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Progression of Hypertrophic Cardiomyopathy Into a Hypokinetic Left Ventricle: Higher Incidence in Patients With Midventricular Obstruction

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The development of segmental or generalized left ventricular hypokinesia is an unusual occurrence in patients with hypertrophic cardiomyopathy. To determine the incidence and possible pathophysiologic mechanisms responsible for this process, the serial clinical and laboratory data of 62 patients with the diagnosis of hypertrophic cardiomyopathy were analyzed. During a mean follow-up period of 8 years (range 2 to 21), 5 patients (Group A) developed left ventricular hypokinesia, whereas the remaining 57 patients (Group B) continued to exhibit the clinical and laboratory findings of hypertrophic cardiomyopathy.

Three patients developed a dilated left ventricle with generalized hypokinesia; two other patients had segmental left ventricular wall motion abnormalities. None of these five patients who developed left ventricular hypokinesia had fixed coronary artery disease. The mean age, sex, mean duration of follow-up, presence of coronary myocardial bridges and angina pectoris, and an interventricular gradient were all similar in Groups A and B. Midventricular obliteration was seen in 4 (80%) of the 5 patients in Group A and in 4 (7%) of the 57 patients in Group B ($p < 0.001$).

Findings from this study reveal that segmental or generalized left ventricular hypokinesia can develop in patients with hypertrophic cardiomyopathy in the absence of fixed coronary artery disease. Such hypokinesia can occur after an acute myocardial infarction or it can develop gradually without clinical or electrocardiographic evidence of infarction. Patients with the midventricular obliteration variant of hypertrophic cardiomyopathy are at a higher risk of developing segmental or diffuse left ventricular hypokinesia.

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Hypertrophic cardiomyopathy has been reported to progress occasionally into a dilated hypokinetic left ventricle (1–5). This process can occur acutely or chronically and can be associated with a significant deterioration in clinical status. Although the pathophysiology of this process is not fully understood, some cases have been reported after a myocardial infarction (1,3,5) or surgical septal myotomy and myomectomy (2).

In an attempt to elucidate the pathophysiologic mechanisms responsible for this process, 62 consecutive patients with hypertrophic cardiomyopathy were followed up for a mean period of 8 years (range 2 to 21) to determine the incidence and possible predictors of development of left ventricular hypokinesia.

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Methods

Study patients. The medical records of 62 patients with hypertrophic cardiomyopathy followed up by one group of cardiologists were reviewed. In some patients the diagnosis of hypertrophic cardiomyopathy was made before referral to this center. The diagnosis was suspected on the basis of clinical and electrocardiographic findings and was confirmed by the presence of typical echocardiographic or angiographic findings, or both. The echocardiographic criteria included: 1) asymmetric septal hypertrophy; 2) small left ventricular cavity; 3) reduced septal systolic motion; and 4) in the presence of left interventricular obstruction, systolic anterior motion of the anterior mitral leaflet and early systolic closure of the aortic valve. The angiographic criteria included 1) a hypertrophic hypercontractile left ventricle with systolic obliteration of different parts of the left ventricle, and 2) in the obstructive form, the presence of a dynamic intraventricular gradient.

All patients underwent cardiac catheterization and, when

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available, M-mode echocardiography during their initial assessment. Patients were seen at least on a yearly basis. A chest roentgenogram, electrocardiogram and M-mode echocardiogram were obtained during the follow-up visit. Selective coronary angiograms were available in 60 patients. All patients had a left ventricular angiogram.

Laboratory methods. All laboratory results were reviewed by the authors. Left ventricular hypertrophy was assessed electrocardiographically by the scoring criteria of Romhilt and Estes (6). Q waves were considered significant if their duration was 0.04 second or more. The M-mode echocardiographic techniques have been described previously (7).

Hemodynamic measurements obtained during cardiac catheterization included left ventricular end-diastolic pressure, pulmonary capillary wedge pressure, left intraventricular pressure gradient, at rest and after provocative maneuvers (after premature ventricular contractions, after the Valsalva maneuver and after the administration of sublingual nitroglycerin). Catheter entrapment was averted by using end hole catheters only and by injecting contrast medium to ensure a free position of the catheter tip within the left ventricular cavity. Left ventricular volumes and ejection fractions were calculated using the technique of Dodge (8).

The diagnosis of midcavity obstruction was made on the basis of typical angiographic features: hourglass appearance of the left ventricle with midventricular obliteration and an apical chamber that was variable in size and contractility (9). Many of these cases were associated with a pressure gradient at the midventricular level. Selective coronary angiograms were obtained in multiple views.

Follow-up. In patients who exhibited progression to left ventricular hypokinesia, the clinical course was divided into two phases. The hypertrophic phase (phase I) began with the initial cardiac assessment of the patient and covered the time interval during which the disease behaved according to physical and laboratory findings as a hypertrophic cardiomyopathy. The hypokinetic phase (phase II) began with the first detection of clinical or laboratory evidence, or both, of left ventricular segmental or generalized hypokinesia and extended until the last clinical follow-up.

Statistical analysis. For frequency of occurrence variables, a chi-square analysis was performed to determine statistical differences. For continuous variables, the Student's *t* test for paired data was used.

Results

The 62 patients with hypertrophic cardiomyopathy were followed up for a mean total period of 8 years (range 2 to 21). During this follow-up period, five patients developed generalized or segmental left ventricular hypokinesia (Group A). The remaining 57 patients (Group B) continued to exhibit clinical and laboratory findings of hypertrophic cardiomyopathy.

Serial Clinical and Laboratory Findings in Group A

Clinical findings (Table 1). The mean total duration of follow-up in Group A was 11 years (range 4 to 20). In Patients 1, 2 and 4, the progression to left ventricular hypokinesia was associated with a gradual development of congestive heart failure with deterioration in clinical status over a period of several years. Patient 1 had undergone septal myotomy and myomectomy 12 years before the first documentation of left ventricular hypokinesia and had had systemic hypertension for several years, treated with propranolol. Patient 3 had rapid deterioration in symptoms after sustaining an acute anteroseptal myocardial infarction complicated by congestive heart failure. Patient 5 underwent left ventricular myotomy and myomectomy 1 year after detection of a left ventricular apical aneurysm.

Laboratory findings (Table 2). *Electrocardiographic findings.* Left ventricular hypertrophy with or without an associated strain pattern was initially present in all five patients. With the progression to phase II, Patients 1 and 2 lost the voltage criteria for left ventricular hypertrophy. Patient 3 developed new deep Q waves in leads V_1 to V_4 when he sustained an acute anteroseptal myocardial infarction.

Echocardiographic findings. The M-mode echocardiogram, when available in the hypertrophic phase, (phase I),

Table 1. Serial Clinical Findings in Five Patients (Group A) With Left Ventricular Hypokinesia

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	I	II	I	II	I	II	I	II	I	II
Sex	F		F		M		M		F	
Follow-up (yr)	20		17		4		11		4	
Age (yr)	47	62	17	30	58	61	31	39	33	36
NYHA class	II	III	II	III	II	IV	I	III	III	III
Angina	Yes	No	No	No	Yes	No	No	No	No	No

I = hypertrophic phase; II = hypokinetic phase; NYHA = New York Heart Association.

Table 2. Serial Laboratory Findings in Five Patients (Group A) With Left Ventricular Hypokinesia

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5	
	I	II	I	II	I	II	I	II	I	II
Electrocardiographic Findings										
Q wave	+	–	+	–	+	+	+	+	+	+
	I,L	I,L	–	–	L	A,L	L	L	–	–
Echocardiographic Findings										
IVS	1.7	0.8	–	0.9	1.9	1.3	2.0	1.1	1.8	1.8
PLVW	1.6	1.0	–	0.9	1.1	1.0	1.3	1.0	1.5	1.1
LVDS	2.0	3.8	–	4.0	1.7	3.6	2.0	4.2	1.8	2.0
LVDD	4.6	5.8	–	6.0	4.0	5.8	4.2	6.1	4.1	4.8
SAM	Yes	Yes	–	No	Yes	Yes	No	No	No	No
ESC	No	No	–	No	Yes	No	No	No	Yes	No
Angiographic and Hemodynamic Findings										
MCO	+	–	+	–	+	+	–	–	+	+
LVWM	Hyperc	Dif hypok	Hyperc	Dif hypok	Hyperc	Ant hypok ap dysk	Hyperc	Dif hypok	Hyperc	Ap dysk
LVEF(%)	75	35	70	45	75	45	70	30	75	60
IVG (mm Hg)										
Rest	105	0	80	0	100	20	0	0	120	80
Prov	120	0	120	0	140	50	0	0	–	–
Level	?	–	LVOT	–	MV and LVOT	LVOT	–	–	MV	MV
Coronary arteries	–	N	–	N	N	N	MB-LAD	MB-LAD	N	N

I = hypertrophic phase; II = hypokinetic phase; + = present; – = absent. A = anterior; Ap = apical; Dif = diffuse; Dysk = dyskinesia; ESC = early systolic closure of the aortic valve; Hyperc = hypercontractile; Hypok = hypokinesia; I = inferior; IVG = intraventricular gradient; IVS = interventricular septum; L = lateral; LAD = left anterior descending coronary artery; Level = left ventricular level; LVDD = left ventricular end-diastolic dimension; LVDS = left ventricular end-systolic dimension; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVOT = left ventricular outflow tract; LVWM = left ventricular wall motion; MB = myocardial bridge; MCO = midcavity obliteration; MV = midventricle; N = normal; Prov = provocative; PLVW = posterior left ventricular wall; SAM = systolic anterior motion of the anterior mitral leaflet.

showed a hypertrophic hypercontractile left ventricle in all patients, with asymmetric septal hypertrophy in Patients 3 and 4. During the hypokinetic phase (phase II), left ventricular diastolic dimension was above the normal range in four patients. Sequential M-mode echocardiograms obtained during the hypokinetic phase showed progressive increase in left ventricular dimensions in Patients 1, 2 and 4 and no significant changes in Patients 3 and 5.

Hemodynamic and angiographic findings. Hemodynamic studies performed during the hypertrophic phase (phase I) revealed a significant intraventricular gradient in four patients, all of whom had angiographic evidence of midcavity obliteration. The level of obstruction was variable. During phase II, only two patients had an intraventricular gradient that was markedly reduced when compared with that of phase I.

Initially, left ventricular angiograms revealed a hypercontractile left ventricle in all five patients. Left ventricular wall motion abnormalities seen during phase II were global in three patients and segmental in two (Fig. 1 and 2). None of the patients had fixed coronary artery lesions on angiography. Patient 3 was studied 3 days after he sustained an acute myocardial infarction and was found to have normal coronary arteries.

Comparison of Findings Between Groups A and B (Table 3)

Clinical and laboratory findings obtained during the initial assessment of patients were compared between Groups A (segmental or generalized hypokinesia) and B (hypertrophic cardiomyopathy). Mean age, sex, history of angina, incidence of prior septal myotomy and myomectomy, presence of fixed coronary artery disease or myocardial bridges, presence of an intraventricular pressure gradient and duration of symptoms were all similar in Groups A and B, as was the mean duration of follow-up. On the other hand, the presence of midcavity obliteration was statistically more common in Group A ($p < 0.001$). In addition, patients with obstructive hypertrophic cardiomyopathy in Group A had a

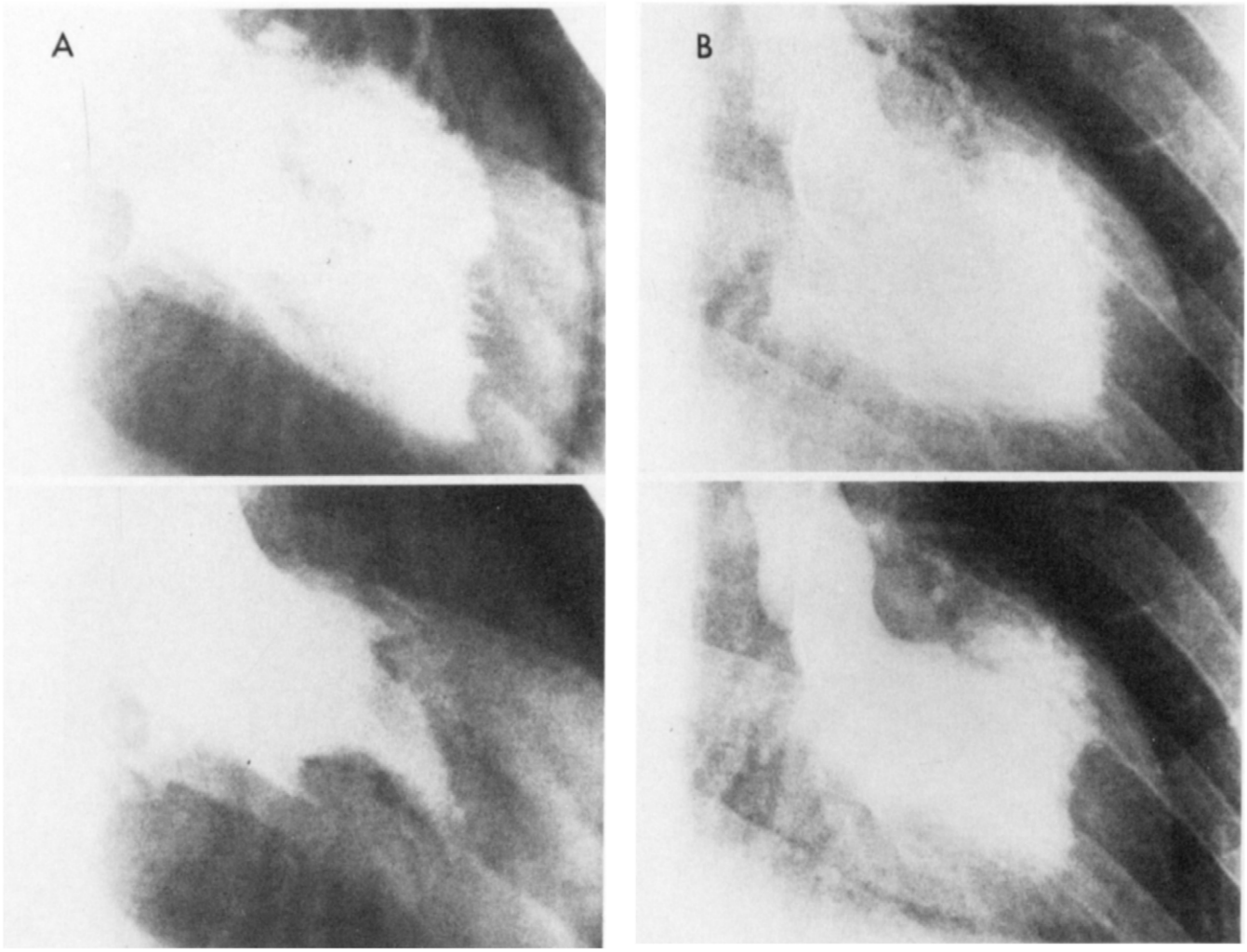


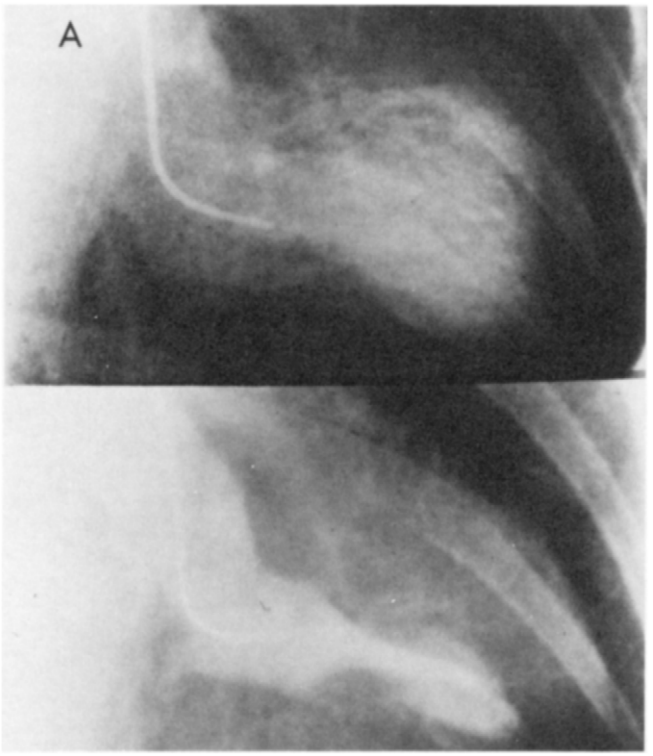
Figure 1. Patient 4. Left ventricular end-diastolic (**upper**) and end-systolic (**lower**) angiographic frames during phase I (hypertrophy) (**A**) and phase II (hyperkinesia) (**B**).

higher mean rest intraventricular gradient compared with that of patients in Group B ($p < 0.05$).

Discussion

Incidence of ventricular hypokinesia. The development of segmental or generalized left ventricular hypokinesia with or without left ventricular dilation is an unusual occurrence in patients with hypertrophic cardiomyopathy. Adelman et al. (10), in a series of 60 patients with hypertrophic cardiomyopathy, reported a 7% incidence rate of congestive heart failure. Ten Cate and Roelandt (2) followed up 50 patients with hypertrophic cardiomyopathy for a mean interval of 4 years. Two patients (4%) developed a dilated poorly contracting left ventricle. In our study of 62 patients followed up for a mean period of 8 years, five patients (8%) (Group A) developed segmental or generalized left ventricular hypokinesia.

Pathophysiologic mechanisms. A small number of patients with hypertrophic cardiomyopathy can develop segmental or diffuse left ventricular hypokinesia (our Group A). This process can follow an acute myocardial infarction (3,5) or it can occur silently without any clinical or electrocardiographic evidence of myocardial infarction (1,2,11). Although the pathophysiologic mechanisms leading to left ventricular wall motion abnormalities can be different in these two clinical situations, the pathologic findings are similar, that is, transmural myocardial infarction and scarring, which can be diffuse or localized to one area of the left ventricle (11). The etiology of the myocardial infarction is still unclear. Morphologic and angiographic studies show normal extramural coronary arteries in the majority of these cases (1,2,11,12). In our study, none of the five patients in Group A had fixed coronary artery disease. Some of the mechanisms thought to be involved in the causation of the



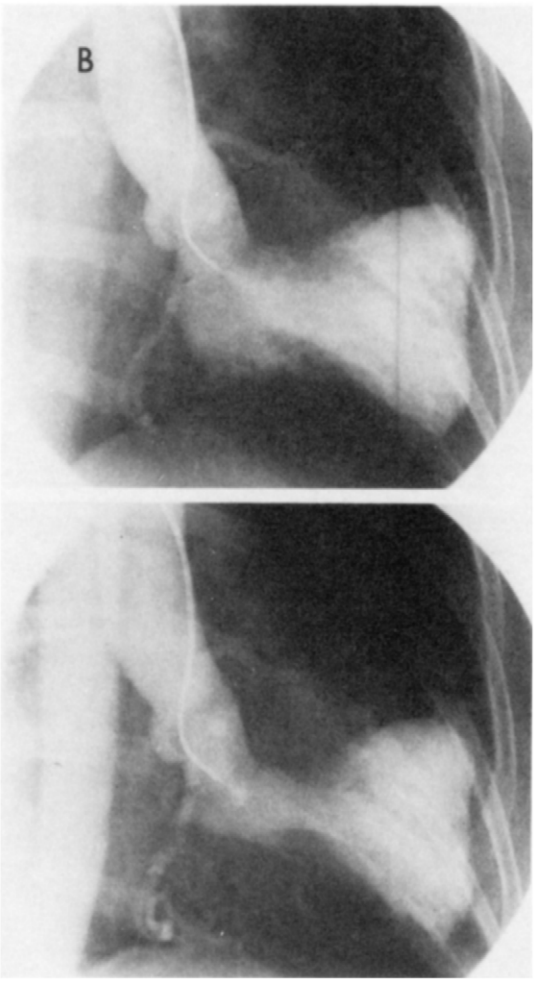


Figure 2. Patient 3. **A**, Left ventricular end-diastolic (**upper**) and end-systolic (**lower**) angiographic frames during phase I (hypertrophy). **B**, Four days after development of an acute anteroseptal myocardial infarction.

myocardial infarction in these cases include: 1) embolization to a major coronary artery branch, 2) coronary artery spasm, 3) myocardial bridging, 4) oxygen supply/demand mismatch, 5) small vessel coronary artery disease, and 6) prior septal myotomy or myomectomy.

In the absence of any documented cases, the role of coronary embolization or coronary artery spasm in the causation of myocardial infarction in patients with hypertrophic cardiomyopathy is purely theoretical.

Table 3. Comparison of Clinical and Laboratory Findings in Groups A and B

	Group A (with hypokinesia)		Group B (without hypokinesia)	
	No.	%	No.	%
Patients	5	8	57	92
Men	2	40	32	56
Mean age (yr)	37		34	
Angina (no.)	2	40	32	56
Follow-up (mean) (yr)	11		8	
CAD	0	0	12	21
Myocardial bridging	1	20	9	16
Previous myotomy/myomectomy	1	20	10	17
IVG	4	80	42	74*
MVO	4	80	4	7†
Mean IVG (mm Hg)	101		63	

* = $p < 0.05$; † = $p < 0.001$. CAD = coronary artery disease; IVG = intraventricular pressure gradient; MVO = midventricular obliteration.

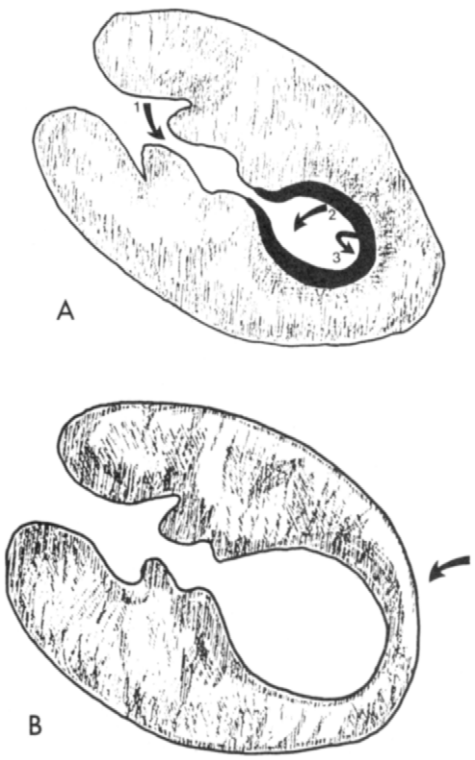


Figure 3. Diagrams of midventricular obliteration with midventricular obstruction, before (**A**) and after (**B**) the development of a left ventricular apical aneurysm. 1 = lower pressure; 2 = higher pressure; 3 = compensatory apical hypertrophy.

Although the incidence of myocardial bridging (13) is higher in patients with hypertrophic cardiomyopathy than in the general population, the role of this finding in the causation of angina or infarction, or both, remains unclear. In our study, the incidence of myocardial bridges was similar in patients who developed left ventricular hypokinesia and those who did not. Some studies (11) have reported that sections of fibrotic myocardium from patients with hypertrophic cardiomyopathy have shown wall thickening with luminal narrowing in the intramural small coronary arteries. It is not known, however, whether this is the cause or the consequence of myocardial fibrosis.

Septal myomectomy can be complicated by septal infarction if it is associated with interruption of the blood supply to the septum. In our study, the only patient in Group A who had prior septal myomectomy had undergone surgery 12 years before the detection of left ventricular hypokinesia.

Oxygen supply/demand mismatch due to excessive myocardial thickness has been reported for years to be a possible mechanism leading to myocardial scarring. Positron emission tomographic studies (14) performed on some patients with hypertrophic cardiomyopathy have shown reduction in blood flow and free fatty acid uptake in the septum as compared with the left ventricular free wall. Other studies (15) suggest that decreased subendocardial blood flow resulting in subendocardial ischemia can occur frequently in patients with hypertrophic cardiomyopathy, even in the absence of angina.

Role of midventricular obliteration. It has already been shown (16) that marked variation in the distribution of left ventricular hypertrophy occurs in patients with hypertrophic cardiomyopathy. Midventricular obstruction is an uncommon variant of hypertrophic cardiomyopathy in which the hypertrophic process predominates at the midventricular level tract, resulting in some cases in a high pressure apical chamber (9,17,18,19). Gordon et al. (20) reported midventricular obstruction in three who had an associated apical aneurysm. In these three cases it was not known whether the midventricular obstruction was the consequence of apical infarction in patients with hypertrophic cardiomyopathy and cavity obliteration or whether it was the cause of apical infarction and apical aneurysm formation (21). In our study, we established that patients with hypertrophic cardiomyopathy and midventricular obstruction can develop an apical aneurysm or more generalized left ventricular wall motion abnormalities.

Mechanisms. Although we are uncertain why midcavity obliteration leads to left ventricular hypokinesia in these patients, we are suggesting two mechanisms. Midcavity obliteration in this study was associated with a large pressure gradient across the midventricular level in many patients. This obstruction to flow during systole might lead to further compensatory apical hypertrophy, which by itself could make midventricular obstruction more severe. A stage is reached where the pressure overload in the apical chamber leads to myocardial dysfunction with dilation of the apical chamber (Fig. 3). Another mechanism that can be involved in this situation is related to the sequence of myocardial fiber shortening during systole. Although the left ventricle in hypertrophic cardiomyopathy is hypercontractile, the effective shortening of the total left ventricular axis (junction of aorta and left ventricle to epicardial apex) is reduced (15). The hypercontractile septum is thought to splint the long axis of the left ventricle, preventing apical retraction. This inability to elevate the apex toward the base can be more exaggerated in the presence of midcavity obliteration, resulting gradually in apical dyskinesia and dilation of the apical chamber. It is unclear if development of generalized hypokinesia is related to formation of an apical aneurysm in these patients.

Conclusions. Hypertrophic cardiomyopathy can occasionally progress to segmental or generalized left ventricular hypokinesia. In this series of 62 patients, the rate of this progression was close to 1%/patient per year. This progression can follow an acute myocardial infarction or it can develop gradually without clinical or electrocardiographic evidence of infarction. The incidence of coronary artery disease, coronary myocardial bridging, left intraventricular dynamic obstruction and previous septal myotomy-myomectomy was similar in patients who developed left

ventricular hypokinesia and in those who did not. Patients with the midventricular obliteration variant of hypertrophic cardiomyopathy are at a higher risk of developing left ventricular hypokinesia.

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