Because the left ventricular end-diastolic pressure was not elevated markedly, it would seem reasonable to conclude that the compliance of the left ventricle was not decreased markedly and that the comparison of cell diameters at least should be directionally correct. There was no evidence of congestive heart failure in any of the animals studied. Minimal fibrosis was present in the left ventricle, but appeared to be recent, perhaps related to the second operation necessary for instrumentation. The fibrosis was <5% of all samples, and was limited primarily to the endocardial layers. However, samples in which fibrosis was present were compared to samples in which no fibrosis could be detected, and there was no statistical difference between the flows during either control conditions or after reactive hyperemia. Thus, the data of myocardial blood flow distribution were not influenced by the presence of fibrosis. The dog with congenital subvalvular aortic stenosis demonstrated a tight subvalvular fibrotic ring and poststenotic dilatation of the aorta. The histologic examination of the heart and the myocardial blood flow distribution, during both the control state and after reactive hyperemia, were the same in this animal as in the dogs with coarctation banding.

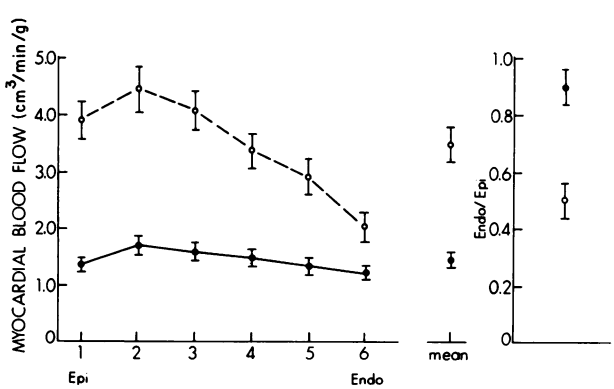

FIGURE 3 Transmural blood flow during ischemic-induced vasodilatation in six dogs. (●) represent data obtained from the region of the heart not made ischemic and (○) represent data from the previously ischemic area. Data are presented as in Fig. 2.

In the dogs with hypertrophy, the left ventricles generated an average peak systolic pressure of 249±12 mm Hg. This was associated with a peak systolic pressure gradient of 126±12 mm Hg across the coarctation and 121 mm Hg across the subvalvular ring. The diastolic pressure, during both the control state and reactive hyperemia, was the same proximal and distal to the coarctation. Therefore, the coarctation-banding model appears to be more consistent with the hemodynamic findings in patients with aortic stenosis than in those with systemic hypertension; i.e., the diastolic pressure is essentially within normal limits. A similar normal diastolic pressure has been reported in patients with congenital supravalvular aortic stenosis (16).

The recordings of phasic coronary blood flow demonstrated that in the dogs with coarctation banding, ≅52% of the total flow occurred during systole. One might speculate that the distribution of myocardial flow during the control state might be the result of this finding, because it has been shown by Rembert et al. (17) that when coronary flow is limited to systole, the majority of the flow perfuses only the epicardial layers. However, the coronary flow, as measured by the flowmeter probes, does not take into account the volume of blood which is retained in the epicardial coronary vessels during systole as a result of the distensibility of the vessel. Douglas and Greenfield (18) demonstrated that in the left coronary of the normal dog, a 50-mm Hg pulse pressure was associated with ≅0.06-cm^3 increase in volume of the left circumflex coronary artery. In the dogs with hypertrophy, the mean pulse pressure was ≅175 mm Hg. Although the pressure-volume relationships in the coronary vessels of the hypertrophied dog are not known, it seems reasonable to conclude that a major portion of the systolic blood flow measured by the flowmeter actually distends the epicardial vessels and does not perfuse the myocardium during systole. Hence, the distribution pattern of flow found at rest is probably not related to the increase in systolic flow. Corroborating evidence of this fact is demonstrated by the dog with congenital subvalvular

aortic stenosis in which only 5% of the coronary flow occurs during systole, and the myocardial blood flow distribution at rest was the same as in the coarctation-banding dogs.

Several investigators have studied the coronary blood flow and oxygen consumption per gram of myocardium in dogs with left ventricular hypertrophy. West et al. (3) employed renal hypertension to produce left ventricular hypertrophy. Banding of the ascending aorta was carried out by Malik et al. (4). Marchetti et al. (5) studied animals with hypertrophy secondary to a peripheral arteriovenous fistula. These investigators found normal values for both mean coronary flow and oxygen consumption. Geha et al. (19) noted in dogs with banding of the aorta, that left ventricular blood flow was decreased when compared to normal dogs, but because myocardial oxygen extraction was greater, myocardial oxygen consumption remained within normal limits. The data presented in Fig. 2 demonstrate that the mean blood flow per gram of myocardium was slightly, but significantly, higher in the animals with hypertrophy than in the 32 dogs with normal-sized left ventricles studied in our laboratory. However, there was a significant difference between the resting heart rates; i.e., 72 as compared to 86 beats/min in the control and hypertrophy animals, respectively. It is likely that the difference in myocardial blood flow can be explained by the faster heart rates.

In comparing blood flow distribution data from animals with a normal-sized left ventricle to the hypertrophied dogs, the possibility must be kept in mind that the differences noted may be due, at least in part, to the effects of the initial surgical procedure carried out to prepare the coarctation; i.e. a sham-operated control group was not prepared. This would seem to be quite unlikely because during this operation dissection was not carried out near either the vascular or neural supply to the heart.

Of primary interest is the distribution of myocardial blood flow which occurred during resting conditions. Previous studies by Marcus et al. (9) demonstrated that the transmural blood flow in animals with left ventricular hypertrophy, secondary to renal vascular hypertension, was normal (endo/epi 1.2 ± 0.05, whereas the data of Einzig et al. (10) from anesthetized animals in whom the hypertrophy was secondary to aortic banding yielded an endo/epi of 0.89 ± 0.05. In the present study, the endo/epi was 0.88 in the hypertrophied dogs and 1.27 in the control animals and is consistent with the findings of Einzig et al. (10). One major difference between the dogs with hypertrophy due to hypertension and the dogs with coarctation banding, is in the higher diastolic pressure in the former group. Thus, there is a higher pressure at the time when the endocardial layers are perfused. However, it is not likely that the increased diastolic perfusion pressure is responsible solely for the difference in blood flow distribution between these two models of hypertrophy and may be due, at least in part, to the degree of hypertrophy.

There are two distinct explanations for the abnormal blood flow distribution in the hypertrophied ventricle: (*a*) the endocardial layer is, in fact, chronically underperfused or (*b*) the blood flow is adequate to meet a reduced metabolic requirement. Because it was found that during both reactive hyperemia and adenosine infusion, flow in the endocardial layers increased by at least 2.5-fold, it is not reasonable to conclude that the subendocardial flow during the control state was maximal; i.e. represented a completely vasodilatated state. Thus, the possibility that the endocardial layer is chronically underperfused is remote. In the normal dogs, during control conditions, subendocardial flow is invariably higher than subepicardial flow (13). This finding may be ascribed to the fact that the systolic wall stress is greatest in the endocardial layer and hence a higher flow is required to provide for the increase in metabolic demands. In examining Fig. 2, it is apparent that the first four layers of the hypertrophied ventricle have a flow distribution which is quite similar to that seen in the normal dog. The two endocardial layers of the hypertrophied dog have a reduced flow which one might speculate is related to a decrease in wall stress; i.e., in the hypertrophied ventricle the middle layers bear the greater systolic stress. Thus, it seems quite likely that flow to the endocardial layers, in the resting state, is sufficient to meet the metabolic requirements. Supportive evidence of this hypothesis is the finding that the diastolic pressure time index per tension time index, during the control state, was 1.06, implying adequate subendocardial perfusion (15). However, because the validity of this index has not been tested in the hypertrophied ventricle, the interpretation of these data is clouded somewhat.

The possibility that the abnormal endo/epi found in the hypertrophied heart is related in some way to the marked increase in aortic impedance created by the stenosis would seem a plausible hypothesis in view of the findings reported by Buckberg et al. (15). In open chest dogs, subjected to acute proximal aortic constriction, these investigators reported a mean peak systolic blood pressure of 211 mm Hg, a mean left atrial pressure of 39 mm Hg, and a heart rate of 206 beats/min. During these conditions, the endo/epi fell from an average control value of 1.01 to 0.37. Obviously, these hemodynamic conditions are markedly different from those which occur in the awake hypertrophied animals, because the heart rates and left ventricular filling pressures in the hypertrophied dogs were within normal limits. Recently, a study was completed in our laboratory in which chronically instrumented awake dogs were subjected to acute proximal aortic constriction (20). In these dogs, the heart rate was held constant

at 151 beats/min and acute aortic constriction was initiated to increase the systolic left ventricular pressure to ≅200 mm Hg. Myocardial blood flow distribution was measured at 5 and 30 s after the onset of aortic constriction. At 5 s, the mean endo/epi was 0.36; however, at 30 s the endo/epi was 1.14, which is within the normal range found during control conditions. Thus, in the awake dog, acute reduction in subendocardial flow secondary to a marked increase in aortic impedance is rapidly compensated, and the subendocardial blood flow quickly returns to normal. Thus, the reduced flow to the endocardial layer in the chronically hypertrophied ventricle is not likely to be related to a great extent to the hemodynamic conditions imposed by the marked increase in aortic impedance.

The reactive hyperemic response, after a 20-s occlusion, can be compared to that noted in the normal dogs studied by Bache et al. (21). The mean duration of the response of 77±7 s and flow debt repayment of 440±35% in the dogs studied by Bache et al. are not significantly different from duration of 66±7 s and flow debt repayment of 437±104% found in the hypertrophied dogs. Peak flows of ≅85 cm^3/min after a 20-s occlusion were recorded in normal dogs by Coffman and Gregg (14). In the dog with hypertrophy secondary to an arteriovenous fistula, Marchetti et al. (5) found a peak flow of 159.9±19.9 cm^3/min after a 20-s occlusion. However, this was not significantly different from the peak flow of 143.9±13 cm^3/min they obtained in normal dogs (5). It is apparent that the peak flows of 302 ±72 cm^3/min recorded in the present study are considerably greater than recorded previously in either normal or hypertrophied hearts. Because the flow increased from 0.97±0.03 to 3.5±0.30 cm^3/min per g during reactive hyperemia, the fourfold increase in peak coronary flow is to be expected. The magnitude of the flow increase implies that the coronary vessels of the dog with left ventricular hypertrophy are able to transport a higher peak flow rate than has been recorded in the normal dog.

Myocardial blood flow distribution, during a reactive hyperemic response, is illustrated in Fig. 3, in both the nonischemic and ischemic portions of the left ventricle. Flow to the nonischemic area increased from mean control value of 0.95±0.05 to 1.48±0.13 cm^3/min per g presumably related to the increase in myocardial work which occurred during occlusion in this portion of the heart. The endo/epi remained approximately the same so that flow increased uniformly through the wall. During the reactive hyperemic response to the ischemic area, mean transmural myocardial flow increased to 3.50±0.30 cm^3/min per g. Flow in the epicardial layers increased to levels previously reported in normal dogs by Cobb et al. (22). Although flow increased from control values of 0.80±0.07 to 2.04±0.25 cm^3/min per g in the endocardial layer, the endo/epi fell significantly to 0.52±0.06. Similar findings were noted in the animal who received an infusion of adenosine (endo/epi, 0.38). This is clearly an abnormal response because, in dogs with a normal-sized left ventricle, transmural blood flow distribution either favors the subendocardium or is uniform during reactive hyperemia (22) and adenosine infusion (13). Because the endocardial layers are relatively underperfused in the hypertrophied dogs during reactive hyperemia, one might expect a prolongation of the reactive hyperemia response and an increase in the flow debt repayment. This was not the case. However, Bache et al. (21) have shown that a flow debt repayment of only 115±10% in the normal dog is adequate to restore vasomotor activity of the coronary vasculature, and the findings in the hypertrophied dogs are consistent with this observation.

The explanation for the decreased relative perfusion of the endocardial layer, during the reactive hyperemic response, is not readily apparent. The most likely explanation for this finding is that, during general vasodilatation of the myocardium, the caliber of the arterial vessels penetrating the markedly thickened left ventricle are not adequate to deliver a high flow and, as a result, the subendocardium is relatively underperfused. Another distinct possibility for the reduced subendocardial flow is that the capillary density in the subendocardium does not increase proportionally during the hypertrophy process and is inadequate during high flow states. Whatever the cause, during maximum vasodilatation, reduced subendocardial blood flow occurs in spite of a normal diastolic perfusion pressure. Because the reactive hyperemic response is usually attended by a decrease in transmyocardial arteriovenous oxygen difference, one cannot assume that the myocardium, under these conditions, is ischemic. However, during heavy exercise, flow in the endocardial layer in the normal dog was found, in our laboratory, to increase to 3.82±0.3 cm^3/min per g which is considerably higher than the endocardial flow of 2.04±0.25 cm^3/min per g found in these dogs with hypertrophy during maximum vasodilatation (23). Thus, in situations requiring high flow to meet the metabolic requirements to the heart, e.g. exercise, the endocardial layer of the markedly hypertrophied left ventricle may not receive adequate flow and become truly ischemic. If this is the case, the findings in these dogs are consistent with the frequent clinical observations of subendocardial underperfusion; i.e. angina pectoris, which occurs in patients with left ventricular hypertrophy secondary to valvular aortic stenosis and without obstructive lesions in the coronary arteries.

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