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# HYPERTROPHIC CARDIOMYOPATHY: A REVIEW

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## INTRODUCTION

Hypertrophic cardiomyopathy (HCM) was first described in 1957 by Sir Russell Brock, who reported on a patient referred for surgical correction of presumed aortic stenosis but who was found at surgery to have left ventricular outflow tract narrowing by a massive hypertrophy of the septum (1). In 1958, Dr. Donald Teare described the pathology of a familial disease characterized by marked asymmetric hypertrophy of the septum, extensive disarray of the myocardial fibers, and sudden death in the young (Figure 1). Subsequent clinical and pathological descriptions focused on the variable and provocable hemodynamics and obstruction to outflow of the left ventricle caused by the hypertrophied septum (3-4). This is reflected in the multitude of "obstructive" names given to this disease (5).

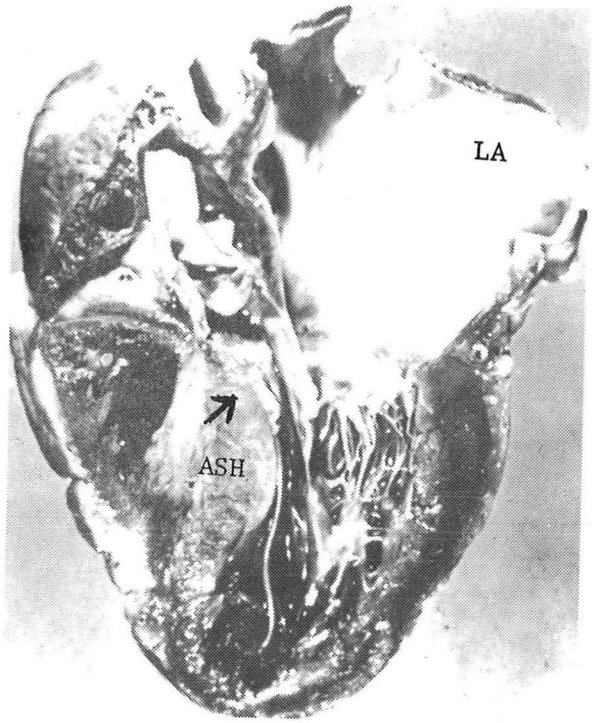
Application of echocardiography (ECHO) to the disease entity of HCM has allowed for a better identification and elucidation of its natural history and diverse clinical, morphological, hemodynamic and pathophysiological manifestations. As our understanding of this disease has increased, initial concepts have been broadened, modified, and even discarded. So too has its management from surgery for obstruction being the only option to the current use of beta adrenergic and calcium-channel blockers in conjunction with adjuvant anti-arrhythmic agents. In light of these developments, it seems timely to review this fascinating disease with emphasis on pathophysiology, natural history, and approach to management.

## DEFINITION OF HCM

Early definitions of HCM through the mid-1970's were based upon the anatomic and M-mode ECHO features of the disease (Figure 2) since the true etiology was unknown. It was defined as a disease with a normal or small LV cavity, marked asymmetric hypertrophy of the upper anterior septum (ASH) relative to the posterior wall (thickness ratio $\geq$ 1.3) and, in patients with obstruction, by systolic anterior motion of the anterior mitral leaflet (SAM) (16). Although other ECHO criteria were identified (7-8) the presence of the above two findings were considered pathognomonic hallmarks of the disease, especially ASH, which was thought to be present in all patients whether or not obstruction was present (9). However, it soon became apparent that none of these features were pathognomonic since they could be seen in normal hearts and in various congenital and acquired heart diseases (10-13).

Use of wide-angle two-dimensional (2D) echocardiography (ECHO) in the late 1970's (14-22), and more recently magnetic resonance imaging and thallium-201 emmision-computed tomography (23-25), has demonstrated a substantial degree of heterogeneity in the distribution and extent of LV hypertrophy and is not limited only to the upper anterior septum seen by M-mode ECHO. In addition several studies have demonstrated that abnormal diastolic compliance and impaired ventricular relaxation may be the

Figure 1. Hypertrophic cardiomyopathy with asymmetric hypertrophy of the septum(ASH) compared to the posterior wall. Also note the dilated left atrium, the small ventricular cavities, the thickened anterior mitral leaflet, and the endomyocardial plaque(arrow) opposite the anterior mitral leaflet. (Courtesy of L. M. Buja, MD. Dept. of Pathology, UTHSCD/SMS)



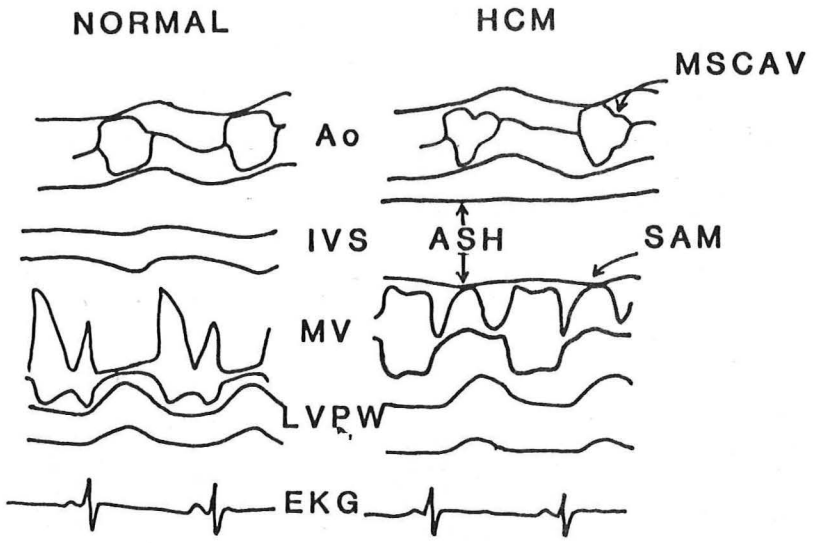




Figure 2. Schematic representation of the classic M-mode echocardiographic findings in patients with obstructive HCM. Ao = aortic valve, IVS = interventricular septum, MV = mitral valve, LVPW = left ventricular posterior wall, MSCAV = mid-systolic closure of the Ao, SAM = systolic anterior motion of the MV, ASH = asymmetric septal hypertrophy.

predominant pathophysiological processes that are present in many patients and that the intraventricular gradient is a highly variable and less important component (3,4,26,27). Thus, terms which emphasize a specific characteristic such as ASH or stenosis have been replaced by the more general and inclusive term hypertrophic cardiomyopathy which, in fact, was used first by Goodwin in the early 1970's (28,29). This term emphasizes the unknown hypertrophic myopathic process which is common to all patients with the disease. Specifically, hypertrophic cardiomyopathy is now usually defined as a primary myocardial disease of unknown etiology that is characterized by a hypertrophied, nondilated left ventricle in the absence of a cardiac or systemic disease that can produce LV hypertrophy. The hypertrophy typically involves the septum but may exhibit marked variability in anatomic site. Intraventricular gradients can often be demonstrated. Systolic function, as assessed by ejection fraction, is usually normal or increased, and diastolic function is typically abnormal.

## CLASSIFICATION OF HCM

As just noted, several groups have used 2D ECHO to identify a wide variety of patterns of left ventricular hypertrophy in patients with HCM which is not limited to the subaortic region (14-22). A morphological classification of the disease based on the location and symmetry of the hypertrophy is shown in Figure 3. HCM may be divided into 2 subgroups based on whether the hypertrophy is symmetric or asymmetric. Symmetric cardiomyopathy is uncommon and may involve the ventricle diffusely or be concentrated in the apical region. In most series, concentric HCM is rare and occurs in 1-7% of cases of HCM (16,18,21), although in the series by Shapiro and McKenna (19), 30% of patients had this form of the disease, (probably due to their patient population and selection criteria). Symmetric apical HCM was first described in Japanese patients; it was thought to occur only in that population but recently has been reported in two small series of patients in Israel and in the United States (22,31).

The vast majority of patients with HCM have the asymmetric form of the disease which includes septal hypertrophy of several types and regional free wall hypertrophy. Free wall, mid-septal and apical septal asymmetric hypertrophy are uncommon, occurring in only 10-15% of patients with asymmetrical cardiomyopathy (15-17,20,21). Most patients with asymmetric cardiomyopathy have what can be called typical asymmetric hypertrophy of the septum. I refer to it as typical because this is the morphology commonly identified by M-mode ECHO (Figure 2). Studies in the 1970's used M-mode ECHO criteria to identify patients with HCM and thus selected this morphological subgroup of HCM. Although this subgroup comprises most of the patients seen with HCM, it is important to realize that other forms do occur.

HCM also has been classified into hemodynamic subgroups based on the type of septal involvement and presence or absence of an intraventricular pressure gradient between the left ventricle (LV) and the LV outflow tract (LVOT) demonstrated at cardiac catheterization (3) or estimated by ECHO

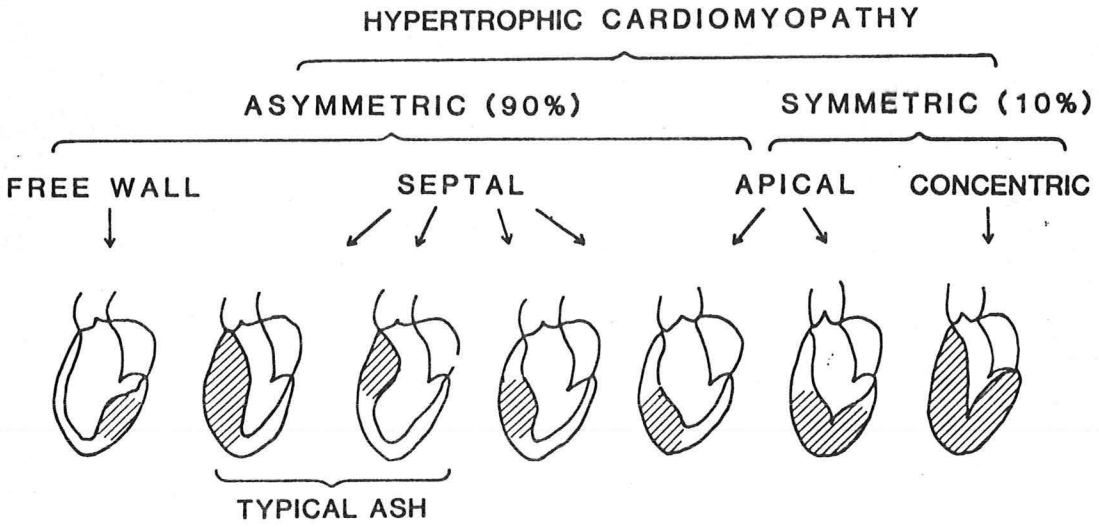



Figure 3. Classification of hypertrophic cardiomyopathy by morphology. (Modified from Ref. 30)

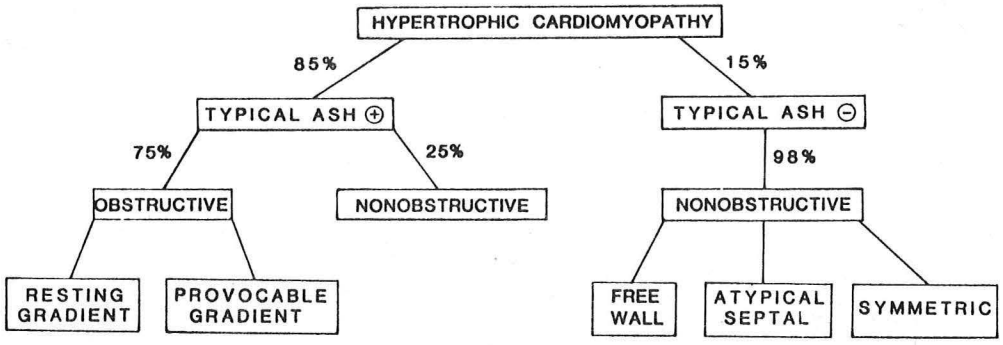



Figure 4. Classification of hypertrophic cardiomyopathy by typical septal involvement and hemodynamics.

criteria (32-33) (Figure 4). Gradients occur almost exclusively in patients who have typical ASH and may either be present at rest or present only with provocative manuevers that alter LV preload, afterload or contractility (3). These patients are said to have the obstructive form of HCM. It is important to realize that patients with typical ASH may not have resting or provocable gradients and are said to have the nonobstructive form of the disease. In most series the majority of patients with typical ASH have the obstructive form of the disease but this depends on the patient population and on the definition of a significant gradient. Values of 5, 10, 20 or 30 mmHg, either at rest or after provocation, have been used as the "cutoff" point with values below these being considered in the "nonobstructive" category (34-37). This is an important factor to consider when comparing studies.

Maron (16), Wigle (21), and Spirito (38) have used 2D ECHO to further classify patients with typical ASH based on the site and extent of septal hypertrophy and have tried to correlate these groups with the hemodynamic subgroups. These studies cannot be combined or compared directly because different 2D ECHO views were used to assess the extent of septal hypertrophy. However, in both studies extensive hypertrophy involving the entire septum was typically associated with anterolateral free wall hypertrophy whereas localized subaortic septal hypertrophy was not. Nearly 75% of patients with a resting gradient had septal and free wall hypertrophy and were significantly more symptomatic and functionally limited than those with less extensive hypertrophy (16,21). Only 50% of nonobstructive patients had extensive hypertrophy involving the free wall. The Spirito study (38) reported no other correlations between morphologic type and hemodynamic state, but Wigle (21) showed that mild, localized subaortic hypertrophy occurred in over 50% of patients with provocable gradients compared to 8% and 14% of patients with resting gradients or no gradient. Whether these hemodynamic-morphological correlations are clinically or prognostically important remains to be determined.

In the absence of typical ASH, an intraventricular gradient at rest or with provocation is very uncommon (14,16,22) although exceptions have been reported (20,39,40). Therefore, patients with isolated free wall, atypical septal and symmetric hypertrophy fall into the nonobstructive category. As noted above, patients with typical ASH without a resting or provocable gradient are in this category as well. In most studies, nonobstructive HCM refers to those patients with typical ASH unless otherwise stated.

## ETIOLOGY

As the name implies, the etiology of hypertrophic cardiomyopathy remains a mystery. Previous studies (41,42) have documented the familial occurrence of typical ASH in about 1/3 of the patients with the disease. The other 2/3 of the patients are considered sporadic occurrences. These reports demonstrated a high familial prevalence of HCM when typical ASH, detected by M-mode ECHO, was used as the disease marker. This genetic defect was shown to be transmitted as an autosomal dominant trait with a high degree of penetrance. More recently patterns of inheritance in

hypertrophic cardiomyopathy have been reassessed using 2D ECHO which has allowed identification of relatives with patterns of LV hypertrophy other than typical ASH. Ciro (43) demonstrated that only 40% of first-degree relatives had the same pattern of left ventricular hypertrophy as the proband in their series of 40 patients and 66 relatives. Maron (44) examined 70 family pedigrees and found that the disease was genetically transmitted in 55% and occurred sporadically in 44%. Probands with the familial or sporadic forms did not differ from each other with regard to the clinical or morphological expression of their disease. Probands typically showed functional limitation (81%), resting obstruction (53%) and extensive septal and free wall hypertrophy (59%). In contrast, affected relatives typically showed no functional limitation (72%), no resting obstruction (94%) and had localized and unusual sites of hypertrophy (60%). A complex mathematical pedigree analysis detected no particular pattern of inheritance as characteristic of the entire group. They suggested that HCM might not be a single etiologically distinct disease and may well have non-genetic causes. However, in the pedigrees that showed familial transmission, 76% were most consistent with an autosomal dominant transmission. It has been suggested that different forms of HCM can be related to HLA-antigens. Kishimoto et al (45) demonstrated a familial obstructive form of HCM linked to the HLA-A,B system, and a sporadic form not linked to the HLA-antigens. The significance of these findings is unknown and needs to be confirmed in a larger series of patients. In the genetic form of the disease no unique metabolic, biochemical, or structural abnormality or deficiency has yet been detected.

Although there are many theories and speculations regarding the pathogenesis of HCM, there is no strong experimental evidence as yet to support any of them largely because of the lack of appropriate experimental models. A potentially useful model is the spontaneously occurring hypertrophic cardiomyopathy in dogs and cats but it limited by the occurrence rate (46). A list of current theories and experimental models is provided in Table I. An extensive review of each of these is beyond the scope of the discussion and the reader is referred to the references noted in the table. None of the theories by itself has been shown to adequately reproduce the entire spectrum of clincial, morphological, pathological and pathophysiological expressions of HCM. Most consider hypertrophy as a secondary or reactive phenomenon rather than primary myocardial abnormality.

Of these theories, the calcium overload theory has received attention recently. Increased calcium uptake and intracellular calcium content are associated with an enhanced contractile state (47) and impaired diastolic relaxation (48), abnormalities which are characteristic of patients with HCM. The impetus for this theory has been the hereditary dilated cardiomyopathy of the Syrian hamster which exhibits increased myocardial calcium uptake and content and which can be prevented by the administration of the calcium antagonist, verapamil (49). However, there is obviously little clinical resemblance between dilated cardiomyopathy and human hypertrophic cardiomyopathy. Nevertheless, there are some experimental similarities which suggest that calcium may be important in the pathogenesis of HCM. Recurrent microvascular spasm and focal ischemia have

**TABLE 1. PROPOSED ETIOLOGIES OF HCM**

I. Hyperadrenergic/catecholamine theory (52)
   A. Increased circulating levels in utero and /or
   B. Fetal receptor hypersensitivity
   C. Failure of regression of normal fetal myofibrillar disarray and septal hypertrophy as a result of A and B.
   D. Clinical associations
      i. Pheochromocytoma
      ii. Neurofibromatosis
      iii. Lentiginosis
      iv. Friedrich's ataxia
   E. Experimental associations
      i. Subhypertensive doses of norepinephrine in dogs
      ii. Nerve growth factor (stimulates growth and development of sympathetic nerves) in dogs.

II. Cytosolic calcium overload theory (53,54)
   A. Abnormal membrane permeability
      i. Primary (Genetic)
      ii. Catecholamine-induced
   B. Ischemia
      i. Microvascular spasm
      ii. Small vessel disease
   C. Clinical association
      i. Hyperthyroidism
   D. Experimental associations
      i. Syrian hamster cardiomyopathy (dilated)
      ii. TRIAC administration to pregnant rats (thyroid hormone metabolite-triodothyroacetic acid)

III. Abnormal adenosine metabolism (55)
   A. Impaired receptor function
   B. Experimental associations - none

IV. Structural abnormalities (56)
   A. Catenoid shape of septum
   B. Clinical Associations
      i. Congenital heart disease

V. Primary myocardial hypertrophy

been proposed as causes of the abnormalities in calcium metabolism seen in the hamster (50,51). Both pathological and functional abnormalities in intramural coronary arteries have been demonstrated in patients with HCM (59-61). Quantitative and qualitative abnormalities in the non-histone nuclear proteins, which may be important in the regulation of genetic expression in eucaryotic cells, have been demonstrated in the cardiomyopathic Syrian hamster (57). Interestingly, similar quantitative and qualitative differences in the non-nuclear histone proteins have been demonstrated in surgical specimens from patients undergoing myotomy for HCM (58). Furthermore, Morgan and Morgan have reported preliminary results on the study of intracellular calcium transients measured with the photoluminescent protein aequorin in cardiac muscle removed at surgery from patients undergoing myectomy for HCM (62). The intracellular rise in free calcium occurred rapidly and normally in myocytes from these patients, but the decline in free calcium following activation was slowed and prolonged. This correlated with a slow decline in muscle tension measured simultaneously. Thus, it seems reasonable that abnormalities of myocardial calcium metabolism, perhaps based on expression of a genetic defect, may be important in the pathogenesis of HCM. Whether the defect is related to small vessel disease or is a primary cellular abnormality remains to be determined. This theory does provide a rationale for the use of calcium antagonists in HCM.

## PATHOPHYSIOLOGY

Three pathophysiological concepts need discussion since an understanding of the mechanisms responsible for alterations in left ventricular function and the influence of ischemia on such function allows for a rational approach to the management of patients with HCM.

### Systolic Events

Experimental studies in patients with resting or provocable intraventricular gradients have consistently demonstrated hyperdynamic LV contractility with high ejection fractions and rapid, near complete (>80%) emptying of the left ventricle in the first half of systole (34,63-65). Controversy prevails as to whether a measurable intraventricular gradient represents actual obstruction to left ventricular outflow (65-67), or is simply a manifestation of a hypercontractile LV producing early cavity obliteration and thereby continued pressure development in the absence of flow (68-70). Recent observations on LV-Aortic flow-pressure relationships suggest that a gradient does represent obstruction to flow at the level of the left ventricular outflow tract (LVOT) (65,71-73).

The rapid ejection of blood past the septal hypertrophy is considered to result in turbulent flow and the generation of Venturi forces which draw the mitral valve leaflets toward the septum (21,72,73) (Figure 5). Contact of the leaflets with the septum creates an obstruction to left ventricular outflow and results in the production of a gradient. The involvement of the mitral leaflets in the production of the gradient is highlighted by the observation that SAM, as demonstrated on M-mode ECHO, is nearly always present in patients with resting gradients, is inducible in

patients with provocable gradients, and is almost never present in patients without a demonstrable gradient (74,76) (Table 2). Simultaneous M-mode ECHO and hemodynamic studies (33,75) have shown that the onset and magnitude of the gradient correlates well with the onset and degree of contact of the mitral leaflet with the septum during systole (Figure 6). In addition, the duration of contact between the mitral valve leaflet and the septum correlates linearly with the severity of the gradient and the LV ejection time (33) (Figure 7). That the outflow tract is narrowed when SAM occurs is shown by quanitative 2D ECHO measurements of the LVOT cross-sectional area (76). LVOT area is smallest in patients with resting gradients ($2.6 \pm 0.7$ $cm^2$) as compared to patients with: (1) provocable gradients ($4.6 \pm 1.6$ $cm^2$), (2) no resting or provocable gradients ($5.9 \pm 1.6$ $cm^2$) or (3) normal hearts ($10.4 \pm 1.6$ $cm^2$). Doppler flow studies of the aorta and left ventricle have characterized flow patterns in patients with and without gradients and have provided support for the hypothesis that obstruction does occur. Doppler flow velocity waveforms at the level of the mid-LV cavity demonstrate continuous flow from the left ventricle for the entire duration of systole (to aortic valve closure, S2) in patients with and without resting gradients (65) (Figure 8). In those patients without resting or provocable gradients aortic flow profiles also persist throughout systole and are similar to the flow profiles from normal hearts (Figure 9). In contrast, in patients with resting gradients the aortic flow velocity curves typically are abbreviated and end well before aortic valve closure or show a bifid flow velocity profile with evidence of late systolic flow persisting to aortic valve closure (65) (Figure 9). One possible explanation for the abbreviated aortic flow is that with the onset of SAM-septal contact and aortic flow deceleration, mitral regurgitation into the low pressure left atrium begins due to impeded forward flow and distorted mitral coaptation (71) (Figure 10). Confirmation of this sequence of events is well demonstrated by Doppler color flow imaging (72) (Figure 11). Soon after LV systole begins color reversal occurs at the level of SAM-septal contact, denoting an increase in velocity consistent with the idea of Venturi force development. The mosaic pattern in the LVOT indicates high-velocity turbulent flow followed by the appearance of mitral regurgitation into the left atrium. Normal flow then continues in the LVOT. The fraction of forward flow that occurs while a pressure gradient is present depends on the time of onset of the SAM-septal contact. The earlier the obstruction occurs in the systolic ejection period the greater the proportion of forward flow that is ejected against a gradient into the aorta and/or the left atrium (65) (Figure 12). From a therapeutic standpoint then, any intervention that reduces LV contractility or decreases the gradient (beta-blockers, $Ca^{2+}$ antagonists, myomyectomy) should be beneficial. Conversely interventions that increase contractility (beta-agonists or digitalis) will be detrimental.

**Diastolic Events**

Abnormal LV diastolic function has long been recognized as an important pathophysiologic mechanism in patients with obstructive and nonobstructive HCM (3,4). The diastolic abnormalities are characterized by: (1) inadequate ventricular filling, and (2) impaired ventricular relaxation, both of which are interdependent (21,26,27,77,78). Several factors contribute to these abnormalities in diastolic function (Table 3).

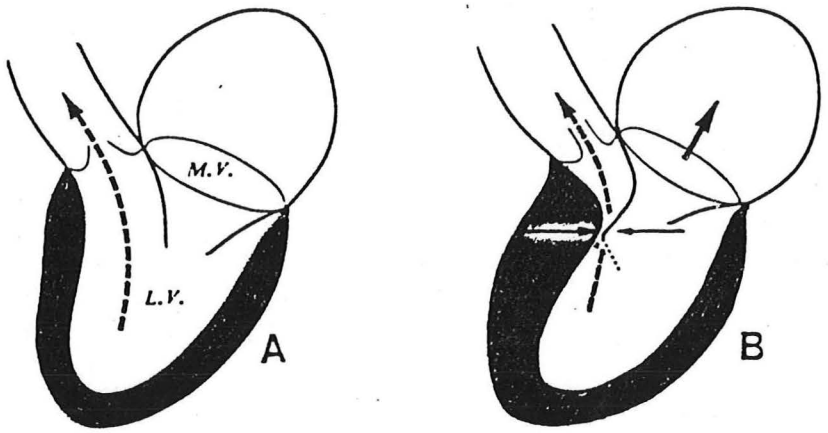



Figure 5. Proposed mechanism of systolic anterior motion of the anterior mitral leaflet in muscular subaortic stenosis. In normal persons(A), blood is ejected from the left ventricle in a relatively direct path into the aorta through a wide open outflow tract. In muscular subaortic stenosis(B), the ventricular septum is thickened(left horizontal arrow), resulting in a narrowed outflow tract. Because of this narrowing, the ejection of blood from the ventricle occurs at a high velocity and the ejection path is closer to the anterior mitral leaflet than is normal. As a result of this, the anterior leaflet is drawn into the outflow tract towards the septum by a Venturi effect(right horizontal arrow). Mitral leaflet-septal contact results in obstruction to the left ventricular outflow. Mitral regurgitation (upper right oblique arrow) results from the anterior mitral leaflet being out of its normal systolic position. LV = left ventricle, MV = mitral valve. (Ref: 21)

Table 2. **OCCURRENCE OF SAM IN RELATION TO INTRAVENTRICULAR GRADIENTS***

| | PATIENTS WITH SAM (Z)# | | | |
|---|---|---|---|---|
| | None | Mild | Moderate | Severe |
| Resting Gradient | 0 | 0 - 5 | 0 - 9 | 86 - 100 |
| Provocable Gradient | 7 - 21 | 21 - 32 | 37 - 61 | 0 - 21 |
| No Gradient | 87 - 90 | 10 - 13 | 0 | 0 |

# Degree of SAM (Systolic Anterior Motion of Mitral Valve)
Mild > 10mm from septum
Moderate < 10mm from septum &/or mild contact with septum
Severe prolonged contact with septum
* From Ref. 74,76

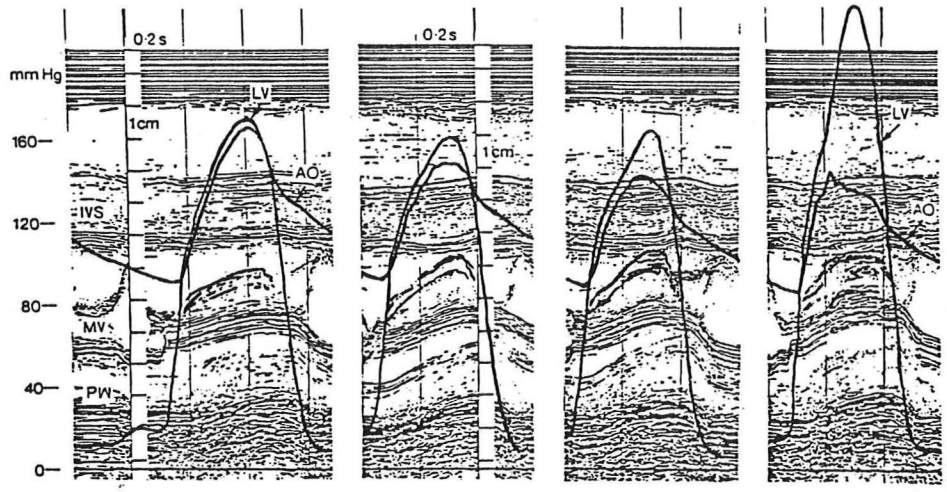



Figure 6 Four separate cardiac cycles from one of the patients, displaying simultaneous echocardiographic and hemodynamic tracings during pharmacologic manipulation of the pressure gradient. SAM without septal contact in the first cardiac cycle is not associated with a significant pressure gradient. When SAM-septal contact first develops late in systole, it is brief and the pressure gradient is low (second cardiac cycle). When SAM-septal contact develops early in systole, it is prolonged and the pressure gradient is high (fourth cardiac cycle during isoproterenol infusion). (Ref. 33)

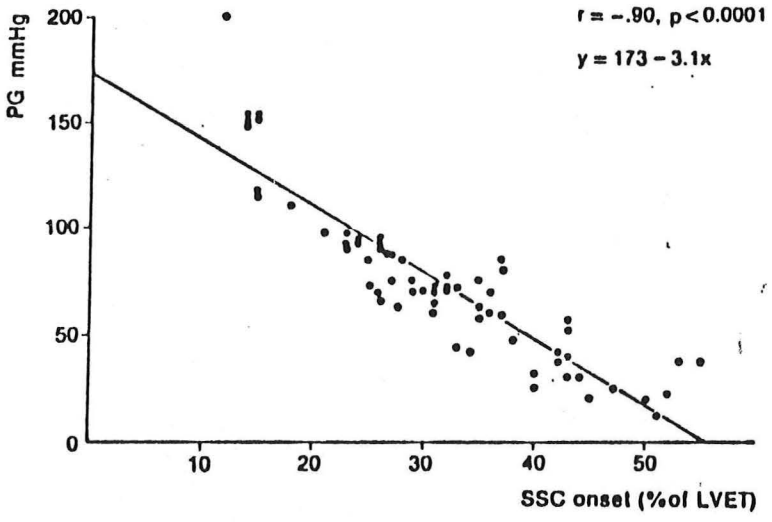



Figure 7. Correlation between the percentage of systolic ejection period that SAM-septal contact first occurs and the pressure gradient (Ref. 33)

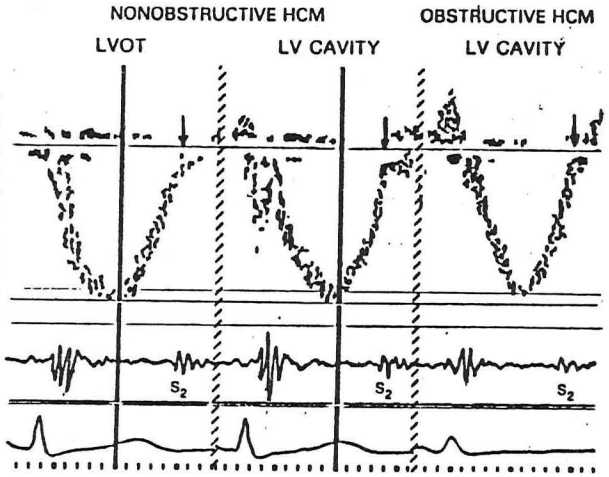



Figure 8. Doppler flow velocity waveforms from the left ventricular outflow tract (LVOT) of a patient with nonobstructive hypertrophic cardiomyopathy (HCM) (**left panel**), the mid-left ventricular (LV) cavity of a patient with nonobstructive hypertrophic cardiomyopathy (**center panel**) and mid-left ventricular cavity of a patient with obstructive hypertrophic cardiomyopathy (**right panel**). In each instance flow velocity is continuous until aortic valve closure (**arrow**). Flow velocity is depicted negative to zero baseline because the direction of flow is away from the scan head. Simultaneous phonocardiogram and lead II electrocardiogram are shown below. **Vertical black bars** are time markers. (Ref. 65)

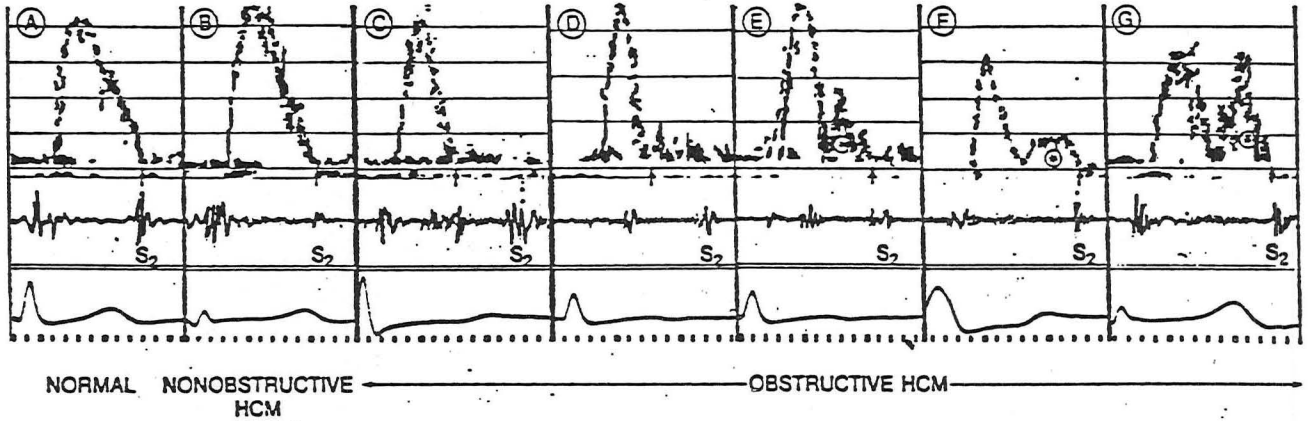



Figure 9. Composite of seven Doppler flow velocity waveforms from a normal subject (A), a patient with nonobstructive hypertrophic cardiomyopathy(HCM)(B) and five patients with obstructive hypertrophic cardiomyopathy (C to G). The point in systole where the Doppler waveform returns to zero baseline is indicated by an arrow. The timing and contours of flow velocity in the normal subjects and the patients with nonobstructive hypertrophic cardiomyopathy are similar, with flow clearly persisting to aortic valve closure. In obstructive hypertrophic cardiomyopathy, flow velocity may occasionally return to zero baseline before aortic valve closure (C and D) or more often show a "bifid" flow velocity profile with evidence of late systolic flow persisting to aortic valve closure in the form of a second peak (*)(E to G). (Ref. 65)

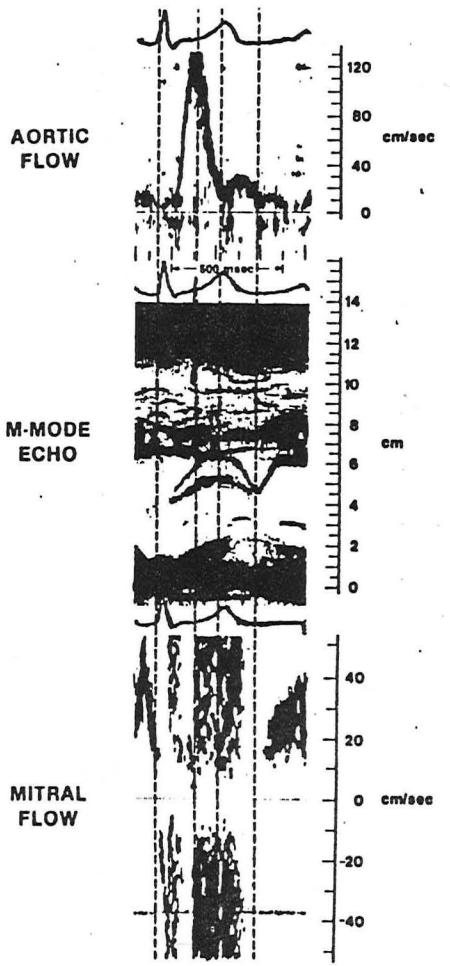



Figure 10. Temporal sequence of systolic events in obstructed hypertrophic cardiomyopathy. **Dashed vertical lines are drawn at the onset** of QRS, onset of systolic anterior motion–septal contact, midsystolic aortic flow velocity nadir, and end of ejection on the aortic flow velocity recording. Flow velocity recorded in the left atrium near the level of the mitral valve shows turbulent systolic flow consistent with mitral regurgitation (bottom). M-mode echocardiogram at the level of the mitral valve shows septal–mitral valve contact (middle). Ascending aortic flow velocity recording shows a rapid midsystolic flow velocity deceleration (top). These 3 records, from patient 12, were matched such that the preceding RR intervals were within 20 ms of each other.(Ref 71)

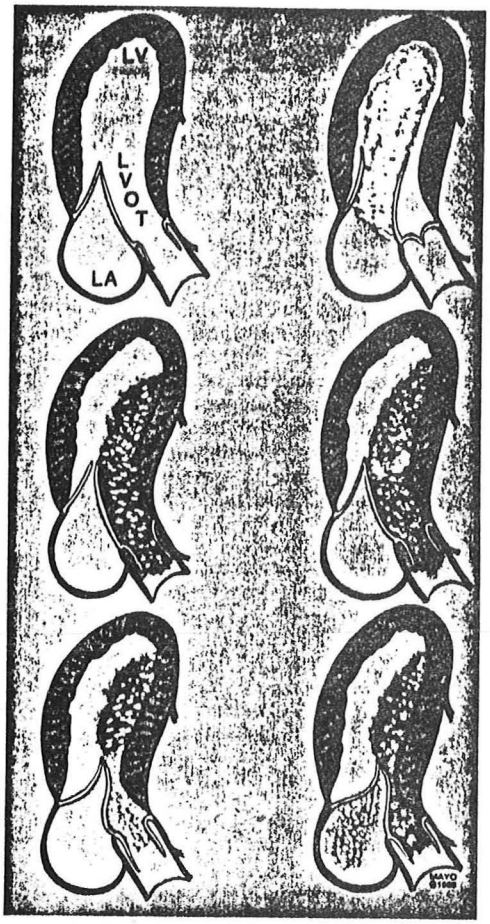



Figure 11. Diagram of Doppler color flow imaging of temporal sequence of events in HCM. Top left, 2-D ECHO long-axis view from apical position. LA=left atrium; LV=left ventricle; LVOT=LV outflow tract. Top right, During diastole low-velocity flow through mitral valve into the LV cavity. Center left, Early systole, demonstrating normal-velocity laminar flow in LVOT. Center right, Color reversal at level of mitral valve-septal contact, denoting an increase in velocity. Bottom left, Mosaic pattern in LVOT, indicating high-velocity turbulent flow. Bottom right, Jet of color into LA, depicting mitral regurgitation that occurs after onset of mosaic pattern in LVOT. The jet is directed laterally and posteriorly into LA. Note that normal velocity is now present in LVOT. (Ref. 72)

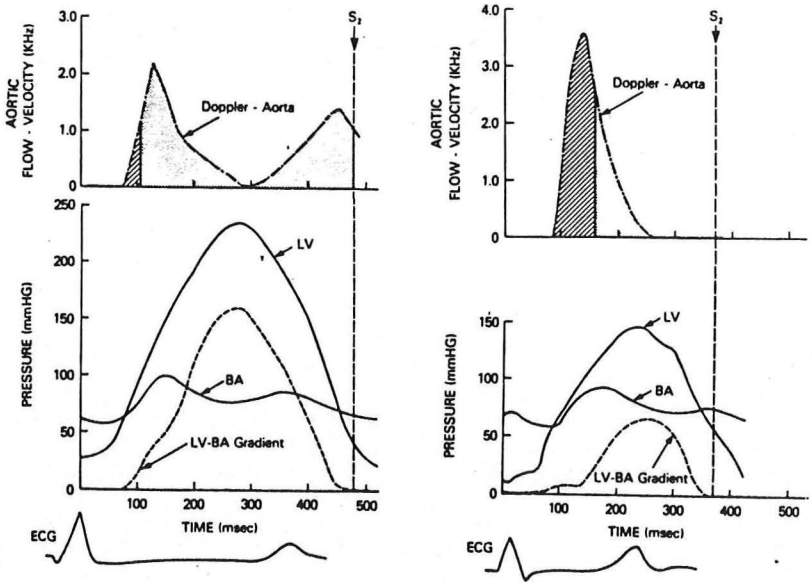



**Figure 12** Simultaneously recorded aortic flow velocity, left ventricular (LV) and brachial artery (BA) pressures and derived pressure gradient throughout systole in two patients with obstructive hypertrophic cardiomyopathy. **Left**, Patient with a marked subaortic pressure gradient of 135 mm Hg and a "bifid" aortic flow velocity profile. A relatively small fraction of aortic flow (12%) occurs in early systole before onset of the gradient (**lined area**), while the vast majority of forward flow occurs *coexistent* with the pressure gradient (**stippled area**). In mid-systole, flow returns to zero baseline at the time the gradient is maximal. **Right**, Patient with a pressure gradient of 65 mm Hg. A much greater proportion of the forward aortic flow velocity integral (79%) is ejected in early systole before the onset of the gradient (**lined area**) and a relatively small proportion of forward flow (21%) occurs while a pressure gradient is present (**stippled area**). In mid-systole, flow returns to zero baseline at the time the gradient is maximal. In late systole, the gradient persists although flow is not detectable by Doppler recording just before aortic valve closure. Lead II electrocardiograms (ECG) are shown below. (Ref. 65)

In patients with HCM with or without obstruction, chamber stiffness is increased due to : (1) greater LV mass secondary to hypertrophy, and (2) abnormal amounts of intercellular connective tissue and fibrosis in the myocardium (78). The relative contribution of these parameters to the increase in chamber stiffness can be expected to differ because of the variability of the extent and distribution of hypertrophy seen in patients with HCM (14-22). The increased LV mass contributes to the small LV cavity and consequently accounts for the small volumes characteristic of HCM. The combination of a stiff ventricle and a small cavity can markedly impair LV filling during diastole. Thus, it can be appreciated that an adequate LV volume must be maintained in order to counteract the increased mass and stiffness. Therefore, volume depletion (e.g. diuretics, nitrates) or increased emptying (e.g. beta-agonists, digitalis) may be very deleterious.

Several factors are important in determining diastolic relaxation of the ventricle (77) (Figure 13). In patients with the obstructive form of HCM both systolic and diastolic factors are important determinants of relaxation whereas in patients without obstruction diastolic factors are of primary importance. In patients with obstruction at rest, the presence of the intraventricular pressure gradient imposes a contraction load on the ventricle which prolongs systole. Consequently, the onset of relaxation is delayed and its duration is prolonged (77). Thus therapeutic interventions which decrease or abolish the gradient (e.g. beta-blockers, calcium antagonists, myomyectomy) should improve relaxation.

Coronary filling occurs during the isovolumic relaxation period which is defined as the time from aortic valve closure to mitral valve opening. Coronary filling increases the thickness and turgor of the myocardium and by way of this intramural loading of the relaxing muscle diastolic relaxation is augmented (77). Therefore, inadequate coronary filling as may occur in HCM due to small or large vessel coronary artery disease, coronary vasospasm, or inadequate capillary density would impair diastolic relaxation (51,59-61). Hence the importance of maintaining coronary flow, e.g. by relieving any vasospasm or by avoiding hypotension.

Activation of contraction occurs when actin-myosin crossbridges are formed in the presence of $Ca^{2+}$ (62). Inactivation is the reverse process involving actin-myosin uncoupling and ATP-dependent re-uptake of myoplasmic calcium by the sarcoplasmic reticulum (Figure 14). This inactivation process is sensitive to the myoplasmic calcium concentration and any mechanism that leads to cytosolic calcium overload (ischemia, abnormal membrane permeability to calcium, excess catecholamines), will impair inactivation and diastolic relaxation (47,53,54,79,80). This provides a major rationale for the use of calcium antagonists which may relieve ischemia and potentially reduce intracellular calcium availability.

Asynchonous contraction and relaxation among different LV wall segments may also impair diastolic filling (21). This is presumably due to the altered geometry of the LV resulting from the variable distribution and extent of hypertrophy seen in patients with HCM, or perhaps from regional

Table 3. PROPOSED FACTORS CONTRIBUTING TO ABNORMAL DIASTOLIC FUNCTION IN HCM

1. Chamber stiffness $\frac{\text{Myocardial Mass x Myocardial Stiffness}}{\text{Ventricular Volume}}$

2. Relaxation

   A. Contraction Loading - systole
      i. Outflow obstruction

   B. Relaxation Loading - diastole
      i. Inadequate coronary filling
         a. Small vessel disease
         b. Microvascular spasm
         c. Low capillary density per unit LV mass
      ii. Impaired ventricular filling
         a. Small ventricular volume

   C. Delayed inactivation
      i. Myoplasmic calcium overload
         a. Genetic defect
         b. Ischemia
            -Small vessel disease
            -Microvascular spasm
            -Low capillary density per unit LV mass
            -Hyperadrenergic activity
         c. Hypertrophy

3. Nonhomogeneous contraction and relaxation of different LV segments

Modified from Ref. 21

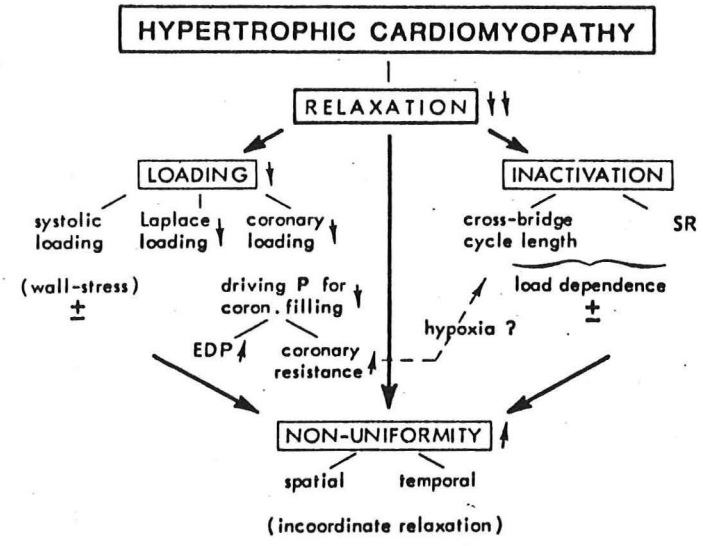



Figure 13. The various determinants of impaired relaxation in hypertrophic cardiomyopathy. P = pressure; EDP = end-diastolic pressure; SR = sarcoplasmic reticulum. (Ref. 77)

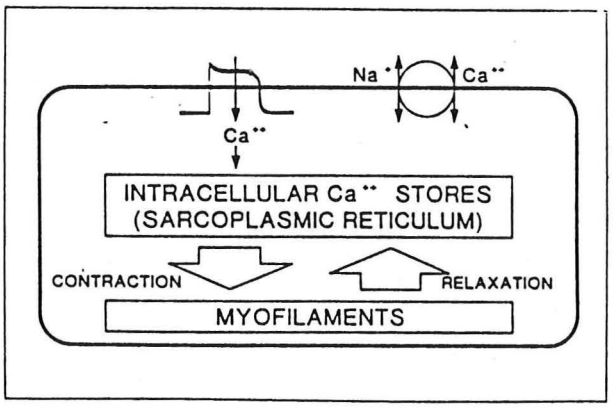
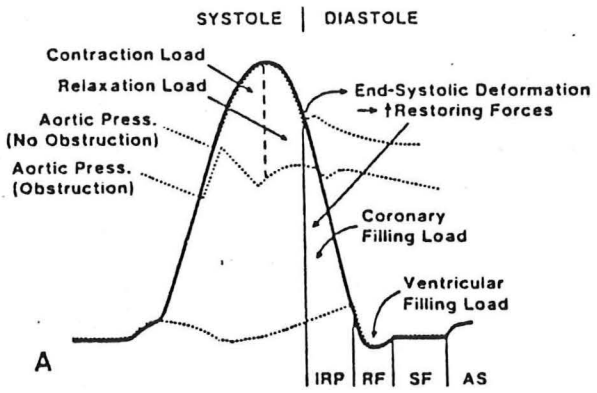



Figure 14. *Major steps of excitation-contraction coupling in mammalian working myocardium.* (Ref. 166)




| Diastolic Period | Isovolumic Relaxation Period | Rapid Filling Period | Slow Filling Period | Atrial Systole |
|---|---|---|---|---|
| Load | Restoring Forces<br>Coronary Filling | Ventricular Filling | | |
| Indices of Relaxation | Isovolumic Relax. Time<br>Relaxation Time Index<br>Time Constant (T) of Isovolumic Press. Decline<br>Peak Neg. dp/dt<br>Geometric Changes<br>L.V. Pressure Waveform | Peak Filling Rate (P.F.R.)<br>Time to P.F.R.<br>Post. Wall Thinning<br>Minor Diameter Lengthening<br>Rapid Filling Volume<br>Rapid Filling Duration<br>L.V. Pressure Waveform | Slow Filling Duration | Atrial Systolic Volume |

B

Figure 15. (A) Diagram of left atrial, ventricular, and aortic pressures(with and without obstruction to outflow) together with the various loads that may affect diastolic relaxation in hypertrophic cardiomyopathy. A contraction load(the obstruction) applied in the first half of systole would delay the onset and slow the rate of relaxation. The coronary filling load(during isovolumic relaxation(IRP)) and ventricular filling load(during rapid filling(RF)) are reduced in hypertrophic cardiomyopathy as a result of the factors listed in Table 3. SF = slow filling period; AS = atrial systolic filling. (B) This chart indicates the relaxation load(s) that are applicable together with the indices of relaxation that are measurable for each time period of diastole. It is important to emphasize that impaired relaxation affects not only the indices measured during IRP and RF but also the duration of the slow filling period and the volume of atrial systolic filling. Thus, slow relaxation prolongs the duration and decreases the volume of rapid filling while shortening the slow filling period and increasing the volume of atrial systolic filling. (Ref. 21,77)

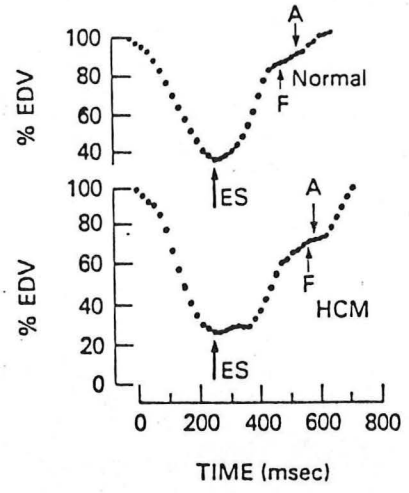



Figure 16A. Left ventricular time-activity curves obtained by radionuclide angiography in a normal subject and a patient with hypertrophic cardiomyopathy (HCM), measuring relative volume changes throughout average cardiac cycle. Impaired diastolic function is evident in hypertrophic curve: prolonged isovolumic relaxation phase, decreased rate of rapid diastolic filling, decreased contribution of rapid filling to left ventricular filling volume and increased contribution of atrial systole. A = onset of atrial systole (measured electrocardiographically); ES = end-systole; F = termination of rapid filling. (Ref. 169)

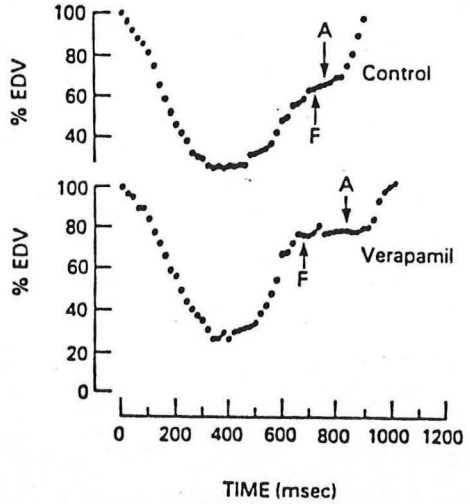



Figure 16B: Left ventricular volume curves by radionuclide angiography at rest and during exercise in patient with hypertrophic cardiomyopathy. Oral verapamil (480 mg/day) results in enhanced diastolic filling at rest: shortened isovolumic phase, increased rate and extent of rapid diastolic filling and reduced contribution of atrial systole to total filling volume. Increased rate of filling is also evident during exercise. Each point represents 20 ms. EDV = end-diastolic volume. (Ref. 169)

ischemia. Several studies suggest that calcium antagonists reduce regional wall motion abnormalities in HCM either by improving relaxation or reducing ischemia (81,82).

The clinical indices of diastolic function that have been measured in patients with HCM are illustrated in Figure 15 along with the corresponding diastolic interval where they are measured. Recent studies using computer-analyzed M-mode echocardiograms, Doppler measurements, gated radionulclide angiograms and hemodynamics have documented abnormalities in most of these clinical parameters and beneficial effects of calcium antagonists (81-92). Verapamil has been the most extensively studied and has been shown to improve indices of LV diastolic function (Figure 16). The time for isovolumic relaxation is typically shortened. During the rapid filling phase the rate and volume of filling are increased and the time to peak filling is decreased. Due to the increased rate and volume of flow during the rapid filling phase, this phase of diastole is shortened, the slow filling phase is lengthened and the contribution from atrial systole becomes less important.

**Ischemia**

Chest pain is a frequent symptom of patients with the obstructive and non obstructive HCM. The exact pathophysiological mechanisms responsible for myocardial ischemia which underlies the chest pain, and may contribute to the diastolic dysfunction, have not been completely elucidated. In patients with HCM over the age of 40, the incidence of coronary artery disease is approximately 20-30% (93-96). Hence, fixed coronary artery disease must always be considered as a cause of ischemia in this age group. The incidence of coronary artery disease in patients with HCM under 40 years is unknown but on the basis of pathological studies is thought to be rare (59). In these patients the mechanism of ischemia must be explained in other ways.

Recent studies have implicated inadequate coronary vasodilator reserve relative to the increased myocardial mass as a cause of ischemia in patients with HCM and normal epicardial coronary arteries. Two studies have investigated patients with symptomatic HCM and angiographically normal coronary arteries by measuring myocardial blood flow and metabolic markers of ischemia at rest and during pacing. In a study by Pasternac et al. (97), patients with HCM had coronary blood flows per unit of LV mass that were inappropriately reduced at rest and also during pacing compared to controls. In addition, patients developed typical changes in markers of ischemia including chest pain, ST-sesgment depression and higher coronary venous lactate levels. In a similar study by Cannon et al (60), patients with HCM demonstrated a significant decrease in coronary blood flow at high pacing rates in contrast to control patients. This was associated with a further rise in left ventricular end-diastolic pressure, angina, and an increase in lactate production. In both studies total coronary blood flow (uncorrected for LV mass) was significantly higher at rest and during pacing compared to controls. These studies indicated that coronary flow at rest was high and with stress further increases in coronary vasodilation

and flow were limited and inadequate to meet the increased metabolic needs. Consequently ischemia developed, anaerobic metabolism increased, and diastolic compliance decreased.

The causes of abnormal vasodilator reserve are unknown, but possibilities include small vessel disease (59,61,98) microvascular spasm (51), or insufficient capillary density in proportion to the increased myocardial mass (60,97). The last possibility is supported by the abnormally low coronary blood flow per unit mass compared to controls demonstrated in the study by Pasternac (97). Additional studies by Cannon in patients without HCM but with angina and normal coronary arteries support the idea of microvascular spasm as a cause of abnormal vasodilator reserve (99,100). In these studies vasoconstrictive maneuvers such as ergonovine administration or cold pressor testing often exacerbated or unmasked abnormalities in vasodilator reserve similar to the changes just described in patients with HCM. Again, these mechanisms for ischemia provide the rationale for the use of calcium antagonists in patients with HCM.

## CLINICAL COURSE AND PROGNOSTIC FEATURES

### Clinical Course

Effective management of patients with HCM requires an understanding of the pathophysiological mechanisms which contribute to symptoms as well as knowledge of the natural history of the disease. Reports from several centers with large numbers of patients with HCM have documented the initial presentation and symptomatic course (37,101-110). A number of factors must be kept in mind when reviewing this data: First, most were retrospective studies of symptomatic patients referred to large tertiary referral centers; Second, many patients were treated medically and therefore, their clinical course is not representative of the natural history of the disease; Third, nearly all patients had typical ASH with or without gradients; and Fourth, the duration of follow-up was usually five years or less with relatively few patients followed up to ten years. Nevertheless, several inferences can be drawn from these studies (Tables 4 and 5): (1) HCM is commonly a disease of young adulthood with nearly 70% of patients presenting before the age of 40 (average age of 20-25); (2) Young patients typically have minimal or no symptoms (functional class 1 and 2) and an 8-10 year history of a murmur; (3) Although older patients tended to be more symptomatic at presentation than younger patients, the prevalence of symptoms in all age groups was essentially equal. The most common major symptoms were dyspnea on exertion, angina, pre-syncope (dizziness), syncope and palpitations; (5) There was no consistent correlation between symptoms, functional class, the presence or absence of a gradient, the severity of the gradient, LV end-diastolic pressure, or EKG findings; (6) During the course of the disease, 60-70% of patients remained stable, 10-20% improved by one functional class, while 10-20% deteriorated one or more functional classes. Patients often remained stable for 5-10 years after the onset of symptoms before clinical deterioration occurred; (7) Older patients with symptoms tended to progress in a shorter period of time than did younger patients who had long asymptomatic periods. Symptomatic progression did not correlate with any particular pattern of symptoms, LV

Table 4.

CLINICAL FEATURES AT PRESENTATION IN PATIENTS WITH HCM*

| | |
|---|---|
| No. of Patients | 1,083 |
| Age Range | 1 - 78 years |
| Male | 60% (44 - 75) |
| Age at initial evaluation | |
| 0 - 19 | 28% (20 - 36) |
| 20 - 39 | 41% (34 - 45) |
| 40 - 59 | 29% (25 - 33) |
| >60 | 2% ( 1 - 3) |
| Functional class at presentation | |
| 1 (no symptoms) | 24% (14 - 37) |
| 2 (mild symptoms) | 50% (40 - 68) |
| 3-4 (moderate to severe symptoms) | 26% (12 - 36) |
| Symptoms | |
| Dyspnea | 66% (40 - 88) |
| Angina | 52% (28 - 74) |
| Pre-syncope | 38% (20 - 55) |
| Palpitations | 38% ( 9 - 55) |
| Syncope | 22% ( 8 - 30) |

*From Ref. 101-110

TABLE 5. RELATIONSHIP BETWEEN AGE AND CLINICAL CLASS IN 190 HCM PATIENTS *

| | AGE | | | |
|---|---|---|---|---|
| FUNCTIONAL CLASS | 0-19 | 20-39 | 40-57 | >60 |
| 1 & 2 | 86% | 69% | 48% | 14% |
| 3 & 4 | 14% | 31% | 52% | 86% |

* Adapted from Ref. 103

Table 6. MODE OF DEATH IN 235 PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY*

| | NO. | % |
|---|---|---|
| Sudden | 117 | 50 |
| CHF | 20 | 9 |
| Cerebral embolus | 5 | 2 |
| Cardiac Surgery | 41 | 17 |
| Ischemic Heart Disease | 3 | 1 |
| Accidental | 6 | 3 |
| Noncardiac | 30 | 13 |
| Unknown | 5 | 2 |
| | 235 | 100 |

*From Ref. 101-103,111,112,162,163

end-diastolic pressure, the presence or severity of LVOT gradient or other clinical parameters; and (8) The annual mortality rate was between 3% and 5%. Overall the most common mode of demise is sudden cardiac death (101-103,111,112,162,163) (Table 6), but this differs depending on the age group. Children under the age of two most often die from congestive heart failure (110), while adults over age 40 often deteriorate and die from congestive heart failure due to progressive left ventricular dilatation and atrial fibrillation (102,103,111). However, the risk of sudden death remains. A high risk for sudden death occurs over the age range of 5-40 years.

McKenna and Goodwin (35,102,112) have developed a natural history flow chart for HCM based on their retrospective analysis of 254 patients aged 1-66 years (mean 34) followed for 1 to 23 years (mean 6) (Figure 17). This summary emphasizes the relationship of age to symptomatic status, the typically slow progression of symptoms, and the marked punctuation of the disease by a high incidence of sudden cardiac death particularly in asymptomatic children and young adults. Thus, the major goals of management are not only the control of symptoms but also the prevention of sudden death.

**Prognostic Features**

Several studies have shown that both age and family history of HCM and sudden death may identify a population at high risk of sudden death. In the study by McKenna (35), discriminant analysis indicated the combination of young age ($\leq$ 14 yrs) syncope at diagnosis, and family history of HCM and sudden death, best predicted poor prognosis (sensitivity 70%, specificity 73%). Of the 32 patients who died suddenly, 40% were under age 30 and 82% were asymptomatic. Patients who had a family history of HCM but not sudden death had a prognosis similar to those without a family history of HCM. In an autopsy study of 78 patients with HCM who experienced sudden death 90% were under age 40 and 54% were asymptomatic at the time of death (113). Maron et al also reported on a group of families with HCM and an unusually high incidence of sudden death (114). Of 69 first degree relatives, 41 had HCM and 31 died - 74% suddenly and 65% without prior symtpoms. Kosa et al (111) followed 136 patients for 1-17 years and noted 14/22 deaths were sudden. Life table analysis demonstrated age < 20 and family history of HCM and sudden death as the best predictors of poor prognosis. These studies showed no correlation between clinical progression of symptoms, functional class, EKG findings, LV end-diastolic pressure, or the presence or magnitude of an outflow tract gradient and the future occurrence of sudden death.

The mechanism(s) of sudden death is unknown but in most cases is thought to be due to arrhythmias. Both atrial and ventricular arrhythmias occur frequently in patients with HCM (Table 7). Five to 10% of patients are in established atrial fibrillation at the time of diagnosis and a further 7% develop this arrhythmia during the course of the disease (119). Although paroxysmal or sustained supraventricular tachycardia (SVT) and atrial fibrillation are often associated with symptomatic deterioration and systemic emboli (102,109,111,120), they have not been specifically correlated to sudden death (102,117,121).

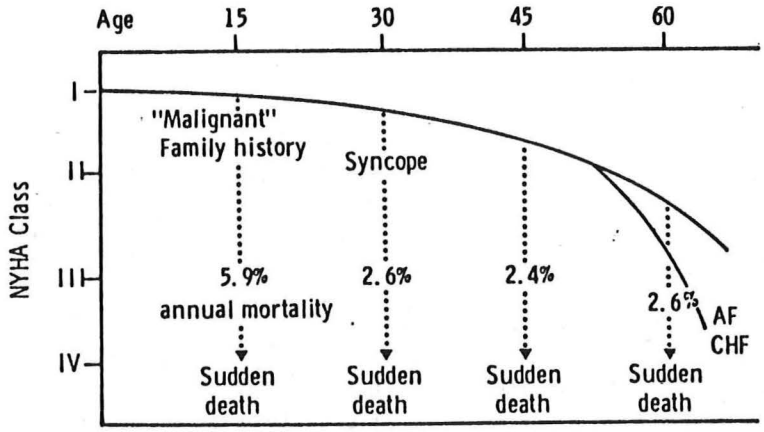



Figure 17. A suggested natural history of hypertrophic cardiomyopathy. AF = atrial fibrillation; CHF = congestive heart failure; NYHA = New York Heart Association.(Ref. 102,112)

Table 7. **PREVALENCE OF SUPRAVENTRICULAR AND VENTRICULAR ARRHYTHMIAS IN PATIENTS WITH HCM**

| Reference | No. of Pts | Age | Duration of Monitoring | Atrial Ectopy | SVT/AF | Ventricular Ectopy | Grade* 3,4a,4b | VT |
|---|---|---|---|---|---|---|---|---|
| 37 | 100 | 9-65 | 24 | 54% | 15% | 83% | 65% | 19% |
| 115 | 30 | 21-71 | 48 | 83% | 41% | 90% | 86% | 17% |
| 116 | 33 | 15-75 | 24 | 70% | 36% | 82% | 88% | 15% |
| 117 | 86 | 6-66 | 72 | 86% | 31% | 62% | 82% | 28% |
| 118 | 22 | 18-83 | 24 | 68% | 32% | 91% | 64% | 14% |
| Totals | 271 | | | 50% | 31% | 82% | 77% | 19% |

*Grade 3 Multiform
4a Couplets
4b Salvos

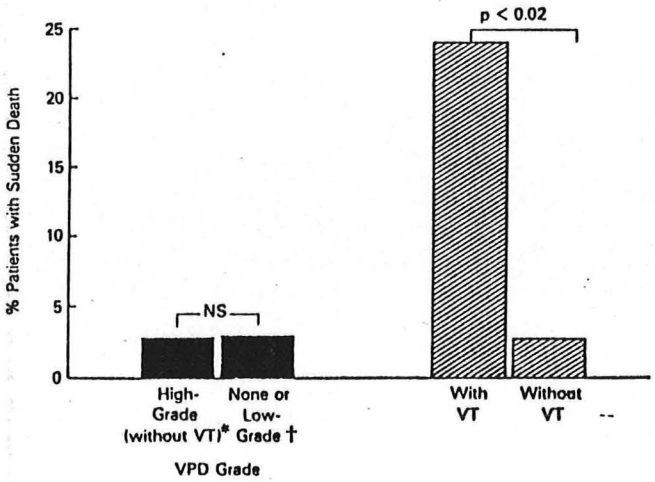



Figure 18. Comparisons of the prevalence of sudden death (or cardiac arrest) in patients with or without high grade ventricular arrhythmias other than nonsustained ventricular tachycardia(VT) and in patients with or without nonsustained ventricular tachycardia. NS = not significant; p = probability; VPD = ventricular premature depolarization. * Arrhythmia grades 3(multiform) and 4a(couplets); + = Grades 0, 1, 2. (Ref. 121)

Table 8. VENTRICULAR TACHYCARDIA AND SUDDEN DEATH IN 169 PATIENTS * WITH HCM AND 3 YEAR FOLLOW-UP

| | SUDDEN DEATH (N=13) | SURVIVORS (N=156) |
|---|---|---|
| VT on Holter | 9 | 32 |
| No VT on Holter | 4 | 124 |
| Incidence of sudden death | | 8% |
| Sensitivity of VT | | 69% |
| Specificity of VT | | 79% |
| Predictive value of VT | | 22% |

*From Ref. 117,121

Table 9. CLINICAL INDICATORS OF INCREASED RISK OF SUDDEN DEATH IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

1. Family history of hypertrophic cardiomyopathy and sudden death
2. Ventricular tachycardia (non-sustained)
3. Age under 30
4. ? Syncope

Ventricular ectopy occurred in nearly 85% of patients with HCM and high-grade ectopy was present in over 75%. About 20% of patients demonstrated ventricular tachycardia (VT) which was characteristically nonsustained, multifocal, and unassociated with symptoms. In contrast to supraventricular arrhythmias, the presence of nonsustained VT appears to be strongly associated with sudden death (Figure 18). Two independent studies by Maron et al (121) and McKenna et al (117) followed a total of 169 patients with HCM for 3 years. Those patients with nonsustained VT had an annual mortality of 8% compared to 1-2% for those without VT. Symptoms (including syncope), functional class, presence or severity of an outflow gradient, or EKG findings did not correlate with sudden death or presence of VT. Patients were not stratified according to other high risk factors (young age or family history). Although 9 of 13 patients with VT on Holter died, 32 of 41 survivors also had VT on Holter. Therefore, the presence of nonsustained VT on Holter may be a marker for sudden death, but it is not very specific and has a low predictive value (Table 8).

From the previous discussion a profile of the high risk patient can now be made (Table 9). The high risk patient is young (age under 30), has a strong family history of HCM and sudden death, and may have nonsustained VT on prolonged ambulatory monitoring.

## THERAPEUTIC APPROACHES

The primary objectives of treatment of HCM are the amelioration of symptoms, the control of arrhythmias, and the improvement of prognosis. It is useful to summarize the effects of current medical and surgical therapies (Table 10) and then present an approach to treatment.

### Symptoms

Since symptoms may be due to obstruction, poor diastolic function, or ischemia, therapy should be directed at reducing obstruction, improving diastolic function, and reducing ishcemia. For over 20 years, medical therapy has relied on beta-adrenergic receptor antagonists (beta-blockers) until recently when calcium channel antagonists have been shown to be beneficial in patients with HCM.

### -Beta-Adrenergic Blockade

Beta-Blockers have been utilized in view of their ability to increase ventricular volume and to decrease contractility and heart rate, particularly during exercise and other conditions of sympathetic overactivity (128). An additional effect is the potential to reduce ischemia by lowering myocardial oxygen consumption. Both intravenous and chronic oral therapy reduce or abolish provocable gradients but have little effect on resting gradients (122-124); hence their use in patients with provocable gradients. No consistent beneficial effect on LV end-diastolic pressure or diastolic function has been demonstrated (124,125,131). About 70% of patients report symptomatic improvement, esspecially angina, and a 20-30% improvement in exercise capacity (126,127,129,137). Sustained

improvement in symptoms is seen in only 30-40% of patients, but may be greater if very high doses of drug are used (>480mg propranolol per day) (116,128,130).

**-Calcium Channel Blockade**

Calcium channel blockade with verapamil has been utilized in view of its negative inotropic action, its salutory effects on relaxation, and its ability to reduce ischemia (141). Resting gradients are usually decreased but provocable gradients may not be prevented (132,138,141). Diastolic relaxation is improved in most patients treated with calcium antagonists (81-89); hence their use in patients who have predominantly diastolic dysfunction. Verapamil improves symptoms (chest pain, dyspnea) in about 70% of patients and increases exercise duration about 30% during short- and long-term administration (133,134,136-138,140,141). Most experience with calcium antagonists has been gained using verapamil (132-134,138,139) but both nidedipine (84) and diltiazem (88) are also efficacious.

Caution must be exercised when calcium antagonists are used in patients with HCM becasue of potentially life-threatening adverse drug effects in a small percentage of patients (95,135). Both verapamil (135) and nifedipine (90) have been shown to cause hypotension, to increase LV filling pressures, and to worsen the outflow gradient in some patients. Pulmonary edema and death have been reported in patients on short and long term verapamil therapy (135). Patients at high risk with verapamil were those with high filling pressures (>20mmHg) or a history of orthopnea and significant outflow tract gradients, preexisting hypotension, sinus or atrioventricular nodal conduction disease without a pacemaker, or the concomitant use of quinidine (135). Therefore, these drugs should be administered with extreme caution to patients with HCM with severe symptoms and hemodynamic impairment. Initiation of therapy in this group of patients should be done in the hospital with consideration given to right heart catheterization for assesssment of filling pressures (141).

The combination of a beta-blocker and calcium channel antagonist has theoretical advantages over either one alone. The calcium channel antagonist would lower the resting gradient and improve relaxation while the beta-blocker would prevent exacerbations of the gradient. Both would improve ischemia by reducing myocardial oxygen consumption. One study (124) has investigated the acute effects of the combination of propranolol and nifedipine in 12 patients with resting gradients and demonstrated more favorable hemodynamic conditions with the combination of drugs compared to either one given alone. No short- or long-term studies in patients to assess the effects on hemodynamics, symptoms, or exercise tolerance has been done. Although this combination of a beta-blocker and calcium antagonist is potentially useful, it may also be detrimental because of their combined effects on contractility, blood pressure, and sinus and AV nodal conduction. Therefore, extreme care must be used if combination therapy is considered in these patients.

**-Surgery**

Although surgery was used as the primary therapy for patients with the obstructive form of HCM in the 1960's it is now used only after medical therapy has failed to control symptoms. The procedure used is a transaortic septal myectomy or myotomy which reduces or abolishes the gradient by surgical enlargement of the LVOT area (142). Perioperative surgical mortality is approximately 10% (range 3 - 16%) (112,143) compared to a medical mortality of 3 - 5% per year, which provides the impetus for medical therapy as primary treatment. Late mortality is about 2% but there appears to be no protection from sudden death (112,143). However, no adequate controlled trial of medical versus surgical therapy has ever been done (147). Following surgery there is marked short- and long-term symptomatic improvement in almost 90% of patients with significant reduction in the resting outflow gradient, systolic anterior motion of the mitral valve, and mitral regurgitation (112,143,146-148). The effects on LV end-diastolic pressure are variable and objective assessment of diastolic function has not been performed. Systolic function appears to be well maintained following surgery (144).

**-Other Therapy**

Recent reports have shown that disopyramide (149) and amiodarone (150-152), both anti-arrhythmic agents, have produced symptomatic improvement in patients with HCM. Therefore they may be useful in those patients who do not respond to, or have contraindications to, propranolol or verapamil. Disopyramide reduces the outflow tract gradient probably because of its negative inotropic action (149). It has not been evaluated extensively and long term effects in patients with HCM are unknown. Effects of amiodarone on LV function in patients with HCM are conflicting. LV ejection and relaxation characteristics assessed by radionuclide tecniques did not change over a six month period in one study (153). In another study (154) resting and exercise filling pressures increased significantly after 5 weeks of therapy, but there was no change in echocardiographic relaxation parameters, which suggested a significant negative inotropic effect or impairment of relaxation. Because of the potential worsening of LV function and its side effect profile (vide infra) amiodarone should be used judiciously in the management of symptoms in these patients.

Diuretic therapy is useful only in a situation of pulmonary venous congestion or pulmonary edema and must be used carefully. Over-diuresis results in volume contraction and worsens the intraventricular gradient. Digitalis is relatively contraindicated because of its positive inotropic effect and potential enhancement of the outflow gradient. Although it could be used for slowing of the rapid ventricular response in atrial fibrillation the beta-adrenergic blockers or calcium antagonists are the preferred drugs. Digitalis and diuretic therapy are indicated for the rare patient with this disease who develops left ventricular dilatation and congestive heart failure, usually after transmural myocardial infarction or surgery. Nitrate therapy is relatively contraindicated in these patients

| | DYSPNEA | ANGINA | EXERCISE DURATION | INOTROPY | LVOT GRADIENT | DIASTOLIC FUNCTION | LVEDP | SUDDEN DEATH |
|---|---|---|---|---|---|---|---|---|
| PROPRANOLOL | ↓ | ↓↓ | ↑ | ↓ | ↓→ | ↑↓ | ↑↓ | → |
| VERAPAMIL | ↓↓ | ↓↓ | ↑↑ | ↓→ | ↓→ | ↑↑ | ↑↓ | → |
| SURGERY | ↓↓↓ | ↓↓↓ | ↑↑ | → | ↓↓↓ | ? | ↑↓ | → |
| AMIODARONE | ↓ | ↓ | ? | ↓→ | → | → | ? | ?↓ |
| DISOPYRAMIDE | ↓ | ↓ | ↑ | ↓ | ↓ | ? | ↓→ | ? |
| OTHER TYPE I | → | → | → | → | → | → | → | ? |
| DIURETICS | ↓ | → | ?↑ | → | → | → | ↓ | → |
| DIGOXIN | ? | ? | ?↓ | ↑ | ↑ | → | → | → |
| NITRATES | ↓↑ | → | ? | → | → | → | ↓ | → |

(↑INCREASE;↓DECREASE;→ NO CHANGE; ? NOT KNOWN)

Table 10. Summary of effects of currently available treatments on symptoms, left ventricular function and sudden death in patients with hypertrophic cardiomyopathy.(Adapted from Ref. 168,169)

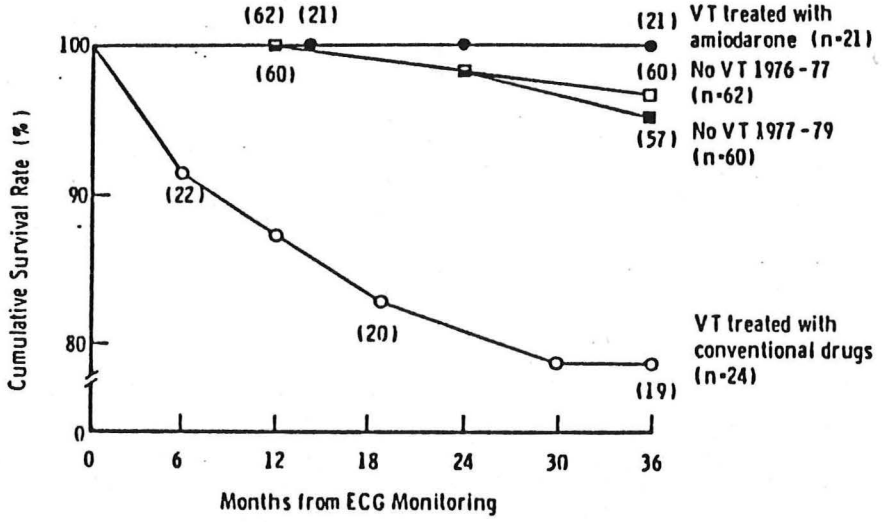



**Figure 19.** Cumulative survival for 24 patients with ventricular tachycardia (VT) treated with conventional antiarrhythmic agents (○), 21 patients with ventricular tachycardia treated with amiodarone (●), 62 patients with no ventricular tachycardia during e.c.g. monitoring between 1976 and 1977 (□) and 60 patients without ventricular tachycardia during e.c.g. monitoring performed between 1977 and 1979 (■). The probability of cardiac death equals the total number of deaths for the year divided by the adjusted number at risk minus the number of deaths due to other causes (Ref. 119)

Table 11. **MAJOR SIDE EFFECTS OF AMIODARONE IN 326 PATIENTS DURING 8 - 19 MONTHS FOLLOW-UP** *

| | |
|---|---|
| Overall incidence | 67% - 72% |
| GI/hepatic | 24% - 29% |
| Skin | 18% - 22% |
| Neuro | 20% - 25% |
| Pulmonary | 4% - 7% |
| Thyroid | 2% - 14% |
| Arrhythmia aggravation | 4% - 5% |

* From Ref. 164,165

because of the reduction in left ventricular volume and potential increase in outflow tract gradient and symptoms.

**Arrhythmias**

Patients with HCM who experience sudden death often demonstrate VT on prolonged Holter monitoring. Therefore, the suppression of VT by appropriate therapeutic agents may lower or abolish the occurrence of sudden death. No prospective study with appropriate controls and risk stratification of patients has been performed to adequately address the question of what is optimal therapy. Neither surgery nor any of the conventional group I anti-arrhythmics, calcium channel blockers, or beta-blockers alone have been shown to decrease the frequency of ventricular tachycardia or to prevent sudden death (103,112,117).

Propranolol in moderate doses (280 mg/day) does not reduce the incidence of ventricular arrhythmias (115) but may be effective when administered in high doses (480 mg/day) in combination with conventional drugs (disopyramide, mexilitine, phenytoin, procainamide, quinidine, tocainide) (116,156). In 29 patients (mean age 49 $\pm$ 16, range 13-79) with sustained supraventricular tachyarrhythmia (SSVT), couplets, or VT, high dose beta-blockade completely suppressed VT in 2 patients, couplets in 5 and SSVT in 2. In 8 patients it partially controlled these arrhythmias but in 12 it failed to control couplets or VT. All 20 patients responded to additional antiarrhythmic therapy after an average of 1.7 trials per patient. The combination of beta-blocker (usually propranolol) plus disopyramide or quinidine proved most effective in controlling ventricular arrhythmias. Side effects of propranolol necessitated downward adjustment of dosage in only 7% of patients. Over an average 5.9 year follow-up period (range 3 to 10 years), the annual mortality rate for deaths related to HCM was 1.4% and the incidence of sudden cardiac death was 0.3% (156). Reservations of this study include: (1) Lack of control groups, (2) Non-randomized design, (3) Small number of patients, (4) No stratification of patients into high- or low-risk subgroups.

Recently, McKenna et al (119,157) reported that amiodarone significantly improved survival in patients with HCM and VT (Figure 19). These studies were done in two consecutive series of patients and compared to historical control patients with HCM but without VT. Both groups were comparable in terms of age (46 vs 44 yrs), duration of follow-up (7 vs 6 years), symptomatic status and treatment, family history of HCM and sudden death (21% vs 14%), and hemodynamic characteristics. One group was treated with conventional antiarrhythmic drugs (quinidine, disopyramide, mexilitine) and the other group was treated with amiodarone (average 300 mg/day). Over 3 years there were no deaths in the amiodarone-treated patients and a 7% annual mortality in the conventionally treated patients. Patients without VT had an annual mortality of 1.1%. The same investigators have shown that amiodarone was effective in the long-term control of ventricular arrhythmias and occurrence of sudden death (152). Side effects were frequent but tolerable and responded in most cases to

reduction in dosage. The problems with this study include the small number of patients, the nonparallel design, the use of historical controls, and the non-stratification of patients into high- and low-risk groups. Relatively few patients were children or young adults and only 20% had a family history of HCM and sudden death.

## MANAGEMENT

In considering the management of patients with HCM based on currently available information, I have devised the following approach aimed at the control of symptoms, the control of arrhythmias, and the prevention of sudden death.

### Symptoms

Management of symptoms is based on whether or not the patient has the obstructive or nonobstructive form of HCM which can be determined noninvasively in most cases (Figure 20). Currently, echocardiography is the modality of choice for establishing the diagnosis of HCM. Combined M--mode, 2-dimensional and Doppler ECHO studies are used to assess the extent and distribution of hypertrophy, LV systolic and diastolic function, presence and severity of a gradient, and the degree of mitral regurgitation. Radionuclide angiography can also be used to assess left ventricular systolic and diastolic function. Both echocardiography and radionuclide studies are non-invasive and highly reproducible techniques which can be repeated serially. Cardiac catheterization should be reserved to assess hemodynamics in patients who are being considered for surgery, to assess coronary anatomy in patients over 40 years of age, to evaluate for the presence of co-existent cardiac diseases, and to confirm the diagnosis when it is in doubt, e.g. when ECHO studies are technically difficult or there is a question of latent obstruction.

If the patient is asymptomatic, then no therapy is needed in either the obstructive or nonobstructive form of HCM. There is as yet no convincing evidence that any current therapy prevents or slows the myopathic process. Therefore, prophylactic therapy is not indicated.

In symptomatic patients with the nonobstructive form of HCM the major pathophysiologic abnormality is poor diastolic function and a calcium antagonist, i.e. verapamil, is used. If symptoms persist a beta-blocker can be tried, either alone or in combination with verapamil. There is no indication for surgery in this category of patients.

In symptomatic patients with the obstructive form of HCM initial therapy should be beta-blockers, i.e. propanolol. If symptoms persist, then a calcium antagonist, i.e. verapamil, is instituted as monotherapy. If symptoms continue then the options include: (1) Combination of propranolol and a calcium antagonist instituted in the hospital (124), (2) disopyramide, or (3) amiodarone. Lastly, surgery (myomyectomy) should be offered if the patients symptoms remain refractory to medical treatment.

**Arrhythmias**

The approach for the assessment and the management of patients with arrhythmias is shown in Figure 21. This approach is indicated for all patients with HCM, irrespective of the presence or absence of symptoms or obstruction. Holter monitoring (48-72 hours) is undertaken for the detection of supraventricular and ventricular arrhythmias. Prolonged monitoring is recommended because of the well-known variability of both simple and complex ventricular ectopy (158,159). Murlow et al (160) performed a probability analysis on 16 patients with HCM and VT but on no treatment to assess the likelihood of not detecting VT for a given occurrence rate. For a 20% incidence of VT (Table 7), the probability of not detecting VT was 75% for 24 hours of monitoring, 56% at 48 hours, 42% at 72 hours and 18% at 144 hours. The optimal duration of monitoring needed to exclude asymptomatic but prognostically important VT is thus uncertain. Prolonged monitoring (5-7days) is not practical and may decrease the specifity of VT. A duration of 48-72 hours was recommended as a pragmatic compromise (160). In addition, prolonged monitoring should be done at least annually. A recent study by Frank et al (161) reported the rate of detection of VT (in patients on beta-blockers alone and without VT on initial evaluation) as 18% at 5 years and 40% at 10 years for an annual incidence of occurrence of VT of 4%. The occurrence of VT was not heralded by new symptoms or progression of existing symptoms. Exercise testing is no more sensitive than Holter monitoring for the detection of high-grade arrhythmias in these patients (36,115).

**Ventricular**

If nonsustained VT is detected, then a decision must be made whether or not to treat these patients with antiarrhythmic agents. Since high risk patients are often children or young adults long-term antiarrhythmic treatment would be required. Since the predictive value of VT for subsequent sudden death is low (20%, Table 8), I believe it is inappropriate to recommend therapy for all patients with HCM in whom nonsustained VT is demonstrated. A subgroup of patients with nonsustained VT in whom treatment can be justified are those who are young (under age 30) and who have a strong family history of HCM and sudden death. Although the effect of amiodarone on prognosis is promising (Figure 19), I prefer not to use amiodarone as the initial therapy in this group of patients because of its potentially severe and life-threatening side effects (Table 11), which are dose- and duration-related. Furthermore, it must be noted that this data is based on a small series of relatively low risk (age >40, <20% family history) patients in a matched but nonparallel study using historical controls. Hence, at present, I would use high dose beta-blockade (propranolol 480 mg/d) in combination with a Type I antiarrhythmic (quinidine, disopyramide, mexilitine in that order) as therapy in this high-risk subgroup (156). Amiodarone therapy should be initiated if the combination regimen is limited by side effects or VT is not controlled. If amiodarone is unsuccessful in controlling VT or is limited by side effects, then electrophysiological mapping should be undertaken prior to any consideration of surgical ablation of the arrhythmogenic focus.

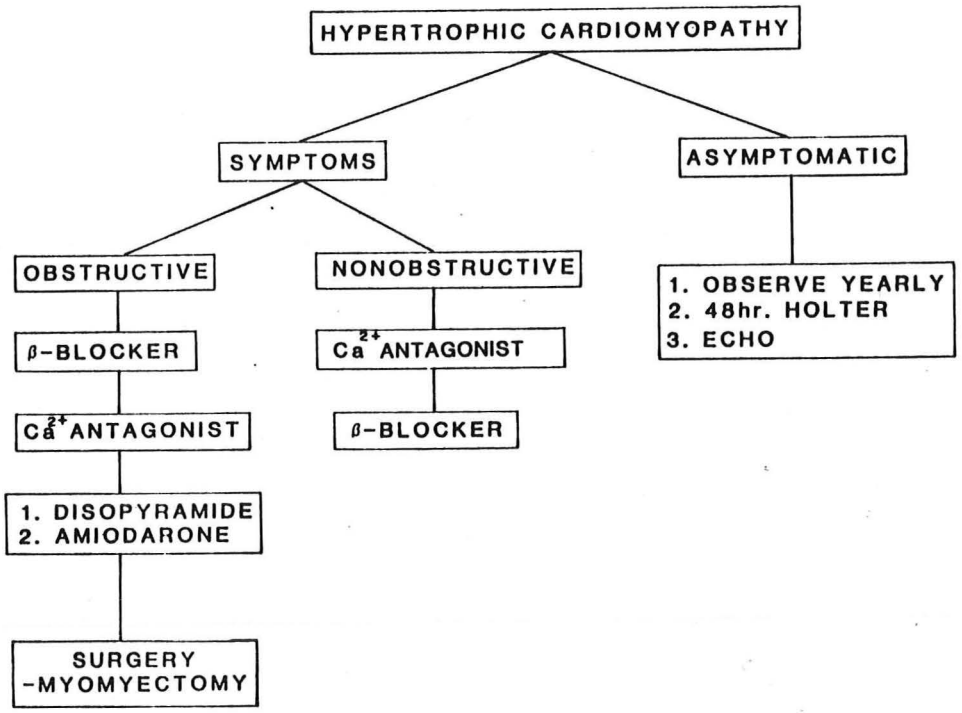



Figure 20. Outline for management of asymptomatic and symptomatic patients with hypertrophic cardiomyopathy.

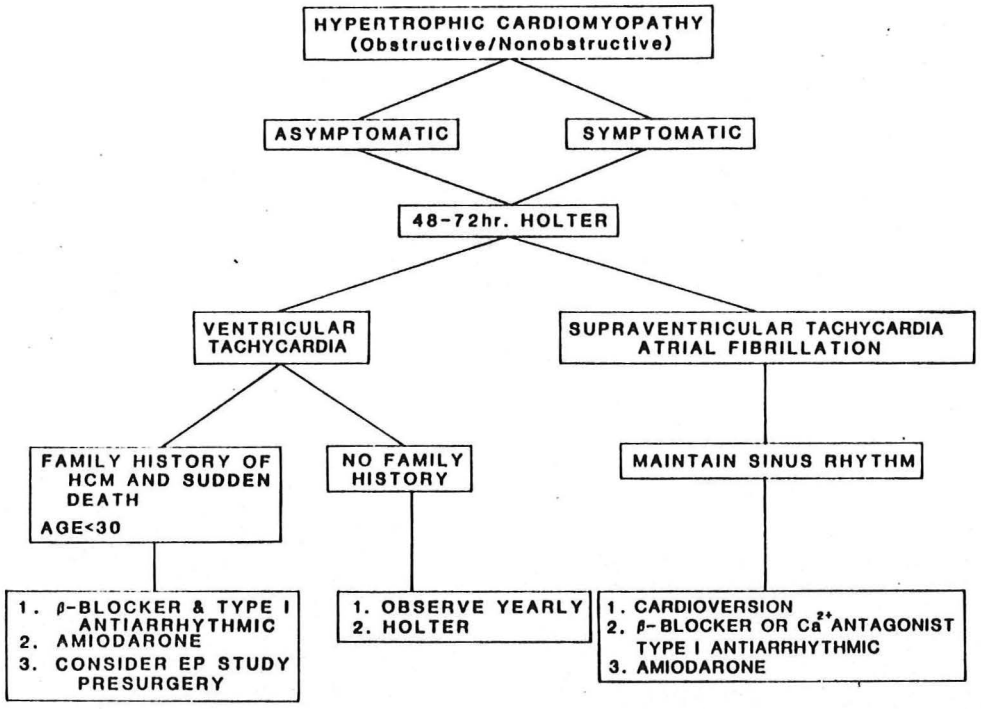



Figure 21. Outline for manangement of arrhythmias in patients with hypertrophic cardiomyopathy.

In patients with VT but without other high-risk indicators, I favor frequent observation but no specific drug therapy. Observation of this group will provide information on the necessity of antiarrhythmic therapy in these patients.

It is pertinent to ask whether electrophysiological (EP) testing should be undertaken routinely in these patients. Nonsustained VT is merely an indicatior of sudden death while sustained VT or ventricular fibrillation (VF) is presumably the actual mechanism of sudden death. A rational approach would be to determine the occurrence of sustained VT or VF in patients with HCM and nonsustained VT and then to direct antiarrhythmic therapy to such patients. Such information is not available at the present time. Furthermore, widespread use of EP testing should be tempered by the fact that sudden death has actually occurred when VT or VF is induced by EP testing and patients with HCM are notoriously difficult to resuscitate. Many of the pharmacologic agents that are used in resuscitative measures are beta-adrenergic agonists which worsen the gradient in patients with the obstructive form of the disease. Also, there is insufficient information demonstrating clear superiority of EP testing over Holter monitoring in assessing antiarrhythmic drug efficacy. Therefore, I do not recommend routine EP testing in patients with HCM and nonsustained VT on Holter monitoring.

### Supraventricular

Patients often deteriorate symptomatically when sustained supraventricular tachyarrhythmias (SSVT) occur, especially atrial fibrillation. This is because of the shortened diastolic filling time and loss of atrial contribution to filling (87). Therefore, sinus rhythm should be maintained if at all possible, but if not then the ventricular response should be controlled. Either propranolol or verapamil is preferred over digoxin for control of the ventricular response in patients with established atrial fibrillation. Propranolol or verapamil can be used in conjunction with a Type I antiarrhythmic agent following cardioversion. Amiodarone has also been shown to be useful in the management of SSVT and has restored sinus rhythm in one-third of patients with HCM and longstanding, refractory atrial fibrillation (119,152). Patients with chronic atrial fibrillation should be anticoagulated in the absence of contraindications (120).

## CONCLUDING REMARKS

HCM is a complex disease entity with many diverse clinical, morphological, and pathophysiological manifestations. Much knowledge has been gained in these areas over the past 25 years due to active research efforts by many investigators interested in this disease. Technological advances in cardiology have been very important in this regard. Based on this information and current understanding of the pathophysiology, natural history, and prognostic features of HCM, a reasonable approach to the management of patients with HCM has been presented. Although these

guidelines are useful, management is not optimal since many patients remain symptomatic or die suddenly despite medical or surgical therapy. Thus, our knowledge and understanding of HCM is far from complete. Continued clinical and laboratory investigations of appropriate design are needed to expand our information base in all areas of this disease. This is especially true in the area of basic cellular abnormalities where knowledge is notably deficient. Future research efforts should be directed toward the very basic aspects of the disease so that management of patients can be based on firm fundamental scientific knowledge.

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