JACC Vol. 10, No. 1
July 1987:53–62

Differences in Coronary Flow and Myocardial Metabolism at Rest and During Pacing Between Patients With Obstructive and Patients With Nonobstructive Hypertrophic Cardiomyopathy

RICHARD O. CANNON III, MD, FACC, WILLIAM H. SCHENKE, BA, BARRY J. MARON, MD, FACC, CYNTHIA M. TRACY, MD, FACC, MARTIN B. LEON, MD, FACC, JOHN E. BRUSH, JR., MD, DOUGLAS R. ROSING, MD, FACC, STEPHEN E. EPSTEIN, MD, FACC

Bethesda, Maryland

Fifty patients with hypertrophic cardiomyopathy underwent invasive study of coronary and myocardial hemodynamics in the basal state and during the stress of pacing. The 23 patients with basal obstruction (average left ventricular outflow gradient, 77 ± 33 mm Hg; left ventricular systolic pressure, 196 ± 33 mm Hg, mean ± 1 SD) had significantly lower coronary resistance (0.85 ± 0.18 versus 1.32 ± 0.44 mm Hg·min/ml, $p < 0.001$) and higher basal coronary flow (106 ± 20 versus 80 ± 25 ml/min, $p < 0.001$) in the anterior left ventricle, associated with higher regional myocardial oxygen consumption (12.4 ± 3.6 versus 8.9 ± 3.3 ml oxygen/min, $p < 0.001$) compared with the 27 patients without obstruction (mean left ventricular systolic pressure 134 ± 18 mm Hg, $p < 0.001$).

Myocardial oxygen consumption and coronary blood flow were also significantly higher at paced heart rates of 100 and 130 beats/min (the anginal threshold for 41 of the 50 patients) in patients with obstruction compared with those without. In patients with obstruction, transmural coronary flow reserve was exhausted at a heart rate of 130 beats/min; higher heart rates resulted in more severe metabolic evidence of ischemia with all patients experiencing chest pain, associated with an actual increase in coronary resistance. Patients without obstruction also demonstrated evidence of ischemia at heart rates of 130 and 150 beats/min, with 25 of 27 patients experiencing chest pain. In this group, myocardial ischemia occurred at significantly lower coronary flow, higher coronary resistance and lower myocardial oxygen consumption, suggesting more severely impaired flow delivery in this group compared with those with obstruction. Abnormalities in myocardial oxygen extraction and marked elevation in filling pressures during stress were noted in both groups.

Thus, obstruction to left ventricular outflow is associated with high left ventricular systolic pressure and oxygen consumption and therefore has important pathogenetic importance to the precipitation of ischemia in patients with hypertrophic cardiomyopathy. Patients without obstruction may have greater impairment in coronary flow delivery during stress.

(J Am Coll Cardiol 1987;10:53–62)

The most characteristic feature of hypertrophic cardiomyopathy is hypertrophy of the left ventricle without obvious physiologic explanation (1). In many patients with this disease, an intraventricular pressure gradient can be demonstrated, localized to the site of apposition of the mitral valve with the septum (2–5). However, controversy exists as to whether this phenomenon represents true mechanical obstruction to left ventricular systolic ejection (5–10). In symptomatic patients with fixed mechanical obstruction to left ventricular outflow, such as aortic stenosis, a high left ventricular systolic pressure results in elevated absolute basal coronary flow and myocardial oxygen consumption (11–13), and limited coronary flow reserve has been demonstrated intraoperatively (14). The present study was performed to examine whether patients with and patients without basal obstruction to left ventricular outflow differ with regard to coronary and myocardial hemodynamics and therefore verify whether the subaortic gradient and elevated intraventricular pressures in hypertrophic cardiomyopathy are of pathophysiologic consequence.

From the Cardiovascular Diagnosis Section, Cardiology Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Manuscript received October 27, 1986; revised manuscript received January 14, 1987, accepted January 26, 1987.

Address for reprints: Richard O. Cannon III, MD, Building 10, Room 7B-15, National Institutes of Health, Bethesda, Maryland 20892.

0735-1097/87/$3.50

JACC Vol. 10, No. 1
July 1987:53–62

Methods

Patient selection. We studied 50 patients with an echocardiographic diagnosis of hypertrophic cardiomyopathy. All patients had a hypertrophied, nondilated left ventricle in the absence of another cardiac or systemic disease capable of causing myocardial hypertrophy (1) and had angiographically normal epicardial coronary arteries. Thirty-six patients were men and 14 were women, ranging in age from 22 to 60 years (mean 43). No patient had previously undergone cardiac surgery. All patients were severely symptomatic (New York Heart Association functional class III to IV) and 48 of the 50 described chest pain as a major symptom. This study represents a consecutive series of patients with hypertrophic cardiomyopathy who underwent the catheterization study protocol. Patients were considered to have basal obstruction to left ventricular outflow if their basal pressure gradient was ≥30 mm Hg. Data from 18 of these patients have been reported previously (15). Informed consent for this study was obtained from all patients.

Echocardiographic studies. A combined M-mode and two-dimensional echocardiographic examination was performed in each of the 50 study patients. M-mode echocardiograms were performed with an Irex System II ultrasound unit with either a 2.25 or 3.5 MHz transducer. Two-dimensional echocardiograms were performed with either a Varian V-3400 or ATL (Advanced Technology Laboratory, Inc.) MK-500 ultrasound system with 2.25 or 3.5 MHz transducers, respectively. In 42 of the 50 study patients in whom two-dimensional echocardiograms were of adequate quality, assessment of the magnitude of left ventricular hypertrophy was made primarily from the parasternal short-axis cross-sectional plane, as previously described (16). The ventricle was divided into four regions that identified the anterior and posterior ventricular septum and the lateral and posterior left ventricular free wall. Wall thickness of each region was measured directly from the television monitor with calipers, using a calibration scale produced by the instrument. A wall thickness index was calculated by adding the measurements of maximal wall thickness obtained in each of the four segments into which the ventricle had been divided. The calculated score was considered a quantitative expression of the overall magnitude of left ventricular hypertrophy. All measurements were performed by one investigator without knowledge of the catheterization study results.

Cardiac catheterization: coronary flow and myocardial metabolism. All medications, including β-adrenergic blockers and calcium channel blockers, were terminated at least 48 hours or 5 drug half-lives before cardiac catheterization. After sedation with diazepam, 10 mg orally, patients were taken to the catheterization laboratory, usually at 8:00 AM in the fasting state and without any other premedication. A Baim thermodilution flow catheter (17) (Elecath Corp.) was introduced into the right atrium through the right internal jugular vein. The great cardiac vein, which is the recipient of blood from the left anterior descending artery system, was cannulated through the coronary sinus. Hand injections of contrast dye were recorded on cine film, demonstrating the catheter tip at the junction of the anterior interventricular vein and great cardiac vein without adjacent marginal veins in all cases. The catheter position was kept constant throughout the study by frequent inspection of the relation of the electrodes on the catheter to bony landmarks by fluoroscopy. The thermodilution technique for determining great cardiac vein flow has been described previously (18,19). All temperature determinations were fed directly into an IBM PC/XT computer, averaging 20 seconds of infusate-blood mixture for each flow determination, with on-line calculation of great cardiac vein flow using a standard formula (17).

This method of coronary flow measurement was chosen for two reasons: First, in our experience, the catheter advanced into the great cardiac vein is stable in position with minimal or no movement even during pacing, and reproducible flow measurments may be achieved at rest and during pacing. Second, measurements of venous flow from the anterior left ventricular wall may allow estimation of coronary flow and myocardial metabolism in that portion of the ventricle most abnormal in the majority of patients with hypertrophic cardiomyopathy, that is, the anterior septum and free wall (16). Coronary sinus flow measurements were not recorded because of concern for right atrial reflux during pacing (20). Coronary resistance was calculated as the mean blood pressure divided by the great cardiac vein flow.

A 20 gauge catheter was placed in the left brachial artery for arterial pressure measurements. An 8F end-hole pigtail catheter (in 31 patients, a transducer-tipped catheter, Millar Instruments) was advanced into the left ventricle. Cardiac output and pulmonary artery wedge pressures were measured with a thermodilution catheter in the pulmonary artery. Cardiac index was calculated as cardiac output divided by the body surface area. Systemic vascular resistance index was calculated as mean systemic blood pressure divided by the cardiac index. Arterial and left ventricular pressures and electrocardiographic (ECG) monitor leads 1, aVF and V_3 or V_5 were recorded with each flow measurement in the great cardiac vein. Lactate samples were obtained from the great cardiac vein and brachial artery and immediately transferred to tubes containing sodium fluoride and potassium oxalate for inhibition of glycolysis, with immediate centrifugation at 4°C at 5,000 rpm for 5 minutes. The supernatant was then processed for lactate content on a DuPont automatic clinical analyzer by a modification of the technique of Marbach and Weil (21). Lactate consumption was calculated as the difference between the arterial and great cardiac vein lactate concentrations multiplied by the great cardiac vein flow. Oxygen content was determined with a

Lex-O_2-Con oxygen analyzer (Lexington Instruments) at rest and during pacing. Myocardial oxygen consumption in the anterior circulation was calculated as the difference between the arterial and great cardiac vein oxygen content multiplied by the great cardiac vein flow.

Diagnostic catheterization: ventricular outflow obstruction. Before the pacing coronary flow study, all patients underwent diagnostic right and left heart catheterization. Obstruction to left ventricular outflow was defined as the presence of an intraventricular gradient of ≥30 mm Hg localized to the left ventricular outflow tract during pullback of an end-hole catheter. Care was taken to exclude artifactual distortion of the left ventricular pressure by catheter entrapment as described by Wigle et al. (22). Although maneuvers to provoke an outflow gradient, including the Valsalva maneuver, amyl nitrite inhalation and isoproterenol infusion, were used to assess the presence and severity of a left ventricular outflow gradient in many patients, only the basal left ventricular outflow gradient was used to distinguish patients with from those without obstruction to left ventricular outflow in this study. In 47 patients, coronary arteriography, using multiple angulated views, was performed after completion of hemodynamic studies. In the remaining three patients, coronary arteriography was performed before referral to the Cardiology Branch, National Heart, Lung, and Blood Institute. Left ventriculography was performed in 45 study patients. Left ventricular ejection fraction was estimated from the left ventriculogram in the 45° right anterior oblique projection using the area-length method of Sandler and Dodge (23).

Pacing coronary flow study. The study protocol was initiated at least 20 minutes after the use of angiographic contrast material to eliminate any effects of the dye on coronary flow and myocardial metabolism (24). Great cardiac vein flow, lactate and oxygen content were determined at rest as were measurements of cardiac output, mean pulmonary artery wedge pressure and left ventricular peak systolic and end-diastolic pressures. Pacing through the coronary sinus thermodilution catheter was initiated at a heart rate of 100 beats/min in the 45 patients whose basal heart rates were <100 beats/min, and increased by increments of 10 beats/min at 1 to 2 minute intervals up to a heart rate of 150 beats/min in 48 patients. Atropine, 0.5 to 1.0 mg, was given intravenously to seven patients to facilitate rapid atrial pacing. In two patients, pacing was terminated at 130 beats/min because of the severity of chest pain. Arterial and left ventricular pressures and great cardiac vein flow were measured at each heart rate. Left ventricular end-diastolic pressure was measured at heart rates of 100, 130 and 150 beats/min. At heart rates of 100 and 130 beats/min, the left ventricular end-diastolic pressure was measured after sudden termination of pacing in 31 patients and during pacing in the rest, with an average of pressures over a 10 second interval, excluding the first four postpacing beats. After pacing for 2 minutes at a heart rate of 150 beats/min, the left ventricular end-diastolic pressure was measured immediately after termination of pacing in 48 patients using the same criteria. Cardiac output determinations were made in triplicate at heart rates of 130 and 150 beats/min and averaged. Blood specimens from the great cardiac vein and brachial artery were obtained at heart rates of 130 and 150 beats/min for oxygen and lactate content. ECG analysis was performed only in the immediate postpacing ECG, which was compared with the record obtained before pacing.

Statistical analyses. Data were analyzed by the two-tailed Student's *t* test for paired and unpaired data when appropriate, with the probability (p) value <0.05 considered statistically significant. Regression analyses were performed when indicated. All group data are reported as mean ± 1 SD.

Results

Echocardiographic evaluation (Table 1). In each of the 50 study patients, hypertrophy of the anterior ventricular septum (thickness ≥15 mm) was identified by both M-mode and two-dimensional echocardiography. In 42 patients (21 with obstruction, 21 without obstruction), two-dimensional echocardiographic studies were of satisfactory quality to permit estimation of the magnitude and extent of left ventricular hypertrophy. The maximal thickness of the anterior septum (the region of the left ventricle drained in part by the great cardiac vein) was 20 ± 3 mm in patients with obstruction and 20 ± 6 mm in those without obstruction.

Table 1. Quantitation of Left Ventricular Hypertrophy

	HCM-N	HCM-O	p Value
No. of patients	21	21	NS
Male/female	17/4	14/7	NS
Maximal thickness of LV (mm)	22 ± 5	19 ± 5	NS
Thickness of anterior septum (mm)	20 ± 6	20 ± 3	NS
Index of overall LV hypertrophy (mm)	61 ± 15	60 ± 14	NS

HCM-N and HCM-O = nonobstructive and obstructive hypertrophic cardiomyopathy, respectively; LV = left ventricle.

There was no significant difference in the distribution or severity of hypertrophy between patients with and without basal left ventricular outflow obstruction.

Angiographic evaluation. By study inclusion criteria, all patients had entirely normal epicardial coronary arteries. Basal coronary flow in the left coronary artery appeared in most patients to be higher than normal as evidenced by rapid transit of contrast medium injected into the coronary ostia. There was often a complete cessation of dye movement in systole, with rapid transit in diastole. Systolic compression of septal perforating vessels was noted in 19 (86%) of 22 patients with obstruction and 16 (64%) of 25 patients without obstruction whose coronary arteriograms were available for review. Systolic compression of epicardial vessels was noted in one patient with obstruction and two patients without obstruction. Left ventriculography generally demonstrated an elongated, hyperdynamic ventricle with massive hypertrophy of papillary muscles, giving a "ballerina slipper" appearance. Evidence of mitral regurgitation was noted in 19 (86%) of 22 patients with obstruction and 8 (35%) of 23 patients without obstruction whose ventriculograms were available for review. The angiographic ejection fraction was increased in both groups: 81 ± 8% in the nonobstructive group, 81 ± 10% in the obstructive group.

Basal coronary and myocardial hemodynamics (Table 2, Fig. 1 and 2). In the basal state, 23 patients had an intraventricular gradient of ≥30 mm Hg (77 ± 33) localized to the left ventricular outflow tract; 27 patients had either a minimal or no basal gradient (3 ± 7 mm Hg). There was a significant relation between the basal left ventricular systolic pressure and great cardiac vein flow ($r = 0.51$, $p < 0.001$) (Fig. 1A) and coronary resistance ($r = 0.41$, $p < 0.01$) (Fig. 2B), although wide variation was noted. Whereas the left ventricular systolic pressure was higher in patients with obstruction, the mean systemic pressure was significantly lower in patients with than in those without obstruction (88 ± 12 versus 96 ± 13 mm Hg, $p < 0.05$). Additionally, the basal heart rate was higher in patients with obstruction (83 ± 13 versus 75 ± 11 beats/min, $p < 0.005$). The basal great cardiac vein flow was significantly higher (106 ± 20 versus 80 ± 25 ml/min, $p < 0.001$) and coronary resistance lower (0.85 ± 0.18 versus 1.32 ± 0.44 mm Hg·min/ml, $p < 0.001$) in the patients with obstruction (Fig. 2) and was associated with greater myocardial oxygen consumption in the anterior left ventricular septum and free wall than that in patients without obstruction (12.4 ± 3.6 versus 8.9 ± 3.3 ml oxygen/min, $p < 0.01$). Myocardial oxygen consumption, even when normalized for heart rate, was still significantly higher in the group with obstruction (0.15 ± 0.05 versus 0.12 ± 0.04 ml oxygen/min, $p < 0.025$). Left ventricular filling pressures, as estimated by the left ventricular end-diastolic and mean pulmonary artery wedge pressures, were similar for the two groups.

Coronary and myocardial hemodynamics during pacing (Table 2, Fig. 2 to 4). In the 45 patients whose basal heart rate was <100 beats/min, atrial pacing was initiated at 100 beats/min. Two patients (one with and one without obstruction) experienced chest pain at this heart rate. The left ventricular systolic pressure was significantly higher (181 ± 30 versus 136 ± 21 mm Hg, $p < 0.001$) and mean systemic blood pressure significantly lower (91 ± 16 versus 100 ± 14 mm Hg, $p < 0.05$) in the patients with than in those without obstruction to left ventricular outflow. Coronary resistance decreased in both groups in response to the stress of pacing, but was significantly lower (0.76 ± 0.27 versus 1.09 ± 0.44 mm Hg·min/ml, $p < 0.005$) and the great cardiac vein flow higher (132 ± 46 versus 104 ± 38 ml/min, $p < 0.05$) in patients with obstruction. The left ventricular end-diastolic pressure was minimally increased from basal measurements at this heart rate.

Pacing at a heart rate of 130 beats/min (performed in each of the 50 patients) resulted in anginal chest pain in all but 9 patients, regardless of the presence or absence of outflow obstruction. In response to this stress, mean systemic pressure rose in both groups, and was no longer significantly different. Additionally, the left ventricular systolic pressure fell in the group with basal outflow obstruction, resulting in a reduction of outflow gradient to 49 ± 30 mm Hg. Still, the left ventricular systolic pressure was significantly higher in the group with obstruction (173 ± 28 versus 132 ± 25 mm Hg, $p < 0.001$), as was coronary flow (155 ± 40 versus 125 ± 42 ml/min, $p < 0.025$) and myocardial oxygen consumption (18.1 ± 6.8 versus 13.0 ± 4.2 ml oxygen/min, $p < 0.01$). Coronary resistance was significantly lower in the group with obstruction (0.67 ± 0.17 versus 0.95 ± 0.42 mm Hg·min/ml, $p < 0.005$). Metabolic evidence for ischemia was apparent in both groups at this heart rate, along with a decline in lactate consumption, reflecting decreased lactate extraction compared with baseline measurements, and actual lactate production in four patients (Fig. 3). Further evidence for ischemia was the significant elevation in left ventricular end-diastolic pressure in both groups compared with the basal state. Despite the onset of ischemia in the majority of patients in both groups, there was no overall increase in oxygen extraction in either group (Fig. 4).

At a heart rate of 150 beats/min in 48 patients, all but 2 patients (both in the group without basal obstruction) experienced chest pain, often to a severe degree. The mean systemic pressure further increased in both groups. As the cardiac index fell in both groups compared with basal measurements, the increase in mean systemic pressure in both groups was related to an increase in systemic vascular resistance. Although the left ventricular systolic pressure and outflow gradient fell further in the group with basal obstruction, the left ventricular systolic pressure was still signifi-

Table 2. Hemodynamic Data During Pacing Study in 50 Patients With Hypertrophic Cardiomyopathy

	Basal			Pacing: 100 beats/min			Pacing: 130 beats/min			Pacing: 150 beats/min		
	HCM-N	HCM-O	p Value	HCM-N	HCM-O	p Value	HCM-N	HCM-O	p Value	HCM-N	HCM-O	p Value
Heart rate (beats/min)	75 ± 11	83 ± 13	<0.005	100	100		130	130		150	150	
Mean systemic pressure (mm Hg)	96 ± 13	88 ± 12	<0.05	100 ± 14	91 ± 16	<0.05	103 ± 16	98 ± 13		107 ± 21	103 ± 14	
LV systolic pressure (mm Hg)	134 ± 18	196 ± 33	<0.001	136 ± 21	181 ± 30	<0.001	132 ± 25	173 ± 28	<0.001	133 ± 25	157 ± 25	<0.005
LV outflow gradient (mm Hg)	3 ± 7	77 ± 33	<0.001	3 ± 7	64 ± 27	<0.001	1 ± 4	49 ± 30	<0.001	1 ± 4	32 ± 25	<0.001
Cardiac index (liters/min per m^2)	3.1 ± 0.6	3.0 ± 0.4					3.0 ± 0.7	3.0 ± 0.4		2.7 ± 0.8	2.7 ± 0.5	
Systemic vascular resistance index [(mm Hg·min·m^2)/liter]	32.7 ± 8.1	30.1 ± 6.7					35.9 ± 9.8	32.6 ± 7.0		42.7 ± 13.8	39.6 ± 10.1	
GCV flow (ml/min)	80 ± 25	106 ± 20	<0.001	104 ± 38	132 ± 46	<0.05	125 ± 42	155 ± 40	<0.025	130 ± 41	140 ± 32	
Coronary resistance (mm Hg·min/ml)	1.32 ± 0.44	0.85 ± 0.18	<0.001	1.09 ± 0.44	0.76 ± 0.27	<0.005	0.95 ± 0.42	0.67 ± 0.17	<0.005	0.90 ± 0.31	0.76 ± 0.15	
Arterial O_2 (ml O_2/100 ml)	17.9 ± 2.0	18.1 ± 3.0					17.8 ± 2.2	18.1 ± 2.8		18.4 ± 2.2	18.5 ± 3.2	
GCV O_2 (ml O_2/100 ml)	6.7 ± 1.5	6.5 ± 1.7					7.0 ± 1.1	6.8 ± 1.7		7.2 ± 1.5	7.2 ± 1.6	
(A − V) O_2 (ml O_2/100 ml)	11.2 ± 1.6	11.6 ± 1.9					10.9 ± 1.4	11.5 ± 2.0		11.3 ± 2.0	11.4 ± 2.0	
							13.0 ± 4.2	18.1 ± 6.8	<0.01	15.2 ± 5.1	16.1 ± 5.4	
$M\dot{V}O_2$ (ml O_2/min)	8.9 ± 3.3	12.4 ± 3.6	<0.001				20.8 ± 29.0	17.0 ± 23.4		3.0 ± 51.8	−20.8 ± 35.3	
Lactate consumption (m*M*·ml/min)	25.4 ± 20.3	30.0 ± 22.3										
LVEDP (mm Hg)	17 ± 7	16 ± 6		18 ± 7	18 ± 7		22 ± 10	21 ± 8		27 ± 10	28 ± 7	
PCW (mm Hg)	14 ± 7	12 ± 4					18 ± 9	19 ± 4		22 ± 10	21 ± 7	
Patients with chest pain/No. of patients	0 of 27	0 of 23		1 of 26	1 of 19		22 of 27	19 of 23		24 of 26	22 of 22	

(A − V) O_2 = arterial − great cardiac vein oxygen difference; GCV = great cardiac vein; LVEDP = left ventricular end-diastolic pressure; $M\dot{V}O_2$ = myocardial oxygen consumption in the anterior circulation [(A − V) O_2 × GCV flow]; O_2 = oxygen; PCW = mean pulmonary artery wedge pressure; other abbreviations as in Table 1.

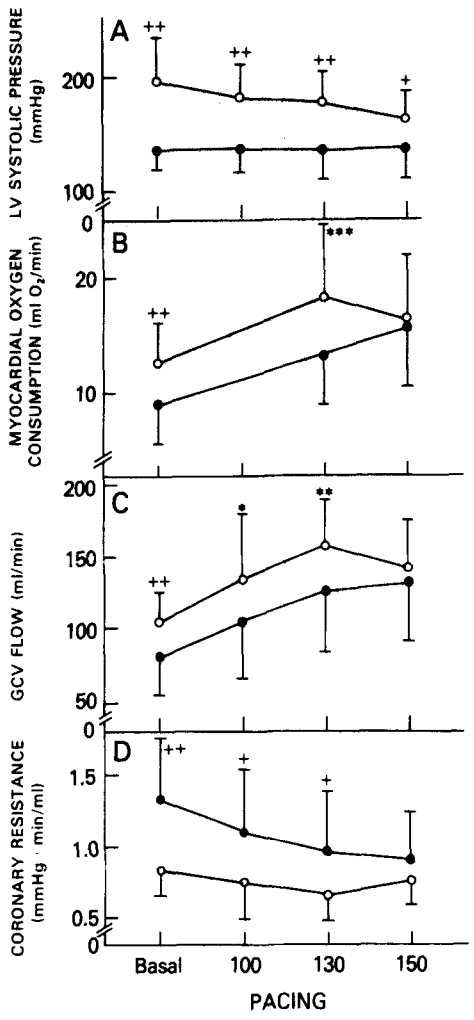


Figure 1. **A,** Left ventricular (LV) systolic pressure; **B,** myocardial oxygen consumption in the anterior coronary circulation; **C,** great cardiac vein (GCV) flow; and **D,** coronary resistance in the anterior circulation for patients with hypertrophic cardiomyopathy. With (**open circles**) and without (**closed circles**) obstruction to left ventricular outflow. Mean values with 1 SD are plotted in the basal state and during pacing. *$p < 0.05$, **$p < 0.025$, ***$p < 0.01$, +$p < 0.005$, + +$p < 0.001$ versus patients without obstruction to left ventricular outflow.

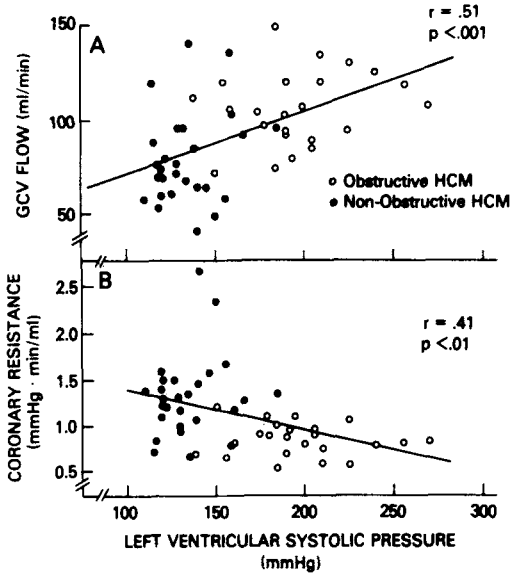
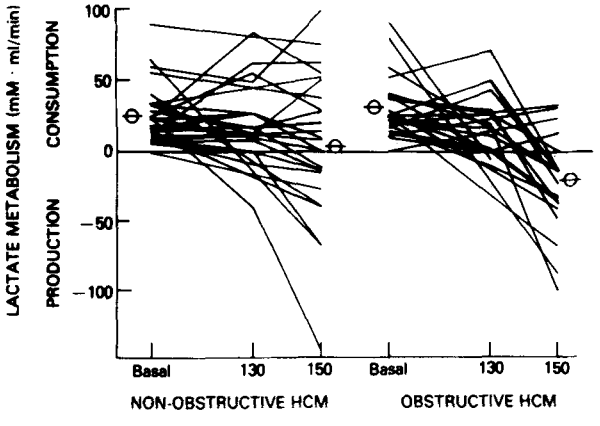


Figure 2. Relation of **(A)** great cardiac vein (GCV) flow and **(B)** coronary resistance in the basal state to left ventricular systolic pressure in obstructive and nonobstructive hypertrophic cardiomyopathy (HCM).

cantly higher in that group compared with the group without basal obstruction (157 ± 25 versus 133 ± 25 mm Hg, $p < 0.005$). Coronary flow and resistance changed little in the group without obstruction, but coronary flow actually fell and resistance rose in the group with basal obstruction at a heart rate of 150 beats/min compared with a heart rate of 130 beats/min (0.67 ± 0.17 to 0.76 ± 0.15 mm Hg·min/ml, $p < 0.01$). At a heart rate of 150 beats/min, left ventricular filling pressures increased markedly in both groups, and there was clear metabolic evidence of myocardial ischemia: 14 of 22 patients with basal obstruction and 11 of 26 patients without basal obstruction produced lactate (Fig. 3). Despite evidence of severe ischemia, there was no overall change in oxygen extraction in either group: 10 of 22 patients with basal obstruction and 15 of 26 patients without basal obstruction actually extracted less oxygen than during the basal state (Fig. 4).

Electrocardiographic changes during study. Despite precipitation of ischemia that was often severe symptomatically and metabolically, only seven patients (three with and four without basal obstruction) demonstrated discernible ST segments shifts (depression in all seven cases) in one or more of the three monitored leads (I, aVF or V_3 or V_5) recorded immediately after cessation of pacing. There was

Figure 3. Lactate consumption in the basal state and during pacing at rates of 130 and 150 beats/min in patients with hypertrophic cardiomyopathy (HCM) with and without obstruction to left ventricular outflow. Lactate consumption <0 indicates production of lactate by the myocardium.



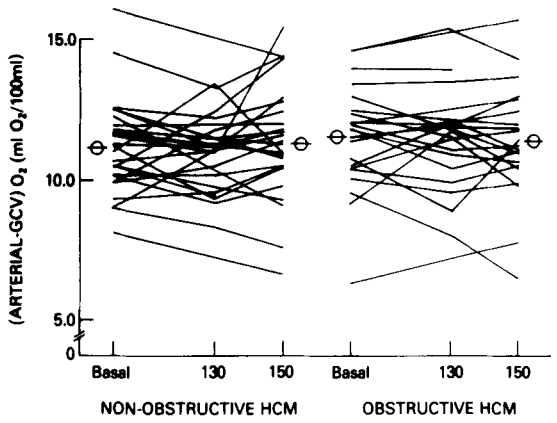


Figure 4. Arterial minus great cardiac vein (GCV) oxygen content in the basal state and during pacing in patients with and without obstruction to left ventricular outflow. HCM = hypertrophic cardiomyopathy.

no attempt to evaluate ST segment shifts during pacing because of artifact in ST segments produced by pacing.

Discussion

Coronary flow in hypertrophic cardiomyopathy. We have previously shown (15) that in the portion of the left ventricle drained by the great cardiac vein, that is, the anterior septum and free wall, patients with hypertrophic cardiomyopathy have higher absolute rest coronary flow in the basal state than do patients without structural heart disease. This finding is presumably related to higher basal myocardial oxygen requirements owing in part to the increased muscle mass present in patients with hypertrophic cardiomyopathy. Further, within the group of patients with hypertrophic cardiomyopathy, those with a significant basal outflow pressure gradient had higher basal flow than did those without obstruction. In the present larger series of patients with hypertrophic cardiomyopathy, the significant relation between coronary resistance and left ventricular systolic pressure (Fig. 2) indicates that the greater coronary vasodilation present in patients with obstruction occurred, at least in part, to satisfy higher myocardial oxygen requirements due to a higher left ventricular systolic pressure analogous to findings in patients with aortic stenosis (11–13). Compatible with this concept are the results of our preliminary studies, which show that surgical relief of outflow obstruction and reduction of left ventricular systolic pressure are accompanied by a reduction in basal and stress-related coronary flow and associated with a reduction in metabolic indexes of ischemia during pacing and improvement in anginal threshold (25). Although the magnitude of basal coronary flow and resistance was related to the left ventricular systolic pressure in our patients, great individual variation existed (Fig. 2). This could be explained by differences in absolute muscle mass in the anterior left ventricular wall, extent of the anterior coronary circulation drained by the great cardiac vein or abnormalities of the intramural coronary circulation.

Hemodynamic and metabolic responses to cardiac pacing. We also extended the results of our prior study by comparing the hemodynamic and metabolic responses of the left ventricle with the stress of cardiac pacing in patients with and without basal obstruction. In response to the stress of pacing at heart rates of 100 and 130 beats/min, coronary resistance fell in both groups, but to a significantly lower level in patients with obstruction. At a heart rate of 130 beats/min, coronary resistance was lower and coronary flow and myocardial oxygen consumption were significantly higher in the patients with obstruction. The lower coronary resistance and higher coronary flow and myocardial oxygen consumption probably reflect the same physiologic significance of a higher left ventricular systolic pressure in this group, as was observed at rest. The heart rate of 130 beats/min represented the anginal threshold for most patients; at this rate lactate consumption decreased and left ventricular filling pressures increased to comparable levels in both groups. Left ventricular systolic pressure and outflow gradient decreased in patients with significant basal obstruction, probably because of ischemia-induced decrease in contractility and reduction in ejection velocity, which in turn caused less systolic anterior motion of mitral valve leaflets. Alternatively, the increase in afterload during stress, probably mediated by pain-related increases in systemic vascular resistance, might have distended the left ventricular outflow tract, thus lessening outflow obstruction.

With further increase in stress to a heart rate of 150 beats/min, all but two patients (both without basal obstruction) experienced chest pain. In patients with basal obstruction, the increase in stress at this heart rate was associated with an actual increase in transmural coronary resistance, demonstrating that maximal functional flow reserve had been exhausted in most patients at a heart rate of 130 beats/min. The increase in resistance may have reflected the compressive effects of elevated filling pressures on the maximally vasodilated coronary bed in patients with obstruction. In this regard, Domenech (26) showed detrimental effects of elevation in preload on coronary flow in the pharmacologically vasodilated coronary bed, but not the coronary bed that still had the capacity to autoregulate. Alternatively, more severe ischemia in this group might have depressed contractility, thereby reducing myocardial oxygen and flow requirements and causing, by autoregulatory mechanisms, an increase in coronary resistance (27). In contrast, coronary resistance fell slightly in the group without basal obstruction when heart rate was increased from 130 to 150 beats/min.

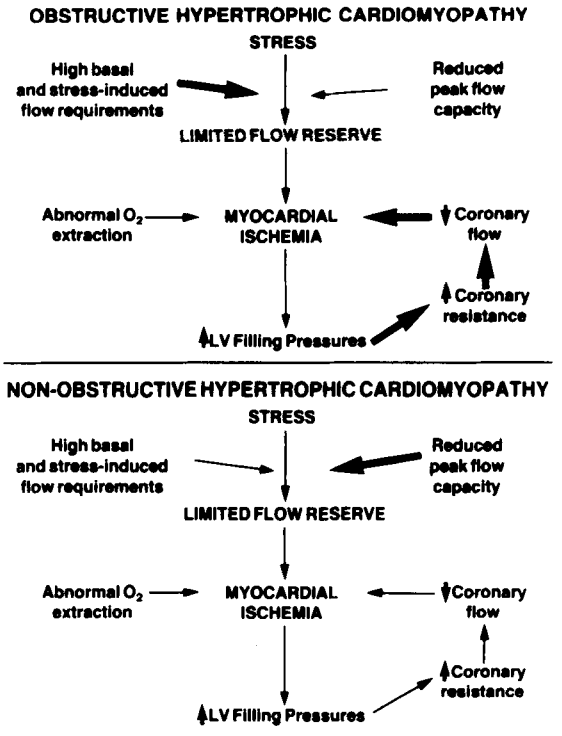
Limited coronary flow reserve in patients with hypertrophic cardiomyopathy. Patients with obstruction developed a higher absolute coronary flow than did those without obstruction. It is possible that this finding was caused

by the greater muscle mass present in patients with obstruction, although there were no group differences in the echocardiographically estimated extent or severity of hypertrophy (Table 1). Another explanation might be that patients with obstruction have greater capillary density and thus greater absolute coronary flow capacity than do patients without obstruction, although higher flows during stress in this group did not prevent ischemia. Indeed, the peak flows achieved by many patients with obstruction were similar to those achieved after dipyridamole infusion in patients with a normal left ventricle using the same method of coronary flow measurement (28).

Thus, it seems that the greater peak coronary flow of patients with obstruction compared with that of patients without obstruction is due to a greater impairment in the capacity for augmenting coronary flow delivery of the latter group rather than an augmented capacity of the former. However, although patients with obstruction had lower coronary resistance and higher coronary flow at a heart rate of 130 beats/min, the variation was large. Thus, many patients with obstruction appear to have impairment in coronary flow delivery as well. Possible explanations for impaired coronary flow delivery in the patients with obstruction are 1) greater dependence of myocardial perfusion on diastole because of systolic vascular compression with prolonged systolic ejection time (29–31), and 2) lower coronary perfusion pressure secondary to the subcoronary obstruction (Table 2). Additional possible explanations for impaired coronary flow for *either* the patients with or those without obstruction are 1) abnormalities in diastolic relaxation, which might impair early filling of the coronary reservoir (32–36), 2) high left ventricular filling pressures in response to ischemia with resulting compression of subendocardial coronary microcirculation (15), 3) reduction in normal cross-sectional area of the coronary microcirculation due to replacement by abnormal myocellular architecture or fibrosis (37,38), 4) small vessel disease with diminished luminal area of intramural coronary arteries (39–41), and 5) systolic compression of septal perforating coronary arteries (which occurred slightly but not significantly more frequently in patients with basal obstruction). Which of these considerations were most important in limiting appropriate coronary flow delivery during stress cannot be determined from our study.

Oxygen extraction by ischemic myocardium. There was evidence of severe myocardial ischemia in both groups in response to high paced heart rates. Although more patients with basal obstruction produced lactate across the coronary bed, and the group response to pacing stress was lactate production (Fig. 3), the mean value of lactate consumption of patients with and without obstruction did not differ significantly. As noted previously (15), there was no augmentation of oxygen extraction from the coronary circulation in either group, despite metabolic evidence of severe ischemia. This is in contrast to the response seen in dogs with epicardial coronary artery limitation to coronary flow (42) and in patients with ischemia due to coronary artery disease (43). In fact, in many patients in both groups, less oxygen was extracted during stress compared with the basal state. We could not demonstrate a relation between myocardial oxygen extraction and the presence and severity of obstruction, severity of ischemia by lactate production, absolute flow response to stress or elevation of left ventricular filling pressures. Thus, the mechanisms responsible for this finding cannot be determined from the present study, but one possibility might be arteriovenous shunting within the myo-

Figure 5. Proposed mechanisms of myocardial ischemia in hypertrophic cardiomyopathy (**large arrows** indicate mechanisms of greater importance than those indicated by **small arrows**). **Top panel,** Patients with significant basal left ventricular (LV) outflow obstruction have high basal flow requirements primarily because of high left ventricular systolic pressure and wall stress. Flow requirements increase further with stress, rapidly exhausting peak flow capacity, which in absolute terms may be relatively normal. Abnormal oxygen extraction capacity may also contribute to or aggravate ischemia. Elevated filling pressures resulting from ischemia have a deleterious compressive effect on the maximally vasodilated transmural coronary bed resulting in increased coronary resistance and a decrease in flow. **Lower panel,** Patients with little or no obstruction and lower left ventricular systolic pressure have lower basal flow requirements (although higher than that of patients without structural heart disease [15]). During stress, flow reserve may be compromised by greater impairment in the capacity for augmenting coronary flow delivery, resulting in ischemia at lower coronary flow and myocardial oxygen consumption than in patients with obstruction. Abnormal oxygen extraction capacity may contribute to or aggravate ischemia. Elevation of filling pressures related to ischemia appears to have a less deleterious effect on coronary flow than that in patients with obstruction.



cardium in the presence of high subendocardial compressive forces.

We have already outlined the major mechanisms we believe to be potentially responsible for precipitating ischemia. However, an additional contributing factor may be the high ventricular pressure occurring in a ventricle with obstruction to left ventricular outflow, in which there is asymmetric distribution and magnitude of hypertrophy unlike the concentric, uniform hypertrophy present in valvular aortic stenosis. Thus, transmural wall stress may vary markedly within various regions of the same ventricle, that is, lowest in the most hypertrophied region and highest in regions of normal wall thickness. These latter regions might be particularly susceptible to the development of stress-induced ischemia.

Limitations of study. We have previously discussed (15) the advantages and disadvantages of estimating coronary flow by the thermodilution method. Ideally, measurement of coronary flow and calculation of resistance per unit mass would allow greater in sight as to mechanisms responsible for the limited flow reserve in hypertrophic cardiomyopathy. Unfortunately, there characteristically is marked heterogeneity in the distribution and amount of hypertrophy in a given patient and from patient to patient in this disease. This means that the mass of left ventricle supplied by a coronary artery (for contrast densitometric or Doppler determinations of flow velocity) or drained by the great cardiac vein (for thermodilution measurements) in a given patient cannot be defined, thereby making it impossible to normalize flow for left ventricular mass. Inert gas washout techniques, which do measure flow per unit mass, require too long a sampling period (up to 20 minutes) during stress to be practical and safe. Although no attempt was made to normalize flow to mass in our study, we do not believe the differences we observed between the patients with and those without obstruction could be explained by difference in mass. The reason for this is that there was no group difference in the severity of hypertrophy between patients with and patients without obstruction to left ventricular outflow (Table 1). Further, it seems unlikely that the great cardiac vein anatomy would differ between the two groups, and therefore unlikely that different drainage patterns exist. In further support of the assumption that the higher great cardiac vein flow in patients with obstruction reflects a true increase in myocardial oxygen demand, and not anatomic differences in coronary venous drainage, is the observation (25) that operative relief of outflow obstruction reduces basal and stress-induced flow, lessens the severity of ischemia in response to stress and lowers anginal threshold.

Despite this limitation, we believe that the thermodilution estimate of coronary flow in this study provides insight as to the mechanisms responsible for the limitation in flow reserve in patients with hypertrophic cardiomyopathy (Fig. 5). For example, in most patients with obstruction, we were able to demonstrate that limited flow reserve is related primarily to elevated basal flow and stress requirements, rather than to an impaired peak flow capacity, which is equal to values observed by us in patients with a normal left ventricle and coronary arteries after dipyridamole administration (28). In contrast, limited flow reserve in patients without obstruction does appear to be due to an impairment in peak flow capacity in most patients.

Another limitation in this study is the calculation of coronary resistance, derived by mean arterial pressure divided by great cardiac vein flow. This ignores the contribution of elevated left ventricular filling pressures on the coronary perfusion pressure, an effect that undoubtedly differs across the ventricular wall, being greatest in the endocardium. The postpacing end-diastolic left ventricular and pulmonary artery occlusive pressures were similar in the two groups, and thus the difference in calculated coronary resistance during pacing between patients with and patients without obstruction is unlikely to be related to omission of the effect of left ventricular filling pressure on coronary perfusion pressure.

Conclusions. The pathogenetic mechanisms causing myocardial ischemia differ between patients with obstructive and nonobstructive hypertrophic cardiomyopathy. Coronary flow reserve in patients with obstructive hypertrophic cardiomyopathy is limited because of high basal and stress-induced coronary flow requirements related to a high left ventricular systolic pressure, a situation analogous to that in valvular aortic stenosis, and in some patients, because of limited maximal flow capacity. Patients with nonobstructive hypertrophic cardiomyopathy develop ischemia as a result of severe impairment of maximal coronary flow capacity.

We thank Imogene Surrey for excellent secretarial assistance. Additionally, the technical assistance and support of Beverly Barber, Cecilia Bergamo, Donna Jo Fleagle, Terry Rumble, Carroll L. Hanson, Greg Johnson, Rita Mincemoyer, Carl Newman, Annette Stine, Ronald White and Judith B. Winkler are gratefully acknowledged.

References

1. Maron BJ, Epstein SE. Hypertrophic cardiomyopathy: a discussion of nomenclature. Am J Cardiol 1979;43:1242–4.
2. Goodwin JF, Hollman A, Cleland WP, Teare D. Obstructive cardiomyopathy simulating aortic stenosis. Br Heart J 1960;22:403–14.
3. Wigle ED, Heimbecker RO, Gunton RW. Idiopathic ventricular septal hypertrophy causing muscular subaortic stenosis. Circulation 1962;26: 325–40.
4. Braunwald E, Lambrew CT, Rockoff SD, Ross J, Morrow AG. Idiopathic hypertrophic subaortic stenosis. I. A description of the disease based upon an analysis of 64 patients. Circulation 1964;30(suppl IV): IV-3–213.
5. Ross J, Braunwald E, Gault JH, Mason DT, Morrow AG. The mechanism of the interventricular pressure gradient in idiopathic hypertrophic subaortic stenosis. Circulation 1966;34:558–78.
6. Criley JM, Lewis KB, White RI, Ross RS. Pressure gradients without obstruction. A new concept of "hypertrophic subaortic stenosis." Circulation 1965;32:881–7.

7. Murgo JP, Alter BR, Dorethy JF, Altobelli SA, McGranahan GM. Dynamics of left ventricular ejection in obstructive and non-obstructive hypertrophic cardiomyopathy. J Clin Invest 1980;66:1369–82.
8. Maron BJ, Gottdiener JS, Arce J, Rosing DR, Wesley YE, Epstein SE. Dynamic subaortic obstruction in hypertrophic cardiomyopathy: analysis by pulsed Doppler echocardiography. J Am Coll Cardiol 1985;6:1–15.
9. Bonow RO, Ostrow HG, Rosing DR, et al. Dynamic pressure-volume alterations during left ventricular ejection in hypertrophic cardiomyopathy: evidence for true obstruction to left ventricular outflow (abstr). Circulation 1984;70(suppl II):II-17.
10. Criley JM, Siegel RJ. Has 'obstruction' hindered our understanding of hypertrophic cardiomyopathy? Circulation 1985;72:1148–54.
11. Fallen EL, Elliott WC, Gorlin R. Mechanisms of angina in aortic stenosis. Circulation 1967;36:480–8.
12. Trenouth RS, Phelps NC, Neill WA. Determinants of left ventricular hypertrophy and oxygen supply in chronic aortic valve disease. Circulation 1976;53:644–50.
13. Bertrand ME, LaBlanche JM, Tilmant PY, Thieuleux FP, Delforge MR, Carre AG. Coronary sinus blood flow at rest and during isometric exercise in patients with aortic valve disease. Am J Cardiol 1981;47: 199–205.
14. Marcus ML, Doty DB, Hiratzka LF, Wright CB, Eastham CL. Decreased coronary reserve: a mechanism for angina pectoris in patients with aortic stenosis and normal coronary arteries. N Engl J Med 1982;307:1362–6.
15. Cannon RO, Rosing DR, Maron BJ, et al. Myocardial ischemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressures. Circulation 1985;71:234–43.
16. Spirito P, Maron BJ, Chiarella F, et al. Diastolic abnormalities in patients with hypertrophic cardiomyopathy: relation to magnitude of left ventricular hypertrophy. Circulation 1985;72:310–6.
17. Baim DS, Rothman MT, Harrison DC. Improved catheter for regional coronary sinus flow and metabolic studies. Am J Cardiol 1980;46: 997–1000.
18. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow by continuous thermodilution in man. Circulation 1971;44:181–95.
19. Pepine CJ, Mehta J, Webster WW, Nichols WW. In vivo validation of a thermodilution method to determine regional left ventricular blood flow in patients with coronary disease. Circulation 1978;58:795–802.
20. Mathey DG, Chatterjee K, Tyberg JV, Lekven J, Brundage B, Parmley WW. Coronary sinus reflux: a source of error in the measurement of coronary sinus blood flow. Circulation 1978;57:778–86.
21. Marbach EP, Weil MH. Rapid enzymatic measurement of blood lactate and pyruvate. Clin Chem 1964;13:314–25.
22. Wigle ED, Marquis Y, Auger P. Muscular subaortic stenosis: initial left ventricular inflow tract pressure in the assessment of intraventricular pressure differences in man. Circulation 1967;35:1100–17.
23. Sandler H, Dodge HT. The use of single plane angiocardiograms for the calculation of left ventricular volume in man. Am Heart J 1968;75: 325–34.
24. Wisneski JA, Gertz EW, Neese R, et al. Myocardial metabolic alterations after contrast angiography. Am J Cardiol 1982;50:239–45.
25. Cannon RO, Rosing DR, McIntosh CL, Epstein SE. Hypertrophic cardiomyopathy: improved hemodynamics, metabolism, and anginal threshold following surgical relief of outflow obstruction (abstr). Circulation 1985;72(suppl III):III-447.
26. Domenech RJ. Regional diastolic coronary blood flow during diastolic ventricular hypertension. Cardiovasc Res 1978;12:639–45.
27. Henry PD, Eckberg D, Gault JH, Ross J. Depressed inotropic state and reduced myocardial oxygen consumption in the human heart. Am J Cardiol 1973;31:300–6.
28. Cannon RO, Schenke WH, Leon MB, Rosing DR, Urqhart J, Epstein SE. Limited coronary flow reserve after dipyridamole in patients with ergonovine-induced coronary vasoconstriction. Circulation (in press).
29. Pichard AD, Meller J, Teichholz LE, Lipnick S, Gorlin R, Herman MV. Septal perforator compression (narrowing) in idiopathic hypertrophic subaortic stenosis. Am J Cardiol 1977;40:310–4.
30. Ruddy T, Henderson A, Rakowski H, Wigle ED. Systolic constriction of the coronary arteries in hypertrophic cardiomyopathy (abstr). Circulation 1981;64:IV-239.
31. Pasternac A, Noble J, Streulens Y, Elie R, Henschke C, Bourassa MG. Pathophysiology of chest pain in patients with cardiomyopathies and normal coronary arteries. Circulation 1982;65:778–89.
32. Brutsaert DL, Housmans PR, Goethals MA. Dual control of relaxation: its role in the ventricular function in the mammalian heart. Circ Res 1980;47:637–52.
33. St John Sutton MG, Tajik AJ, Smith HC, Ritman EL. Angina in idiopathic hypertrophic subaortic stenosis. A clinical correlate of regional left ventricular dysfunction: A videometric and echocardiographic study. Circulation 1980;61:561–8.
34. Hanrath P, Mathey DG, Siegert R, Bleifield W. Left ventricular relaxation and filling pattern in different forms of left ventricular hypertrophy: an echocardiographic study. Am J Cardiol 1980;45:15–23.
35. Bonow RO, Rosing DR, Bacharach SL, et al. Effects of verapamil on left ventricular systolic function and diastolic filling in patients with hypertrophic cardiomyopathy. Circulation 1981;64:787–96.
36. Wigle ED. Hypertrophic cardiomyopathy: the importance of the site and extent of hypertrophy. A review. Prog Cardiovasc Dis 1985;28: 1–83.
37. Roberts WC, Ferrans VJ. Morphologic observations in the cardiomyopathies. In: Fowler NO, ed. Myocardial Disease. New York: Grune & Stratton, 1973:59–115.
38. Maron BJ, Roberts WC. Quantitative analysis of cardiac muscle cell disorganization in the ventricular septum of patients with hypertrophic cardiomyopathy. Circulation 1979;59:689–706.
39. Maron BJ, Epstein SE, Roberts WC. Hypertrophic cardiomyopathy and transmural myocardial infarction without significant atherosclerosis of the extramural coronary arteries. Am J Cardiol 1979;43: 1086–102.
40. James TH, Marshall TK. De subitaneis mortibus XII. Asymmetrical hypertrophy of the heart. Circulation 1975;51:1149–66.
41. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural "small vessel") coronary artery disease in hypertrophic cardiomyopathy. J Am Coll Cardiol 1986;8:545–57.
42. Weiss HR. Effect of coronary artery occlusion on regional arterial and venous O_2 saturation, O_2 extraction, blood flow, and O_2 consumption in the dog heart. Circ Res 1980;47:400–7.
43. Messer JV, Wagman RJ, Levine HJ, Neill WA, Krasnow N, Gorlin R. Patterns of human myocardial oxygen extraction during rest and exercise. J Clin Invest 1962;41:725–42.