Myocardial ischemia in patients with hypertrophic cardiomyopathy: contribution of inadequate vasodilator reserve and elevated left ventricular filling pressures

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ABSTRACT To study the mechanism and hemodynamic significance of myocardial ischemia in hypertrophic cardiomyopathy, 20 patients (nine with resting left ventricular outflow tract obstruction ≥ 30 mm Hg) with a history of angina pectoris and angiographically normal coronary arteries underwent a pacing study with measurement of great cardiac vein flow, lactate and oxygen content, and left ventricular filling pressure. Compared with 28 control subjects without hypertrophic cardiomyopathy, their resting coronary blood flow was higher (91 ± 27 vs 66 ± 17 ml/min; \( p < .001 \)) and their coronary resistance was lower (1.13 ± 0.38 vs 1.55 ± 0.45 mm Hg/ml/min; \( p < .001 \)). Left ventricular end-diastolic pressure (16 ± 6 vs 11 ± 3 mm Hg; \( p < .001 \)) and pulmonary arterial wedge pressure (13 ± 5 vs 7 ± 3 mm Hg; \( p < .001 \)) were significantly higher in patients with hypertrophic cardiomyopathy. During pacing, coronary flow rose in both groups, although coronary and myocardial hemodynamics differed greatly. In contrast to the linear increase in flow in control subjects up to a heart rate of 150 beats/min (66 ± 17 to 125 ± 28 ml/min), patients with hypertrophic cardiomyopathy demonstrated an initial rise in flow to 133 ± 31 ml/min at an intermediate heart rate of 130 beats/min. At this point, 12 of 20 patients developed their typical chest pain. With continued pacing to a heart rate of 150 beats/min, mean coronary flow fell to 114 ± 29 ml/min (\( p < .002 \)), with 18 of 20 patients experiencing their typical chest pain and metabolic evidence of myocardial ischemia. This fall in coronary flow was associated with a substantial rise in left ventricular end-diastolic pressure (30 ± 9 mm Hg immediately after peak pacing). In the 14 patients whose coronary flow actually fell from intermediate to peak pacing, the rise in left ventricular end-diastolic pressure in the same interval was greater than that of the six patients whose flow remained unchanged or increased (11 ± 8 vs 2 ± 2 mm Hg; \( p < .01 \)). In addition, despite metabolic and hemodynamic evidence of myocardial ischemia, the arteriovenous \( O_2 \) difference actually narrowed at peak pacing. Thus most patients with hypertrophic cardiomyopathy achieved maximum coronary vasodilatation and flow at modest increases in heart rate. Elevation in left ventricular filling pressure, probably related to ischemia-induced changes in ventricular compliance, was associated with a decline in coronary flow. A paradoxical narrowing of the arteriovenous \( O_2 \) difference, despite apparent limitation of coronary flow, may also be of pathogenetic importance to myocardial ischemia in hypertrophic cardiomyopathy.


CHEST PAIN is a frequent symptom of patients with hypertrophic cardiomyopathy, commonly occurring in the setting of angiographically normal epicardial coronary arteries. The chest pain described by these patients often has atypical features: it may occur at rest and often has a variable threshold of onset and prolonged duration. These features are in contrast to the generally reproducible effort angina of patients with obstructive coronary artery disease. Even in the absence of atherosclerotic coronary artery disease, however, patients with hypertrophic cardiomyopathy may demonstrate abnormal lactate metabolism during pacing and may experience myocardial infarction as demonstrated at necropsy by transmural scarring; patchy diffuse myocardial fibrosis is an even more common postmortem finding in patients with hypertrophic cardiomyopathy. Thus, although it seems probable that...
some of the chest pain syndromes experienced by patients with hypertrophic cardiomyopathy reflect myocardial ischemia, the exact mechanisms responsible for the ischemia are obscure. Several possible mechanisms for this ischemia include intramyocardial small-vessel disease, septal perforator artery compression, coronary artery spasm, limitation to increase in myocardial blood flow during pacing despite high oxygen demand, and inadequate capillary density in relation to the increased myocardial mass present in hypertrophic cardiomyopathy. This latter possibility was suggested by Pasternac et al., who found that coronary flow corrected for mass (estimated angiographically) was reduced in patients with hypertrophic cardiomyopathy, both at rest and during pacing, compared with control subjects. The present investigation was designed to study the mechanisms responsible for angina pectoris in patients with hypertrophic cardiomyopathy by examining factors that modify myocardial hemodynamics and coronary blood flow during pacing-induced increases in myocardial oxygen demand.

Methods

**Patient selection.** We studied 20 consecutive patients with a clinical and echocardiographic diagnosis of hypertrophic cardiomyopathy and angiographically normal coronary arteries. Fifteen were men and five were women, ranging in age from 22 to 60 years (mean age 44). All patients described chest pain as their major symptom, although most also complained of exertional dyspnea, fatigue, and presyncope. All patients had been previously treated with $\beta$-blockers and calcium channel-blocking drugs without significant amelioration of symptoms. Cardiac catheterization in 18 patients was carried out to assess the presence and severity of left ventricular outflow tract obstruction and therefore the patient's suitability for operation (septal myotomy-myectomy); in two patients the efficacy of a previous myotomy-myectomy procedure was evaluated by catheterization. Twenty-eight patients without echocardiographic evidence of hypertrophic cardiomyopathy but presenting with chest pain syndromes underwent an identical pacing study without provocation of chest pain and served as control subjects for comparison. Fifteen were men and 13 were women, ranging in age from 29 to 61 years (mean 47), and represent a consecutive series satisfying the above criteria. Twenty-six of these subjects served as controls for another study, the results of which were reported previously. Informed consent for this study was obtained from all patients.

**Echocardiographic studies.** A combined M mode and twodimensional echocardiographic examination was performed in each of the 20 study patients with hypertrophic cardiomyopathy. 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, and were analyzed with regard to the distribution of left ventricular hypertrophy in a fashion previously described.

**Experimental protocol: cardiac catheterization.** All medications, including $\beta$-blockers and calcium-channel blockers, were terminated at least 48 hr before cardiac catheterization. After sedation with 10 mg of diazepam administered orally, patients were taken to the catheterization laboratory, usually at 8 A.M., in the fasting state and without any other premedication. A thermolodation catheter was introduced into the right atrium percutaneously via the right internal jugular vein. The great cardiac vein, which is the recipient of blood from the left anterior descending arterial system, was cannulated via the coronary sinus. The thermolodation technique for determining great cardiac vein flow, has been described previously. 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 with minimal or no movement even during pacing, and reproducible flow measurements may be achieved at rest and during pacing. Second, measurement of anterior circulation venous flow might allow estimation of coronary flow and myocardial metabolism in that portion of the ventricle most diseased in the majority of patients with hypertrophic cardiomyopathy, i.e., the anterior septum and free wall. Position of the thermolodation catheter in the great cardiac vein was verified initially by small injections of contrast material and kept constant throughout the study by frequent inspection of the relation of the pacing electrodes to bony landmarks via fluoroscopy.

A 20-gauge catheter was placed in the left brachial artery for arterial pressure measurements. A No. 8F end-hole pigtail catheter (in 12 patients with hypertrophic cardiomyopathy a transducer-tipped catheter, Millar Instruments) was advanced into the left ventricle. Cardiac output and pulmonary arterial wedge pressure were measured with a Swan-Ganz thermolodation catheter lying in the pulmonary artery. Arterial and left ventricular pressures, and electrocardiographic monitor leads I, aVF, and V\(_5\); were recorded with each flow measurement in the great cardiac vein. Lactate samples were obtained from the great cardiac vein through the thermolodation catheter. Specimens were collected in tubes containing sodium fluoride and potassium oxalate for inhibition of glycolysis and were immediately centrifuged at 4°C at 5000 rpm for 5 min. The decanted serum was then processed for lactate content on a DuPont automatic clinical analyzer by a modification of the technique of Marbach and Weil. Lactate consumption was calculated as the great cardiac vein flow multiplied by the difference between the arterial and great cardiac vein lactate concentrations. Oxygen content was performed on a Lex-O$_2$-Con oxygen analyzer (Lexington Instruments) at rest and during pacing in 18 patients with hypertrophic cardiomyopathy and 20 control patients. Coronary resistance (calculated at rest only) equaled the mean blood pressure divided by the great cardiac vein flow.

**Pacing coronary flow study.** Before the pacing coronary flow study, all patients underwent diagnostic right and left heart catheterization. Contrast ventriculography and coronary angiography with multiple angulated views were then performed. There was no evidence of catheter entrapment in any patient with hypertrophic cardiomyopathy during the recording of left ventricular pressure. All patients had normal coronary arteries (interpreted independently by two experienced observers), as was required for entry into the study. The study protocol was initiated at least 20 min after use of angiographic contrast material so that any effects of the dye on coronary blood flow and metabolism would subside. Great cardiac vein flow, lactate, and oxygen content were determined at rest, as were measurements of cardiac output, mean pulmonary arterial wedge pressure, and left ventricular peak systolic and end-diastolic pressure (LVEDP). Pacing via the coronary sinus thermolodation catheter was initiated at a heart rate of 100 and increased by increments of 10 beats/min at 1 min intervals up to a heart rate of 150 beats/min (16 patients with hypertrophic
cardiomyopathy) or lower if the severity of angina precluded continued pacing (four patients with hypertrophic cardiomyopathy). Four patients with hypertrophic cardiomyopathy received 0.5 to 1.0 mg iv atropine to allow pacing without atrioventricular block. All control patients were paced to a heart rate of 150 beats/min, with eight patients receiving 0.5 to 1.0 mg iv atropine. At each interval, LVEDP was measured on high-speed, high-sensitivity recordings (0 to 40 mm Hg, full scale). At the final paced heart rate, repeat great cardiac vein flow, and lactate and oxygen content measurements for great cardiac vein and arterial blood were made. After termination of pacing, the LVEDP was measured in 18 patients with hypertrophic cardiomyopathy and 20 control patients for 10 sec and averaged, eliminating the first 4 beats.

Data analysis. Data were analyzed with Student’s t test for paired and unpaired data, with a probability value of less than .05 considered significant. Regression analyses were performed where appropriate. All group data are reported as mean ± SD.

Results

Noninvasive diagnostic evaluation. In each of the 20 patients with hypertrophic cardiomyopathy, hypertrophy of the anterior ventricular septum (thickness ≥ 15 mm) was identified by both M mode and two-dimensional echocardiography. In 19 of the 20 patients the region of predominant hypertrophy was located in (or confined to) those portions of the left ventricle most likely to be sampled by our great cardiac vein flow measurements, i.e., anterior ventricular septum and contiguous anterior free wall.

Coronary and myocardial hemodynamic results at rest. At rest, nine patients with hypertrophic cardiomyopathy had a subaortic pressure gradient within the left ventricle of 30 mm Hg or greater (table 1). Of the 11 other patients, six had a provokable gradient of 30 mm Hg or greater during the Valsalva maneuver, amyl nitrate inhalation, or isoproterenol infusion (I).

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there was a relationship between resting great cardiac vein and left ventricular outflow tract gradients, the correlation was modest ($r = .53; p < .05$). The LVEDP was similar for patients with and without obstruction at rest ($15 \pm 4$ and $17 \pm 7$ mm Hg, respectively).

Compared with values in the 28 control patients without hypertrophic cardiomyopathy, the resting great cardiac vein flow was higher ($91 \pm 27$ vs $66 \pm 17$ ml/min; $p < .001$) and the coronary resistance lower ($1.13 \pm 0.38$ vs $1.55 \pm 0.45$ mm Hg/ml/min; $p < .001$) in patients with hypertrophic cardiomyopathy. Patients without resting obstruction had higher great cardiac vein flows than control subjects ($80 \pm 27$ vs $66 \pm 17$ mg/min) but the difference was of marginal significance statistically ($p < .06$). The LVEDP at rest was higher in patients with hypertrophic cardiomyopathy ($16 \pm 6$ vs $11 \pm 3$ mm Hg; $p < .001$) as was the pulmonary arterial wedge pressure ($13 \pm 5$ vs $7 \pm 3$ mm Hg; $p < .001$).

**Coronary and myocardial hemodynamics during pacing.** At the intermediate paced heart rate ($127 \pm 13$ beats/min for patients with hypertrophic cardiomyopathy [table 1], $130 \pm 0$ beats/min for controls), the mean blood pressures of patients with hypertrophic cardiomyopathy were similar to those of control subjects ($102 \pm 19$ vs $101 \pm 13$ mm Hg, respectively). However, the great cardiac vein flows were significantly higher in patients with hypertrophic cardiomyopathy (figure 2) compared with controls ($133 \pm 31$ vs $107 \pm 34$ ml/min; $p < .005$). The LVEDP increased slightly but significantly over resting measurements in patients with hypertrophic cardiomyopathy ($16 \pm 6$ at rest to $20 \pm 6$; $p < .001$). At this intermediate pacing level, despite the higher great cardiac vein flow than in control subjects, 12 patients with hypertrophic cardiomyopathy experienced their typical chest pain. At this point there was no relationship between the change in LVEDP, the change in great cardiac vein flow, and the anginal threshold in the patients with hypertrophic cardiomyopathy as a group (figure 3, A).

With continued pacing to higher heart rates ($147 \pm 7$ hypertrophic cardiomyopathy vs $150 \pm 0$ controls), 18 of 20 patients with hypertrophic cardiomyopathy experienced their typical chest pain. The mean blood pressure in patients with hypertrophic cardiomyopathy was similar to controls ($104 \pm 21$ vs $103 \pm 15$ mm Hg, controls). The left ventricular outflow tract gradient in the nine patients with obstruction at rest fell significantly (from $75 \pm 37$ at rest to $37 \pm 25$ mm Hg.
at peak pacing; p < .001). The great cardiac vein flow in patients with hypertrophic cardiomyopathy actually fell (114 ± 29 at peak pacing vs 133 ± 31 ml/min at the intermediate pacing level; p < .001), achieving similar levels to the great cardiac vein flow of controls (125 ± 28 ml/min) at this heart rate (figure 2). The LVEDP increased significantly between the intermediate and peak pacing levels (20 ± 6 to 28 ± 8 mm Hg peak pacing; p < .001) and increased even further after pacing (30 ± 9 hypertrophic cardiomyopathy vs 12 ± 4 mm Hg controls; p < .001). In the 14 patients with hypertrophic cardiomyopathy whose great cardiac vein flow actually fell between intermediate and peak pacing levels, the increase in LVEDP was greater during the same interval compared with the six patients whose flow remained unchanged or increased (11 ± 8 vs 2 ± 2 mm Hg; p < .01). There was a significant relationship between the change in flow from intermediate to peak pacing and the change in LVEDP in this same interval (figure 3, B).

The 14 patients with hypertrophic cardiomyopathy whose coronary flow fell at the high paced heart rate had a much higher flow at the intermediate paced heart rate (146 ± 21 vs 105 ± 34 ml/min; p < .001) than the other six patients. With continued pacing to 150 beats/min, the flow fell to 114 ± 26 ml/min, whereas the flow continued to rise in the other six patients to 115 ± 37 ml/min.

The cardiac index fell slightly but significantly in patients with hypertrophic cardiomyopathy (3.0 ± 0.5 at rest to 2.7 ± 8 liters/min/m² at peak pacing; p < .001) and remained unchanged in control subjects (3.0 ± 1.0 at rest to 3.2 ± 0.6 liters/min/m² at peak pacing). The pulmonary arterial wedge pressure was 28 ± 8 mm Hg at peak pacing and 23 ± 9 mm Hg after pacing, a significant elevation over the postpacing pulmonary arterial wedge pressure of control subjects (9 ± 3 mm Hg; p < .001).

**Metabolic parameters during pacing study.** Analysis of lactate metabolism at the peak paced heart rate showed that in contrast to control subjects, who had increased lactate consumption from rest to peak pacing, patients with hypertrophic cardiomyopathy had decreased lactate consumption and six patients actually produced lactate (figure 4). There was no significant difference between patients with obstructive and nonobstructive hypertrophic cardiomyopathy with respect to lactate metabolism.

The AVO₂ difference at rest (figure 5) was similar in patients with hypertrophic cardiomyopathy (11.7 ± 1.8 ml O₂/100 ml) and control subjects (12.3 ± 1.7 ml O₂/100 ml). During pacing, patients with hypertrophic
cardiomyopathy had a decreased AVO₂ difference (11.7 ± 1.8 ml O₂/100 ml at rest to 10.9 ± 2.1 ml O₂/100 ml during pacing; p < .01) despite metabolic evidence of myocardial ischemia.

Discussion

The results of our investigation shed some additional light on the mechanisms responsible for precipitating ischemic chest pain in patients with hypertrophic cardiomyopathy. The mechanisms for ischemia we investigated were related to the sequence of events that
occur when myocardial metabolic oxygen demands are increased by cardiac pacing. During pacing, great cardiac vein flow increased at intermediate heart rates in all control subjects and in most patients with hypertrophic cardiomyopathy. At this level of myocardial oxygen demand great cardiac vein flow in the patients with hypertrophic cardiomyopathy was significantly higher than that in control subjects. Although LVEDP in the patients with hypertrophic cardiomyopathy rose significantly, there was no correlation with the change in great cardiac vein flow from rest to intermediate pacing. Despite these findings, 12 of 20 patients with hypertrophic cardiomyopathy began experiencing their typical angina. At higher paced heart rates, control subjects continued to have increased great cardiac vein flow, essentially doubling their flow at rest. In contrast, with continued pacing great cardiac vein flow actually declined in 14 of 20 patients with hypertrophic cardiomyopathy. This was associated with a substantial rise in left ventricular filling pressure from the intermediate pacing levels and with metabolic evidence indicating that myocardial ischemia had developed. At this higher pacing rate, all but two of the patients with hypertrophic cardiomyopathy experienced their typical chest pain.

Thus increasing myocardial metabolic stress by cardiac pacing in these patients appeared to precipitate ischemic pain by two mechanisms. At lower levels of metabolic stress ischemic pain occurred before the development of substantial increases in LVEDP and at a time when myocardial blood flow increased to higher levels than that observed in control subjects paced at comparable rates. Although the mechanisms responsible for causing ischemia under these conditions are unknown, it has been shown in the experimental animal that myocardial hypertrophy occurring as a result of a long-term pressure load leads to a decrease in capillary density relative to the increase in myocardial mass. It has been shown that such changes lead to a reduced vasodilator reserve, when calculated on the basis of flow per milligram of myocardial tissue. In humans with left ventricular hypertrophy and aortic stenosis, decreased coronary vasodilator reserve, as estimated by the ratio of peak to rest coronary flow velocity after a brief coronary occlusion, has been demonstrated. Patients with left ventricular hypertrophy caused by long-standing hypertension have also been found to have reduced pharmacologic vasodilator reserve per gram of cardiac tissue after dipyridamole infusion. This mechanism may also pertain to patients with hypertrophic cardiomyopathy, resulting in increases in flow in response to augmented metabolic demands but with inadequate flow to serve the markedly increased myocardial mass present in this condition.

Alternatively, there could be regional deficiencies of myocardial flow or flow reserve that were not detected by our technique, which samples the venous drainage of the anterior septum and anterior left ventricular wall. That regional abnormalities occur in hypertrophic cardiomyopathy is suggested by thallium perfusion studies, which have demonstrated that even in the absence of coronary disease, many such patients demonstrate reversible perfusion defects during the stress of exercise. In addition, postmortem studies have shown that there is often patchy, diffuse myocardial fibrosis in patients with hypertrophic cardiomyopathy, which might reduce the total cross-sectional area of the coronary microvasculature. Luminal narrowing of small vessels caused by intimal hyperplasia and medial hypertrophy have also been reported in patients with hypertrophic cardiomyopathy, changes that could additionally reduce the effective cross-sectional area of the microcirculation and thereby decrease peak maximal vasodilator reserve. Systolic compression of septal periferal arteries was noted to some degree in virtually all of our patients with hypertrophic cardiomyopathy, but the effect on coronary blood flow is unknown since the majority of coronary blood flow occurs in diastole, when these vessels were widely patent.

The above potential mechanisms relate to the situation that was observed in conjunction with mild-to-moderate increases in myocardial oxygen demands, during which the modest LVEDP increase did not correlate with changes in great cardiac vein flow. With more intensive metabolic stress, however, we observed a marked rise in LVEDP and fall in great cardiac vein flow. At this time most patients developed clinical and metabolic evidence of myocardial ischemia. Although we cannot establish definitively which of these two changes is the cause and which is the effect, it appears likely that the following sequence of events occurred: with increasing metabolic stress more severe and extensive ischemia developed; the greater degree of ischemia then led to a rise in left ventricular filling pressures (probably related to ischemia-induced alterations in the left ventricular diastolic pressure-volume relationship), which in turn caused the marked fall in great cardiac vein flow.

Animal preparations in which coronary pressure-flow relationships have been examined have suggested that a minimum critical perfusion pressure is required to maintain patency of the coronary microvasculature, which is compressed in diastole by a combination of
perivascular, myogenic, and extravascular forces. The coronary “driving” pressure across the coronary bed is thought to equal the difference between mean aortic pressure and this minimum perfusion, or “critical closing,” pressure. It is possible that in patients with hypertrophic cardiomyopathy elevation in left ventricular filling pressures exceeded this critical closing pressure, thus compromising the perfusion pressure gradient across the coronary bed and reducing coronary flow.

Our results also raise another potential mechanism by which ischemia may occur in patients with hypertrophic cardiomyopathy. Normally, increases in myocardial oxygen demand caused by exercise or cardiac pacing are met by appropriate increases in coronary blood flow to allow adequate oxygen delivery to the myocardium. In coronary obstructive disease, increased oxygen delivery can be accomplished in part by an increase in oxygen extraction across the myocardial capillary bed, as has been demonstrated in animals with a flow-limiting stenosis or occlusion. In the majority of our patients with hypertrophic cardiomyopathy, however, despite being paced to the occurrence of severe angina with metabolic evidence of ischemia, we found that the AVO₂ difference paradoxically narrowed. The cause of this decrease in oxygen extraction is unknown but may relate to abnormal myocardial-capillary relationships in hypertrophic cardiomyopathy and decreased oxygen extraction capability at high flow velocities during myocardial stress.

Although we believe the results of our investigation are accurate and valid, we realize that flow measurements obtained with a thermodilution catheter sampling in the great cardiac vein may be subject to some errors. For example, this technique is based on the assumption that the great cardiac vein drains the same vascular bed before and during an intervention. This is probably correct, but no definite evidence of its validity exists. The method may also be subject to error if the catheter moves and thereby measures flow from more or fewer veins draining into the great cardiac vein. However, once advanced into the great cardiac vein, further catheter advancement is difficult and thus the only potential movement during pacing would be out of the great cardiac vein into the coronary sinus. This would have resulted in even higher flows at high paced heart rates by inclusion of more draining veins. In contrast, we observed a decline in flow at high paced heart rates compared with lower paced heart rates in the majority of patients with hypertrophic cardiomyopathy.

It must also be pointed out that the several other nonoperative techniques that can be used to measure myocardial blood flow all have inherent problems. For example, estimates of myocardial perfusion obtained by inert gas or radioactive tracer clearance cannot be used for serial measurements of myocardial flow during stress provocation because of the length of time required for data acquisition and the necessity for stable flow rates during the duration of measurement. In addition, when the coronary sinus is used as the site of venous sampling, either for thermodilution flow determinations or for gas clearance measurements, major interpretive errors may result. The reason for this is that small changes in catheter position can lead to large changes in flow by thermodilution because of the entry of many veins into the coronary sinus, and this sampling site would not reflect regional inhomogeneities of myocardial perfusion that probably exist in hypertrophic cardiomyopathy, where marked variations in the distribution and extent of hypertrophy are present. We elected to use thermodilution measurements of great cardiac vein flow in our study because serial measurements of flow can be rapidly obtained, small changes in catheter position do not alter flow, and the anterior septum and anterior free wall are most commonly hypertrophied in hypertrophic cardiomyopathy; measurements of anterior circulation flow and metabolism might therefore allow evaluation of the most diseased portion of the myocardium in most patients with hypertrophic cardiomyopathy. Thus, although the technique we used is not without its limitations, we believe it provides the best means currently available for answering the questions posed by our study.

The results of our investigation may have practical importance relative to the management of patients with hypertrophic cardiomyopathy. Although volume depletion has been traditionally avoided in patients with the obstructive form of hypertrophic cardiomyopathy for fear of exacerbating the severity of obstruction, high baseline filling pressures could be extremely detrimental. Thus when ischemia-induced changes in the diastolic pressure-volume relation lead to further elevations in filling pressure, the critical closing pressure of the coronary arteries might be reached, leading to an aggravation and perpetuation of ischemia. Many of the prolonged episodes of chest pain experienced by patients with hypertrophic cardiomyopathy, lasting long after the physical stress precipitating the pain is terminated, might be explained by the sequence of events outlined in figure 6. Stress could initially lead to myocardial ischemia because of the inadequate vasodilator reserve relative to the increased myocardial mass.
Ischemia, however, could further increase filling pressure, a situation that might then lead to a self-sustaining cycle of decreasing myocardial flow and exacerbation of ischemia. Hence, the ischemic state could persist even after the precipitating stress was no longer present. Under these conditions, careful use of diuretics and nitrates might be helpful in lowering preload and thereby obviating such a self-perpetuating mechanism. Likewise, use of medication such as verapamil to improve the left ventricular diastolic pressure-volume relationship might also prevent or minimize increases in left ventricular filling pressures with stress, reducing the likelihood that such a series of events would occur.

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