Hypertrophic Cardiomyopathy

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The medical community has shown tremendous enthusiasm for naming the illness now termed Hypertrophic Cardiomyopathy (HCM, Table 1). Fortunately, the efforts in studying this illness have been equally robust and in a relatively short time span (42 years) our understanding of HCM has progressed from simple pathological description to identification of its underlying molecular defects. This review will highlight advances in both the clinical management and genetic basis of HCM.

Table 1: Partial listing of 58 proposed names for Hypertrophic Cardiomyopathy (1).

Asymmetrical hypertrophic cardiomyopathy	Brock's disease
Idiopathic hypertrophic subaortic stenosis (IHSS)	Teare's disease
Familial hypertrophic subaortic stenosis	Diffuse muscular subaortic stenosis
Hypertrophic nonobstructive cardiomyopathy	Non-dilated cardiomyopathy
Hypertrophic obstructive cardiomyopathy (HOCM)	Pseudoaortic stenosis
Idiopathic ventricular septal hypertrophy	Dynamic muscular subaortic stenosis
Hypertrophic hyperkinetic cardiomyopathy	Stenosing hypertrophy of the left ventricle
Subvalvular aortic stenosis of the muscular type	Hereditary cardiovascular dysplasia
Idiopathic stenosis of the flushing chamber of the left ventricle	

History of HCM: Initial descriptions

It is informative to return to some of the initial descriptions of HCM. In Sir Russell Brock's 1957 paper "Functional Obstruction of the Left Ventricle" in *Guy's Hospital Reports* (2), he describes a technique termed a "withdrawal record." This consisted of making a small incision in the left ventricle at the time of thoracotomy, passing a catheter up into the aorta, and then withdrawing it. In two patients with suspected aortic stenosis, he was able to demonstrate that the pressure gradient between the left ventricle and the systemic circulation was not at the level of the aortic valve as was suspected prior to operation but rather several centimeters below the valvar apparatus (Figure 1).

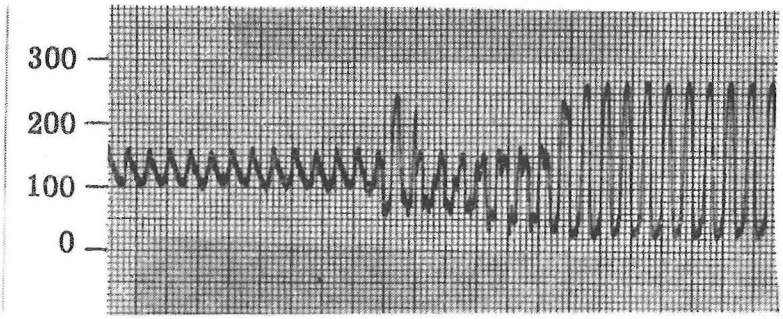


Figure 1: Withdrawal record (2)

The consequences of confusing HCM with aortic stenosis were immediately evident. "This information caused great anxiety because, whereas, in her poor and critical state a rapid valvotomy should been tolerated it seemed unlikely that this would be so with the more severe and probably less satisfactory manipulations needed to relieve a subvalvar stenosis. Only too soon were these forebodings realized because the heart's action began to deteriorate and it was necessary to attempt to relieve the stenosis by forceful dilation with an expanding dilator inserted through the ventricle. Ventricular fibrillation occurred and it was not possible to resuscitate the heart."(2)

The following year, Dr. Donald Teare, a pathologist, described 8 patients with asymmetrical hypertrophy of the interventricular septum (Figure 2) (3). Microscopic examination revealed a "bizarre arrangement of bundles of muscle fibres running in diverse directions....". 7 of the 8 patients experienced sudden death at an average age of 28 years. In an addendum to this paper, the death of a 16 year old brother of one of the above mentioned 8 cases was reported. The siblings had identical pathological findings at autopsy and the familial nature of this disorder was thus established.

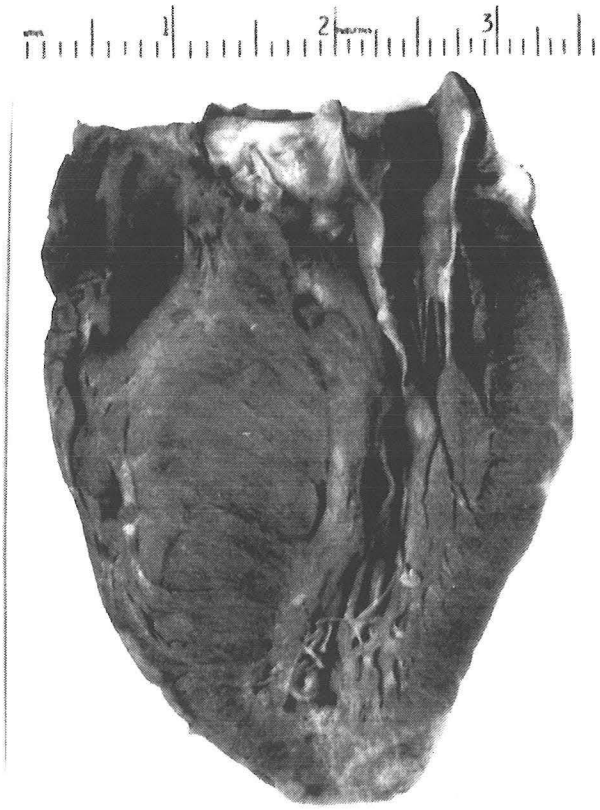


Figure 2: Pathological specimen from a 15 year old boy with HCM from Dr. Teare's original publication (3). The subject had a history of several syncopal episodes. While being chased around his school playground, he collapsed and died.

Pathology of HCM

The pathological changes of the myocardium noted by Dr. Teare are now recognized to be characteristic of this illness. Subsequently, abnormalities of the coronary arteries and mitral valve apparatus in HCM have been described.

Table 2: Pathology of HCM (4)

1. Left ventricular hypertrophy (usually asymmetrical) with nondilated LV
2. Myocyte hypertrophy and disarray
3. Replacement fibrosis (myocardial scarring)
4. Intramural coronary arteries with thickened walls and narrowed lumens ("small-vessel disease")
5. Mitral valve abnormalities
   a. Enlargement/elongation of mitral valve leaflets (5,6)
   b. Anomalous papillary muscle insertion onto anterior mitral leaflet

Clinical presentation

Patients with HCM can present with diverse symptoms.

Table 3: Symptoms of HCM

1. None
2. Pulmonary congestion (dyspnea)
3. Exercise intolerance (fatigue)
4. Chest pain
5. Palpitations
6. Impaired consciousness
7. Sudden death

The early literature describing disabling symptoms in the majority of patients with HCM was plagued by referral bias. As of 1989, 96% of patients described in the literature with moderate-severe symptoms (727 of 757 patients) had been reported by two referral centers (7). Subsequent studies of patients gathered from community surveys suggest many patients with HCM are in fact asymptomatic (8,9). Even these studies likely overestimate the frequency of symptoms because they define patients by the presence of echocadiographic abnormalities rather than by genotyping.

Nevertheless, it is clear that many patients with HCM do have significant symptoms from their illness. The symptoms of dyspnea and fatigue, associated with elevated left-sided filling pressures and limitations in exercise cardiac output (10), are due to a complex interplay between diastolic dysfunction (thick, noncompliant ventricle), ischemia, and subaortic obstruction (when present) (11,12). Superimposed arrhythmias such as atrial fibrillation (13) frequently potentiate this cycle.

A chest pain syndrome is common in patients with HCM and deserves special mention. Even in the absence of epicardial coronary artery stenoses (14), there is convincing evidence for myocardial ischemia including pacing-induced rise in coronary venous lactate concentration (15), exercise-induced abnormalities on perfusion imaging with thallium-201 (16), resting abnormalities consistent with ischemia on ^{31}P NMR spectroscopy [reduced phosphocreatine to ATP ratio and increased P_i-to-PCr ratio, (17)], and positron emission tomography [diminished blood flow with enhanced glucose utilization (18,19)]. In addition to increased myocardial oxygen requirements secondary to increased LV mass, decreased oxygen delivery occurs due to elevated intracavitary filling pressures (15), LV outflow obstruction, myocardial bridging with compression of coronary arteries (20), and abnormalities of intramural coronary arteries (21,22). Coronary vasodilator reserve is impaired (23). Documented ischemia is a poor prognostic sign (16,24).

Presyncope and syncope occur frequently in HCM. The prognostic importance of these events is not well defined (25). Though the obvious concern is that these episodes represent aborted sudden death, this may not always be true. It is important to recognize the numerous potential mechanisms of syncope in this population including tachy- or bradyarrhythmias, myocardial ischemia, outflow obstruction, autonomic dysfunction, or a combination of such events (25,26).

Sudden cardiac death is the most feared presentation of HCM and will be discussed in depth subsequently.

Physical examination

A comprehensive description of the physical examination in Hypertrophic Cardiomyopathy can be found in standard cardiology textbooks (27). A selection of the key signs to detect on physical examination is shown below.

Table 4: Key Signs in Hypertrophic Cardiomyopathy

1. Carotid pulse
   a. Rapid upstroke
   b. Pulsus bisferiens (bifid with two systolic peaks)
2. "Triple-ripple" apical impulse (S_4 + double systolic lift)
3. Labile systolic crescendo-decrescendo murmur
   a. Increases: Valsalva, squat to stand, amyl nitrite
   b. Decreases: passive leg lift, stand to squat, handgrip

Just as in Dr. Brock's era, it is important to distinguish fixed aortic stenosis (AS) from hypertrophic cardiomyopathy. The features on physical examination most helpful are character of pulse (brisk in HCM, slow and weak in AS) and response of murmur intensity to provocative maneuvers (for example, Valsalva: increases in HCM, decreases in AS; squatting: increases in HCM, decreases in AS) (27).

Electrocardiogram

Left ventricular hypertrophy with ST-segment and T-wave abnormalities is frequently present. Q-wave abnormalities in either the inferior or anterior precordial leads ("pseudoinfarction pattern") occur in up 25-50% of patients (28,29). In the era of thrombolytic therapy and primary angioplasty, one needs to be especially aware of this pattern when evaluating young patients with chest pain. The basis of the Q waves remains ill defined. They do not simply correlate with the degree of septal hypertrophy and are rare in patients with massive hypertrophy (30). An imbalance of electrical forces due to disproportionate thickening of the septum as compared to the right ventricle has been noted in patients with Q waves (29).

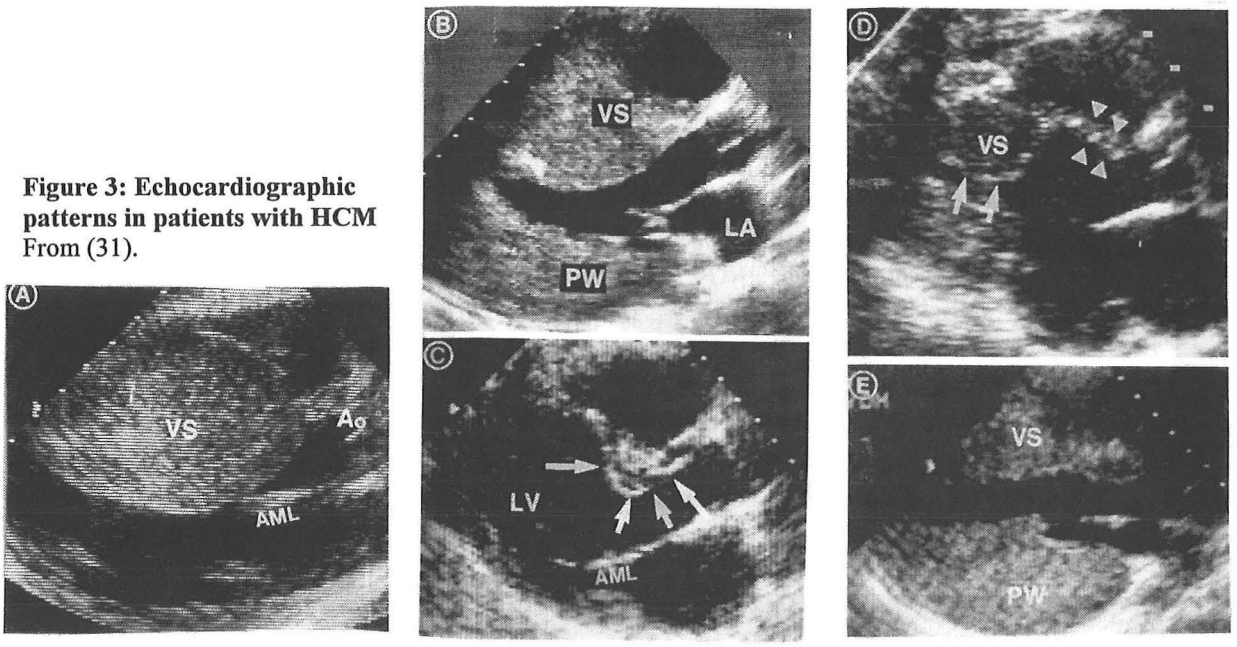
Echocardiogram

The echocardiogram is central to the diagnosis of hypertrophic cardiomyopathy. Important echocardiographic findings include:

1. Left ventricular hypertrophy
2. Systolic anterior motion of the mitral valve
3. Evidence of left ventricular outflow tract gradient

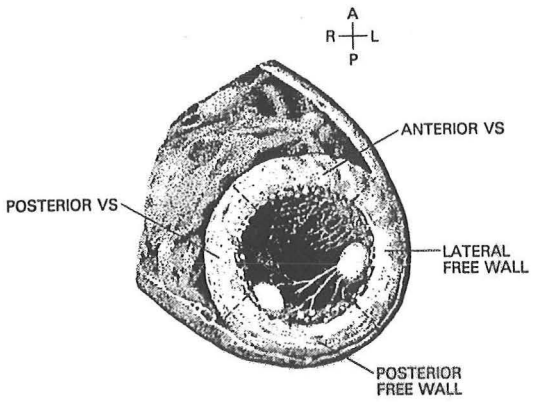
The pattern and degree of left ventricular hypertrophy with HCM varies widely.

Figure 3: Echocardiographic patterns in patients with HCM
From (31).



Echocardiograms were reviewed in a consecutive series of 600 patients studied at two referral centers (NHLBI and University Hospital RWTH in Germany) to define the spectrum of left ventricular hypertrophy (31). The left ventricle was divided into 4 segments: the ventricular septum (anterior and posterior) and the free wall (lateral and posterior) as shown below (Figure 4). Hypertrophy was said to be present in a segment if >50% of its area was ≥ 15 mm thick at end-diastole.

Figure 4: Defining 4 segments of left ventricle on short-axis view of transthoracic echocardiography to classify patterns of hypertrophy
From (6)



This large echocardiographic survey of patients with HCM showed the diverse echocardiographic patterns of hypertrophy seen in this illness.

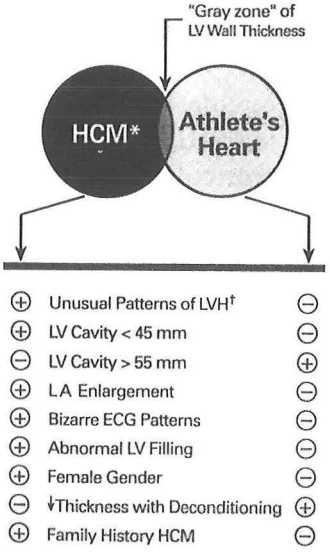
1. Location of hypertrophy: The anterior ventricular septum is almost always hypertrophied (96% of cases) and often exhibits the predominant degree of hypertrophy in the heart (83% of cases). However, in 17% of cases, the other segments of the heart (posterior septum 10%, lateral free wall 4%, posterior free wall 2%, apical 1%) exhibit the predominant degree of hypertrophy.
2. Extent of hypertrophy: The number of hypertrophied segments (of 4) varies widely in HCM. The distribution was 28% with 1 segment, 33% with 2 segments, and 34%

with ≥ 3 segments. Younger patients had more segments involved. Maximal thickness of the left ventricle increased with the number of involved segments.

3. Asymmetry of hypertrophy: The hypertrophy is almost always asymmetric with abrupt transitions between thickened and nonthickened regions. Truly concentric hypertrophy (all segments appearing equally thick) occurred in only 1% of cases.
4. Apical cardiomyopathy was rare (1% of cases). This presentation, more common in Japanese patients (up to 25% of cases in Japanese series), is associated with characteristic giant T wave inversions in the precordial leads (32,33).

An echocardiogram showing asymmetrical hypertrophy of the septum is not diagnostic of HCM. Other entities that can be associated with a similar pattern of hypertrophy include amyloidosis, hypertension, invasive tumors, mural thrombus, or aortic stenosis. (34). The distinction between HCM and physiological hypertrophy ("athlete's heart") is also sometimes difficult (35). Although profound hypertrophy is not usually seen in the healthy athlete (i.e., usually < 16 mm), an overlap in the more mild ranges of hypertrophy (13-15 mm) can occur.

Figure 5: Criteria to distinguish HCM from "athlete's heart"
From (35)



LV outflow obstruction and systolic anterior motion (SAM) of the mitral valve

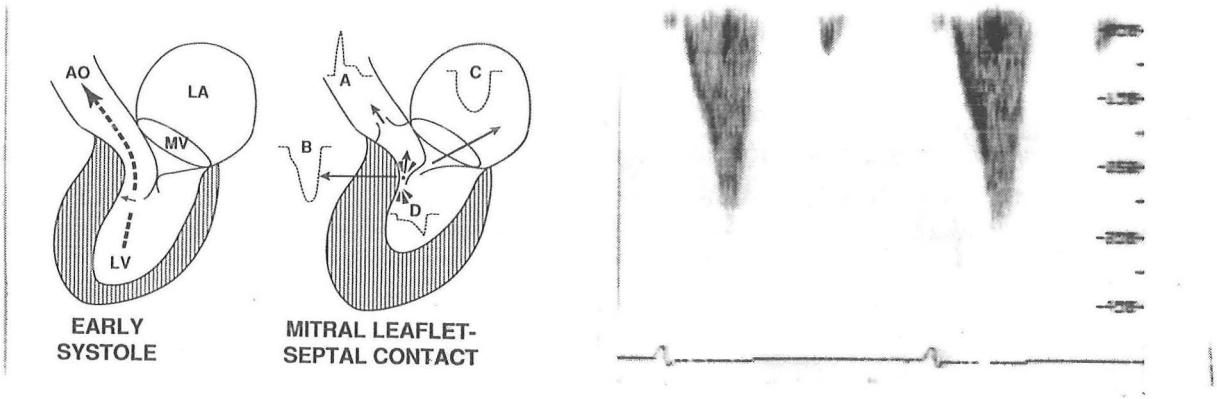


Figure 6: Pathophysiology of left ventricular outflow tract (LVOT) obstruction and SAM (26, 34).

As Sir Russel Brock was able to demonstrate on his "withdrawal record", there is a pressure gradient between the left ventricle and the systemic circulation. Typically this occurs in the subaortic region, but there are variants where the obstruction occurs lower down in the ventricle (midventricular obstruction). A schematic of the pathophysiology leading to subaortic obstruction is shown above in Figure 6 (26).

The left ventricular outflow tract (LVOT) is narrowed due to bulging of the hypertrophied septum and anterior displacement of the mitral valve apparatus. Elongation of the mitral leaflets results in coaptation at the body of the leaflets rather than at their tips. The portion of the anterior leaflet that is distal to the coaptation point is pulled forwards (*systolic anterior motion*) until it makes contact with the septum, thereby creating obstruction to further ejection of blood. There are competing explanations to explain the mechanism of the systolic anterior motion of the mitral valve. One camp espouses the Venturi effect: the high velocity of blood ejected through a narrow orifice leads to a decrease in the pressure in the outflow tract and the mitral valve is "sucked" forwards. The alternative hypothesis is that the mitral valve is pushed forwards by "flow drag", the pushing force of flow. Despite this ongoing debate regarding the fluid mechanics behind SAM, it is clear that SAM follows rapid and early ejection of blood out of the ventricle. When the anterior mitral leaflet moves forward, it separates from the posterior leaflet resulting in mitral regurgitation. This sequence of events has been described as "Eject, Obstruct, Leak" and is a helpful reminder of the underlying pathophysiology (26).

Measurement of the left ventricular outflow tract gradient can be accomplished in the catheterization lab, but echocardiography has to a large degree supplanted the need for such invasive measurements. As would be predicted, the continuous-wave LV outflow Doppler signal has a typical late peaking pattern reflecting the development of the LVOT gradient late in systole (Figure 6, right).

Although the LVOT gradient has fascinated physicians since its description, *most patients (75%) with HCM do not have a LVOT gradient*. There have been a variety of descriptors of the gradient including persistent or resting (present at rest, usually > 30 mm Hg), latent (increases with provocation often to > 50 mm Hg, may be absent at rest), and labile (variable). Drs. Kizilbash, Heinle, and Grayburn from UTSWN have recently shown considerable spontaneous variability of the LVOT gradient independent of heart rate, blood pressure, or left ventricular end-diastolic dimension (36). They estimated that the resting gradient has to change by more than ± 32 mm Hg and the provoked gradient by ± 50 mm Hg if such a change is to be outside of the 95% confidence interval of random variation.

A characteristic feature of the gradient is its dynamic nature, responsive to changes in preload, afterload, or contractility. Such maneuvers are exploited during the physical examination as described above: for example, the strain phase of the Valsalva maneuver (by decreasing preload and afterload) increases the gradient and murmur intensity. Recent additions to the list of standard measures to provoke the LVOT gradient (Valsalva maneuver, amyl nitrite, standing, post-PVC potentiation, isoproterenol, or exercise) are ethanol ingestion (50 ml of 40 percent ethanol) (37) and Sildenafil (38).

Therapy

The goals of therapy for patients with HCM are twofold: relief of symptoms and prevention of sudden death. Because there can be a dissociation between severity of symptoms and risk of sudden death, physicians need to be careful not to be lulled into a false sense of security when evaluating an asymptomatic or minimally symptomatic patient. *All patients with HCM need to be assessed for their risk of sudden death, regardless of severity of symptoms* (39).

A. First goal of therapy: Relief of symptoms

There are a variety of options available to physicians to relieve symptoms in patients with HCM including pharmacological and non-pharmacological strategies.

1. Pharmacological therapy

In patients with the obstructive variant of HCM, negative inotropes can decrease the LVOT gradient and relieve symptoms. Negative inotropes have been shown to blunt the rapid ejection of blood characteristic of HCM. For example, following successful pharmacological therapy, the time from onset of ejection to peak velocity (acceleration time) is increased 31% such that the peak of LV ejection velocity is moved from the first half of systole to its usual position in the second half of systole (40).

Unfortunately, there are limited data to guide selection of pharmacological therapy with a lack of consensus among the experts in this field (7,26). Verapamil may be particularly effective at relieving chest pain and angina in this population (25,41). However, in light of the risk of vasodilation that has been linked to deaths in some patients with a large resting LVOT obstruction, some centers will not use calcium channel blockers (26). Some recommend β-adrenergic blockade as frontline therapy (27) while others initiate therapy with Disopyramide and add β-adrenergic blockers as needed to keep the heart rate less than 70 beats per minute (26). Disopyramide is associated with anticholinergic side effects. A new class IA agent (Cibenzoline) may be equally efficacious as Disopyramide but have less side effects (42). Patients not responsive to β-adrenergic blockers may be successfully treated when crossed over to Verapamil (43). In patients with persistent symptoms of congestive heart failure despite the above measures, cautious trial of diuretics may be attempted (44). In patients with progression to a picture more typical of a dilated cardiomyopathy, therapy is altered to agents used in that illness (e.g., angiotensin converting enzyme inhibitors, Digoxin, diuretics).

2. Nonpharmacological therapy

a. DDD pacing

The role of pacemakers in HCM is controversial. Initially proposed in 1984, the momentum for this therapeutic approach grew following studies emanating from the NIH in 1992 (45) and 1994 (46) which showed that symptomatic patients with the obstructive variant of HCM substantially improve following implantation of a dual chamber

pacemaker. Early after pacemaker implantation (6 – 12 weeks), a significant decline in resting left ventricular outflow tract gradient (87 ± 43 mm Hg to 38 ± 38, p<0.001, n=44) and an improvement in functional status (NYHA 3.4 ± 0.5 to 1.7 ± 0.7, p<0.001) and symptoms was seen. The benefits of pacing were shown to persist after a longer follow-up period (mean 2.3 ± 0.8 years) in 84 patients.

The pacing strategy employed is the following: after sensing of native atrial activity, the pacemaker triggers and depolarizes the ventricle before native conduction occurs. Maximal reduction in outflow tract gradient is often achieved at atrio-ventricular delays short enough to ensure maximal pre-excitation of the right ventricle but not too short to interfere with diastolic function and left atrial emptying (47). The mechanism of the benefit of pacing in HCM is not known. Most frequently sighted is that the alteration in the sequence of ventricular depolarization and contraction [in essence, septal preexcitation (48)] expands the outflow tract area thereby limiting obstruction. This explanation is not the entire answer however. Benefits of pacing have been shown in patients with a LBBB where relative premature RV activation already occurs and also during inadvertent LV apical pacing (46,49). In careful hemodynamic studies, acute pacing in the catheterization lab has been shown to lead to a rightward shift in the pressure-volume relationships, increasing end-systolic volumes and reducing cardiac work (50). Such benefits were seen in patients without outflow tract gradients. Finally, in long term follow-up studies, a reduction in the gradient has been shown to persist even when the pacemaker is deactivated (46). Some studies report regression of LV hypertrophy following prolonged pacing (46) while others have not been able to duplicate these findings (51).

Following these promising reports of the benefits of pacemaker therapy in HCM from the NIH, other centers tested this modality [for review see (47)].

Table 5: Randomized, blinded trials comparing active DDD to "inactive" AAI pacing

Study	N=	LVOT gradient (mm Hg)			Quality of Life	Exercise capacity: Peak VO2 (ml/kg/min)
		Base-line	*AAI*	*DDD*		
Nishimura (52)	19	76 ± 61	83 ± 59	55 ± 38*	DDD better than baseline but not different than AAI	No change
M-Pathy (51)	48	82 ± 33	76 ± 32	48 ± 33*	Blinded AAI and DDD equivalent; 6 months open DDD - better than baseline	No change
PIC (53)	81	71 ± 32	52 ± 34*	33 ± 27*	DDD better than AAI in some measures	No significant change

*P<0.05 vs. baseline

Three of the larger studies are reported above (51-53). The important aspect of these studies, not incorporated previously, was inclusion of a "placebo" arm. Because sham implantation of a pacemaker is not feasible, these trials included an arm where the pacemaker was programmed to an "inactive" modality — AAI mode at a rate of 30 so that it would not pace as long as the atrial rate was 30 beats per minute — effectively serving as a placebo. Each of these trials then proceeded with a randomized, double blind crossover design comparing active ventricular pacing to "inactive" pacing. One of the trials (M-PATHY) followed this approach (3 months AAI, 3 months ventricular pacing, blinded in both cases) with 6 months of "open-label" active pacing (51). Patients were eligible for these studies if they had significant symptoms despite pharmacological therapy and had evidence of LV outflow tract obstruction.

To summarize these results, pacing in HCM:

1. Leads to a significant decline in LVOT gradient
2. Improves quality of life, but not clearly more than an inactivated pacemaker
3. Does not significantly improve aerobic capacity as measured by cardiopulmonary stress testing.

Just as with pharmacological therapy, inclusion of the AAI arms in these trials points to the importance of controlling for the placebo effect when evaluating device therapy.

b. Surgery

Table 6: Recent series of myomectomy for HCM

Study site	N =	Age (years)	LVOT gradient (mm Hg)		NYHA		Periop. mortality	5-year survival
			Baseline	*Post*	*Baseline*	*Post*		
Zurich (54)	110	37	81 ± 41	13 ± 14	2.5	1.5	3.6%	93%
Mayo (55)	65	50		Reduction of 68	3.1	1.6	4.6%	92%
Stanford (56)	158	50	66 ± 39	20 ± 23		95% improve functional class and/or symptoms	3.2%	85%
Cleveland Clinic (57)	178	NA	93	20	2.8	1.4	6%	86%

In patients with the obstructive variant of HCM, surgical therapy consisting of either a myotomy (incision into septum) or myectomy (excision of a piece of septum) can be performed, sometimes in conjunction with coronary artery bypass grafting for concomitant CAD or mitral valve repair. In some cases, isolated mitral valve replacement relieves systolic anterior motion of the mitral valve, reduces the LVOT gradient, and improves symptoms (58). Cardiac transplantation is usually reserved for patients who develop dilation of the left ventricle (see below) and a clinical course of severe congestive heart failure more typical of a dilated cardiomyopathy (59). Spurred on by the recent challenge of DDD pacing as a therapeutic modality for HCM, several centers have recently reviewed their experiences with surgical myomectomy (Table 6 above).

In addition to death, the complications of this procedure (27) include 1. aortic insufficiency (myomectomy often done via a transaortic approach); 2. ventricular septal defect (as would be predicted when removing part of the ventricular septum); 3. complete heart block; and 4. myocardial damage as evidenced by new fixed thallium defects and decreased left-ventricular function, perhaps secondary to limitations of myocardial preservation (60). Older patients and those undergoing combined procedures (myectomy with CABG or MVR) have higher mortality (55,57).

Noting the previously described placebo effect of pacemaker implantation and the dissociation of clinical improvement from LVOT gradient reduction, the purist would argue the basis of the apparent symptomatic improvement in patients following myectomy. More objective support of true clinical benefit is the improvement in exercise capacity as assessed by cardiopulmonary stress testing in 2 other studies (61,62). The Mayo Clinic series was a non-randomized comparison of patients undergoing DDD pacemaker therapy vs. those undergoing surgical myectomy during the same time period ("concurrent cohort").

Table 7: Non-randomized comparison of pacemaker vs. myectomy (62)

		LVOT Gradient			Peak VO2(ml/kg/min)	
Therapy	N =	*Baseline*	*Post*	Improved Symptoms	*Baseline*	*Post*
DDD pacemaker	19	76 ± 61	55 ± 39	47%	19.6 ± 6.5	20.1 ± 6.5
Surgical myectomy	20	76 ± 57	9 ± 17*	90%	19.4 ± 6.4	22 ± 6.5*

*P < 0.005 vs. baseline

This change in aerobic capacity following myectomy was similar to that previously reported in a study of 30 patients (17.1 ± 4.4 to 19.1 ± 4.3 ml O2/min/kg, P<0.05) (61).

In total, these data support surgical myomectomy as a strategy to relieve symptoms refractory to medical therapy in obstructive HCM. In experienced centers, the perioperative mortality is 3-4%. Because it is not known if long term survival is enhanced following myomectomy, this procedure should be reserved for symptomatic patients.

c. Percutaneous septal ablation

Similar to revascularization of coronary artery disease, the cardiology community has attempted to duplicate surgical myectomy via a percutaneous approach. This strategy consists of inducing a myocardial infarction localized to the septum in the subaortic region via injection of alcohol into a septal branch; in essence, a medical myectomy. The first septal branch is cannulated and used if transient balloon occlusion is shown to significantly reduce the LVOT gradient. To avoid leakage of alcohol from the septal branch into the LAD, a balloon catheter is inflated in the septal branch. Before any alcohol is injected, contrast is injected to verify absence of leakage into the left anterior descending artery. This injection also serves to verify that the myocardial territory supplied by the septal branch is in the appropriate location.

The groundwork for this procedure was laid in 1982 by Dr. Ulrich Sigwart who demonstrated that transient balloon occlusion of the first septal branch led to reductions in LVOT gradients. The local ethics committee at University Hospital at Lausanne, Switzerland refused permission to extend this work to inducing "therapeutic myocardial infarction." Ten years later, now working at the Royal Brompton National Heart and Lung Hospital, Dr. Sigwart received ethics committee approval to perform the procedure on a restricted number of patients. In his initial publication (63), he demonstrated reductions in LVOT gradients and improvements in patient symptoms in 3 patients. 1 developed temporary complete heart block. Subsequent studies are shown below.

Table 8: Series of percutaneous septal ablation

	N =	*LVOT gradient (mm Hg)*	*NYHA*		*Post-procedure CK*	*Exercise capacity*		*Complications*
			Pre	Post				
Knight (64)	18	<u>Resting</u> Baseline: 67 ± 20 Post ablation: 25 ± 9 <u>Dobutamine-provoked</u> Baseline: 119 ± 34 Post ablation: 29 ± 15	2.6	1.1	2295	NA		1. 14/18 complete heart block 2. 2 VT/VF 3. 1 EtOH leak down LAD
Segge-wiss (65)	25	<u>Resting</u> Baseline: 62 ± 30 Post ablation: 19 ± 21 <u>PVC provoked</u> Baseline: 141 ± 45 Post ablation: 61 ± 40	2.8	1.4	780 ± 436	Bicycle ergometry (Watts) Pre / Post 67 ± 74 / 111 ± 50*		1. 5/25 Permanent pacemaker 2. 1/25 death-day 8 3. 2/25 VF
Kim (66)	20	<u>Resting</u> Baseline: 58 ± 8 Post ablation: 4 ± 1 <u>PVC provoked</u> Baseline: 143 ± 11 Post alcohol: 40 ± 9	2.7	1.3	2200 ± 520	Peak VO2 (ml/kg/min) Pre / Post 19 ± 2 / 23 ± 1*		1. 2/20 with no-reflow in LAD 2. 2 VT

Concomitant use of myocardial contrast echocardiography likely will become a standard part of this technique (67,68). By injecting an echocardiographic contrast agent into a septal branch before alcohol ablation, it can be verified that the myocardium supplied by the selected blood vessel contributes to obstruction of the LV outflow tract. In one series, this technique resulted in more effective reductions in LVOT gradient while requiring less vessels to be injected thereby limiting myocardial damage as assessed by rise in post-procedure creatine kinase levels (68). In 5 out of 59 patients in this series, the proper septal branch arose not from the LAD but from the intermediate or diagonal branches and would have been missed without the use of contrast echocardiography.

To summarize, percutaneous septal ablation in HCM:

1. Reduces the LVOT gradient.
2. Improves functional class.
3. May improve exercise capacity.
4. Is associated with complications including chest pain, bradyarrhythmias requiring pacemaker implantation, early ventricular dysrhythmias, and death.

Because the technique of percutaneous septal ablation is fairly new, many questions remain unanswered including concerns over creating a focus for arrhythmias (ventricular tachycardia) or precipitating subsequent systolic dysfunction. Nevertheless, given the perioperative mortality (3-4%) of surgical myomectomy even at the most experienced centers, and its need for extracorporeal circulatory support, these early results regarding percutaneous septal ablation are encouraging. Undoubtedly, ongoing studies will clarify the role of this approach in the therapy of patients with obstructive HCM refractory to medical therapy.

B. Second goal of therapy: Prevention of sudden cardiac death

Since the original description by Dr. Teare, hypertrophic cardiomyopathy has been linked to sudden cardiac death (3). Subsequent studies have shed some light on the epidemiology of these catastrophic events. Previously thought to occur more frequently in the young (ages 12 – 35 years), a recent community study reported an equal proportion of sudden deaths in those between the ages of 60-77 years and those less than 30 years (69). A more consistent finding is that nearly one-half of victims of sudden death are asymptomatic prior to their arrest (70,71). One-third of sudden deaths occur during or immediately after exertion (70,71). Though there are limited data available to estimate the incidence of sudden death, more information is available regarding annual mortality rates. Initial estimates of annual mortality rates (3 –6%) from tertiary care centers were plagued by referral bias and have been followed by estimates from population- and community-based studies suggesting the annual mortality in HCM to be approximately 1% (8,70,71). In some studies, survival in patients with HCM is not appreciably different from an age- and sex-matched population (69,72).

Unfortunately, the ability to predict sudden death in patients with hypertrophic cardiomyopathy remains imprecise despite the identification of many risk factors.

Table 9: Risk factors for sudden cardiac death in Hypertrophic Cardiomyopathy

Prior cardiac arrest (73,74)
Prior sustained ventricular tachycardia
Family history of arrest (especially 2 first degree relatives)
Genotype
Abnormal blood pressure response on ETT (71,75,76)
Non-sustained ventricular tachycardia (NSVT) on Holter monitor
Perfusion defects on radionuclide imaging (exercise or dipyridamole) (16,24)
Myocardial bridging (children) (20)
Left ventricular outflow tract gradient (69,71)
Young age (< 30 years) at diagnosis
Degree of left ventricular hypertrophy (69)
Atrial fibrillation (69)
(Pre)syncope (77)
Moderate-severe symptoms
Positive electrophysiological study (74)

Several of these risk factors merit special comment because of recent insights or ongoing controversy. Genotyping will be discussed subsequently in depth.

Abnormal blood pressure response to exercise: In the last 2 years, it has become apparent that the response of systemic blood pressure to exercise has prognostic implications in HCM (71,75,76). An abnormal blood pressure during exercise is defined as an inability to increase systolic BP by 20 mm Hg during exercise ("flat response") or by a decline of 20 mm Hg (compared either to baseline or to the peak systolic blood pressure if there was an initial increase) ("hypotensive response"). It is not known if the flat vs. hypotensive response carries a different prognosis. In the aggregate, however, an abnormal blood pressure response with exercise is associated with higher mortality. Though an abnormal blood pressure response has a low positive predictive value (15%) for sudden death, it has a high negative predictive value (95-97%) (75,76).

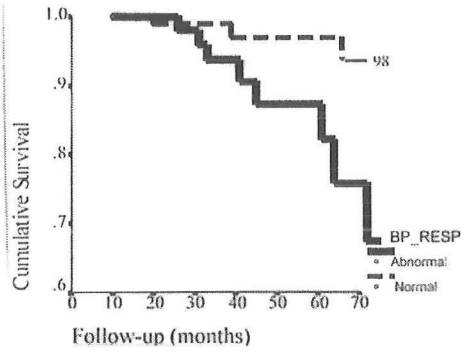


Figure 7: Abnormal blood pressure response (ABPR) and survival. Solid line is ABPR; dashed line is Normal blood pressure response From reference (75).

The mechanism for this abnormal blood pressure response is not known. Some believe it is due to an abnormal peripheral vascular response leading to an inappropriate decline in systemic vascular resistance (75,78) while others link it to subendocardial ischemia (79).

Non-sustained ventricular tachycardia (Holter monitor): In 1981, two studies (80,81) linked the presence of NSVT with an 8-fold increased risk for sudden cardiac death in HCM. Subsequent studies have shown that in the absence of a prior history of symptoms of syncope, detection of NSVT by Holter monitoring does not appreciably increase the risk of sudden death (74,82). More frequent episodes of NSVT may be associated with a higher risk (25,82). Similar to an abnormal blood pressure response to exercise, NSVT has a low positive predictive value and a high negative predictive value (39).

Electrophysiological study: Whether an electrophysiological study aids in risk stratification of patients with HCM is extremely controversial (45,83-85). Several small-moderate sized series have had discordant results (74,83,84) and subsequent reviews either strongly support (86,87) or discount this approach (25,88). The naysayers point out that high-risk patients (i.e., survivors of cardiac arrest) often do not have sustained ventricular tachycardia when stimulated with a standard protocol (2 extrastimuli) while more aggressive protocols (three extrastimuli) lead to polymorphic ventricular tachycardia or ventricular fibrillation. In other disease the induction of such arrhythmias (polymorphic VT or ventricular fibrillation) is felt to be a nonspecific endpoint of unknown clinical consequence. Further study is needed to clarify the role of electrophysiological testing in HCM.

Left ventricular outflow tract gradient: Until recently, there has been no evidence that a basal left ventricular outflow tract gradient is associated with increased mortality. Two studies [one from Japan (71) and one from Minnesota (69)] published this year offer the first data to suggest that such a link may exist. In a Japanese series of 309 patients (71) followed from 1971 through 1994 (mean follow-up 9.4 years), patients with a basal LVOT gradient < 30 mm Hg had a significantly lower mortality than those with a higher gradient (5 year survival with high gradient 89% vs. without high gradient 97%). Of 55 patients with a gradient ≥ 30 mm Hg, 10 had sudden cardiac death. In the Minnesota series of 277 patients followed for an average of 8.1 ± 6.6 years, a LVOT gradient greater than 30 mm Hg was also a significant risk factor for mortality (69).

Degree of LVH: Although intuitively it may be expected that the degree of the hypertrophy of the left ventricle is associated with risk of sudden death (89), until recently there has been a paucity of data to support this link. In fact, two observations argued against this relationship. In a cohort of 78 patients with sudden cardiac death from the NIH, there was no statistically significant difference in septal thickness versus a control population of patients with HCM who did not have sudden death (70). Furthermore, genetic studies of families have highlighted the dissociation of sudden death and degree of LVH. For example, in families with a mutated troponin T gene there is very little LVH but a high incidence of sudden death (90,91). Nevertheless, there remains a concern that patients with massively thickened left ventricles are at high risk of death predominantly because this phenotypic expression is rarely seen in patients over the age of 50 suggesting reduced longevity (25). A recent large study has shown that a left ventricular wall thickness of more than 25 mm is an independent predictor of mortality (69).

Recommendations for assessment of sudden death

Despite the plethora of risk factors, the ability to accurately predict sudden death in HCM is suboptimal (25,88). One approach suggested, which I believe is attractive, is to identify those patients with a very low or very high risk of sudden death. A high risk patient would include those who have already demonstrated a predilection for ventricular dysrhythmias (prior cardiac arrest or sustained VT) or are shown to be carrying a high-risk genetic mutation (either by genotyping or by a family history of sudden death, especially if in two first degree relatives) (25). Two studies of patients who survived a cardiac arrest suggest a recurrent event rate of approximately 30-40% at 5 years follow-up (73,92) sufficient to warrant therapeutic intervention. On a practical point, until widespread genotyping is available, screening for these risk factors requires only a careful history including details of family members.

There is less of a consensus in the identification of a low risk patient in part stemming from the *unanswered question of how many risk factors have to be absent before a patient is considered low risk.* McKenna has suggested that the absence of 4 risk factors, including an abnormal blood pressure response to exercise, syncope, family history of sudden death, and NSVT on Holter monitoring, is sufficient. In his experience, 45% of patients have none of these 4 risk factors and have an extremely low incidence of sudden death (93). Others recommend that a patient be considered low risk if, in addition to the above 4 risk factors, they also do not have any of the other risk factors detailed in Table 9 (25,94). I believe that in addition to baseline studies (history and physical examination and echocardiogram), obtaining a Holter monitor (24-48 hours) and/or an exercise test to assess blood pressure would be prudent measures to assess risk for sudden death. Admittedly, should one or both of these tests be abnormal, it is not clear what therapy is indicated; nevertheless, if McKenna's experience can be duplicated, this algorithm will offer substantial reassurance for nearly one-half of patients with HCM. Undoubtedly, genotyping of patients will become an important consideration in risk stratification over the next decade.

Therapies to prevent sudden death

Therapy with β-adrenergic blockers or calcium channel blockers does not protect patients from sudden death (27). As discussed previously, the impact of surgical myomectomy on survival is not clear. Complicating this analysis is the numerous potential triggers of sudden death including tachyarrhythmias (primary ventricular tachycardia or fibrillation, atrial fibrillation), bradyarrhythmias, myocardial ischemia, LVOT obstruction, or diastolic dysfunction (25,39). In general, three approaches are followed in attempts to prevent sudden death in patients with HCM (25).

1. *Avoid competitive sports*

There is a clear association of exercise and sudden death in HCM. Approximately one-third of patients experience sudden death during or immediately following exertion (70,71). Additionally, in the United States, hypertrophic cardiomyopathy was found to be the most common cardiovascular disease at autopsy in a series of 158 sudden deaths among athletes (95). Such observations led to the 1994 Bethesda conference recommendations (94) that athletes with HCM, whether symptomatic or asymptomatic,

should not participate in competitive sports (the exception being low intensity sports such as billiards, bowling, cricket, curling, golf, and riflery). The recommendations did allow participation for athletes > 30 years on an individual basis in the absence of ALL risk factors (including family history of sudden death, syncope, exercise hypotension, NSVT on Holter, abnormal exercise perfusion imaging, dynamic LVOT gradient ≥ 50 mm Hg, moderate to severe MR, left atrium ≥ 50 mm, and paroxysmal atrial fibrillation). In a more recent review it was suggested that asymptomatic, low risk patients (absence of all risk factors as defined above) could participate in recreational sports, but concurred that "all patients with the disease avoid intense training and competition." (25). A recent study from Italy provides evidence that a national pre-participation screening program that withholds individuals with HCM from competitive sports may decrease their risk of sudden death (96).

2. *Antiarrhythmic therapy*

Amiodarone has been the antiarrhythmic agent most widely used in patients with hypertrophic cardiomyopathy (25). Based on retrospective analyses of patients with NSVT, there appeared to be a survival advantage in those treated with Amiodarone (median dose 300 mg per day) as compared to historical controls (97). A subsequent retrospective study raised concerns of proarrhythmia and increased mortality (98) in patients receiving a higher daily dose of Amiodarone (400 mg). In a small series of 8 patients who had survived a prior cardiac arrest, 2 experienced sudden death despite subsequent Amiodarone therapy (one at 3 months, one at 1.6 years) (73).

3. *Automatic implantable defibrillators (AICD)*

There is a growing experience with the use of AICDs in hypertrophic cardiomyopathy. Such devices would be expected to prevent sudden death due either to tachy- or bradyarrhythmias. In 6 patients who had survived a sudden cardiac arrest or episode of sustained ventricular tachycardia and subsequently had an AICD implanted, 3 patients subsequently received an appropriate AICD shock for recurrent VT or VF at 23, 197, and 1124 days after implantation (73). In such patients at the highest risk for sudden death, AICD implantation is an attractive option (25).

Table 10: Frequency of appropriate AICD shock following implantation in HCM patients

Author	*AICD shock/patients*	*Follow-up (months)*
Primo (99)	2/13 (21%)	40
Silka (100)	25/44 (57%)	31 ± 23
Tripodi (101)	10/31 (32%)	33 ± 7
Borggreefe (102)	6/14 (43%)	48 ± 24

Several pivotal questions remain regarding the role of AICDs in HCM.

1. Is survival improved by AICDs in HCM?
2. Which patients are at a high enough risk for sudden death to justify AICD implantation?
3. Will AICDs confer sufficient protection to enable participation in competitive sports?

Molecular genetics of HCM: Disease of the Sarcomere

In 1990, a genetic basis of HCM was identified with the discovery of mutations within the cardiac β-myosin heavy chain (103,104). A total of 8 genes [β-myosin heavy-chain, cardiac troponin T (105), α-tropomyosin (105), myosin-binding protein C (106,107), myosin essential light chain (108), myosin regulatory light chain (108), cardiac troponin I (109), and cardiac actin (110)] have now been shown to be linked with this disorder. The causal nature of these genetic mutations has been solidified with the demonstration that transgenic mice carrying these sequences exhibit many features typical of human HCM including sarcomere disarray, myocyte hypertrophy, propensity for exertional sudden death, and in one case asymmetrical left ventricular hypertrophy (111-116). Further proof has been the demonstration that some patients with sporadic HCM have de novo mutations in the β-myosin heavy-chain gene (116b)

The 8 genes described above express proteins that are components of the sarcomere. Another gene, as of yet unidentified, has been linked to chromosome 7 in families that have both HCM and Wolff-Parkinson-White Syndrome (117). It is believed that these 8 genes account for only 50 - 66% of the cases of HCM although large epidemiological studies are not yet available (87,118). It is not known whether all cases of HCM will be related to mutations of components of the sarcomere although no exceptions have yet been described.

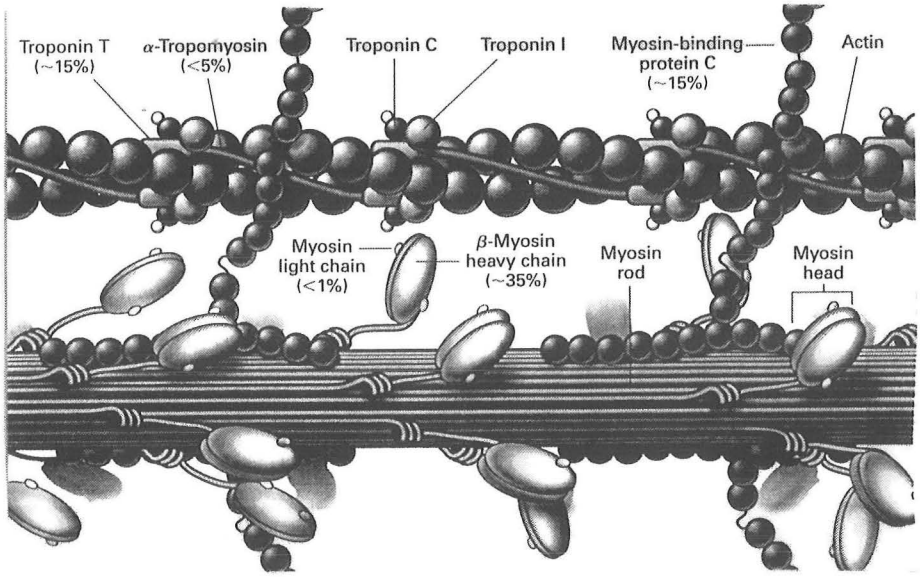


Figure 8. Schematized version of the sarcomere. Percentages are estimates of the frequency that associated mutations cause hypertrophic cardiomyopathy in humans. These percentages are derived from tertiary referral centers and likely are affected by referral bias. The essential and regulatory myosin light chains are not differentiated in this diagram. No estimates regarding the frequency of troponin I or actin mutations are available. From reference (25)

An understanding of the genetic basis of HCM may explain the diverse clinical spectrum of this illness. Two conclusions from studies that correlate genotype with phenotype will be addressed.

Mutations lead to variable degrees of hypertrophy: a tale of incomplete penetrance, modifying genes, and late onset hypertrophy.

The degree of hypertrophy of the left ventricle, and perhaps its pattern, can be related to the underlying genetic defect. Families with mutations of the β-myosin heavy chain have greater left ventricular hypertrophy (LVH) than those with troponin T (91). Mutations of the essential or regulatory light chains of myosin appear to cause the familial mid-cavity variant of HCM (108).

Not all genetically affected members of a family have left ventricular hypertrophy (**incomplete penetrance**) even though other family members with the identical mutation have severe degrees of hypertrophy (119). No large epidemiological study is available to estimate the frequency of this presentation (gene +/LVH -). In a study of 10 families with 9 different mutations in 3 genes, the negative predictive value of echocardiography was 77% (120). Preliminary data suggests that such genetically affected individuals without overt LVH may still have a phenotype. In a study of 100 subjects from 2 families with HCM, investigators measured wall thickness in members without overt LVH (defined as thickness < 13 mm). The genetically affected members (without overt LVH) still had a thicker left ventricular wall after adjusting for age, height, and blood pressure than those not genetically affected (9.7 ± 1.4 mm vs. 8.9 ± 1.4 mm, P = 0.03) suggesting a subtle effect of the genetic mutation (121). The risk of sudden death in genetically affected individuals in the absence of LVH is not known.

The variability of hypertrophy despite the presence of the same underlying mutation suggests that some other process is modifying the expression of the illness. There is growing enthusiasm that other genes (**modifying genes**) are such factors. Several polymorphisms including the insertion/deletion variant of the angiotensin converting enzyme (122, 123), an adenine/cytosine substitution at position 1166 (A/C1166) in the 3' untranslated region of the angiotensin II type I receptor (124), and a polymorphism in the endothelin 1 gene (G80002A in intron 4) have been correlated with variability in LV mass in subjects with hypertrophic cardiomyopathy (125). In a preliminary report, the frequency of polymorphisms of such candidate modifying genes was assessed in 25 genetically affected family members carrying a myosin binding protein C mutation. 14/14 (100%) with LVH had at least one of these polymorphisms but only 5/11 (46%) without LVH had one of these polymorphisms [P < 0.05, (126)]. Such investigations likely will have implications for explaining variability of LV mass in patients without hypertrophic cardiomyopathy.

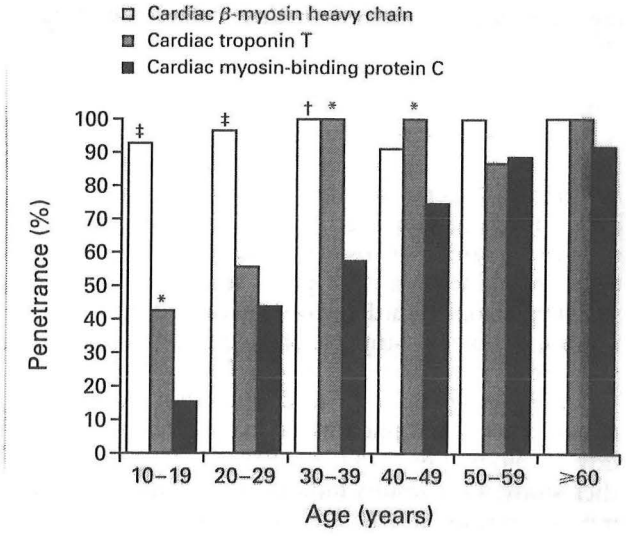


Figure 9: Mutation specific age-related penetrance of LVH From (127)

In addition to variability of extent of hypertrophy, the **age of onset** of hypertrophy also differs depending upon the underlying genotype. Families carrying mutations of cardiac myosin-binding protein C develop LVH later than patients with β-myosin heavy chain or troponin T mutations [Figure 9 above, (127)]. Given this late age of expression in patients with a myosin binding protein C defect, one can easily imagine that LVH would be attributed to non-genetic factors if hypertension, coronary artery disease, or obesity were present. Such erroneous conclusions would inappropriately lead physicians not to screen family members. These findings also suggest that estimates of the frequency of monogenic causes of LVH will require genotyping of a sample population: age of onset and morphologic appearance on echocardiography are not sufficient to exclude a genetic basis of LVH. Presently, the large number of described mutations is an obstacle to such an effort and genotyping remains confined to research centers. However, the development of high throughput DNA sequencing technologies (128,129) likely will allow such studies in the near future as well as allow genotyping to become part of routine clinical assessment in patients with HCM.

Mutations correlate with prognosis.

As discussed previously, clinical variables are weak predictors of sudden death. Evaluation of the underlying genotype holds great promise in this area. It is clear that different mutations within the same gene lead to dramatically different rates of sudden death. Those associated with a poor survival, so called "malignant mutations" include certain β-myosin heavy chain missense mutations [for example, Arg403Gln, the arginine to glutamine substitution at position 403, (130,131)] and cardiac troponin T mutations (90,91). Interestingly, these troponin T mutations are associated with only mild degrees of left ventricular hypertrophy and highlight the dissociation between degree of hypertrophy and risk of sudden death.

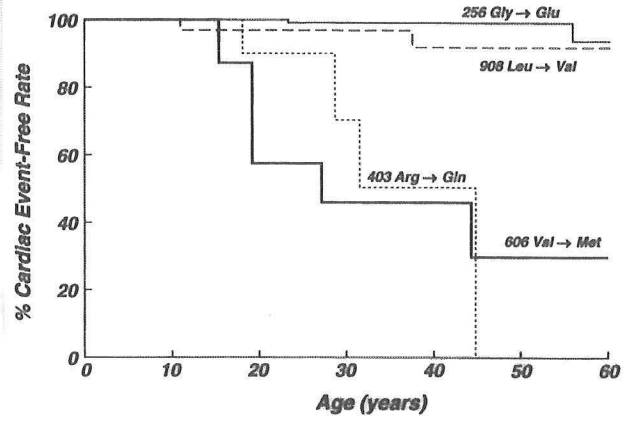


Figure 10: Cumulative sudden cardiac death-free rates in families with different β-myosin heavy chain mutations (131b)

Pathogenesis of hypertrophy in HCM

Despite the rapid progress in the identification of underlying genetic mutations, it is not yet well understood why these defects lead to cardiac hypertrophy. Such explanations will need to account for the autosomal dominant transmission of the illness. One potential mechanism is a **dominant-negative** effect where the mutated protein serves as a "poison polypeptide." Alternatively, the mutated gene may not express any

product that can be incorporated into the sarcomere (**haploinsufficiency**); in such a scenario, only 50% of normal levels of the protein would be expressed (from the non-mutated gene) and this may be insufficient to maintain the stoichiometry of thick and thin filaments (132). The majority of mutations in the β-myosin heavy chain are missense mutations, more consistent with a dominant-negative hypothesis. Several other lines of investigation support this hypothesis including the demonstration that a mutation in the β-myosin heavy chain, which results in severe truncation (in essence, a null allele), does not cause disease (132b). There is less certainty regarding the other genes; in particular, most myosin-binding protein C mutations are predicted to produce truncated peptides (132).

There are several lines of evidence that suggest that these mutations lead to an impairment of force generation by the myocyte. Such experiments include: 1. Myosin from skeletal muscle of patients with β-myosin heavy chain mutations translocates actin filaments slower than normal controls in an in-vitro assay (132); 2. Skeletal muscle fibers from patients with Beta-myosin heavy chain mutations exhibit impaired force-velocity relationships and reduced power output (133); 3. Adenoviral infection of feline cardiac myocytes with mutant troponin T leads to an impairment of cardiomyocyte contractility (134). These data have led to a "**hypocontractile hypothesis**"; specifically, that the hypertrophy in HCM is *secondary* to impaired systolic function, as if normal systemic pressures are perceived as excessive load by the weakened myocardium (135). The demonstration of impaired regional systolic function in patients with HCM by MRI is further support of this hypothesis (136). However, other data suggest that this explanation is too simplistic; for example, 1. Mutations in troponin T (137) and the essential light chain of myosin (108) lead to enhanced actin translocation in the same in-vitro assay where β-myosin heavy chain mutations led to depressed translocation; 2. Skeletal muscle from patients with tropomyosin mutations exhibited enhanced calcium sensitivity, which should lead to enhanced cardiac contractility (138); 3. Mutated troponin T incorporated into rabbit cardiac myofibrils demonstrated enhanced calcium sensitivity and potentiation of maximal ATPase activity (139). Such data have led to a competing hypothesis, the "**hypercontractile hypothesis**"; here, it is suggested that the hypertrophy would be directly induced by an enhanced contractile state through ill-defined mechanisms (135). Ongoing studies of calcium signaling in transgenic mice models of hypertrophic cardiomyopathy may help clarify this issue (140,141).

A discussion of pathogenesis of left ventricular hypertrophy would be incomplete without consideration of the role of calcineurin. As elegantly demonstrated by Dr. Eric Olson's laboratory (142), activation of the phosphatase calcineurin leads to dephosphorylation of the transcription factor NFAT3 and results in NFAT3 translocation to the nucleus with activation of the hypertrophic pathway. Calcineurin appears to be critical in cardiac hypertrophy and therefore a logical target for therapeutic interventions in HCM. Pharmacological agents that block calcineurin (Cyclosporin and FK506) can prevent the development of hypertrophic cardiomyopathy in transgenic mice carrying mutations in myosin light chain (143). Confirmation of the ability of calcineurin inhibitors to prevent HCM is not yet available in other transgenic models.

Is there a link between Hypertrophic and Dilated Cardiomyopathy?

Traditionally, hypertrophic and dilated cardiomyopathies are considered distinct entities. Recent observations suggest there may be an overlap of these conditions. In animal studies, two sublines of a parent Syrian cardiomyopathic hamster were established, one with a dilated cardiomyopathy and one with a hypertrophic cardiomyopathy (similar to the founder). Recently, it has been shown that both the hypertrophic and dilated hamsters carry the same mutation in the δ-sarcoglycan gene (144). Presumably, the difference in phenotypes (dilated or hypertrophic cardiomyopathy) is secondary to a superimposed genetic defect, the nature of which has not yet been elucidated. A substantial body of evidence from human studies also suggests an overlap between HCM and dilated cardiomyopathy. The left ventricle of approximately 10% of patients with HCM progressively dilates and becomes dysfunctional, appearing indistinguishable form a pure dilated cardiomyopathy ("burned out" or "end stage" HCM) (145,146). A lack of increase in fractional shortening in response to an isoproterenol infusion may predict those who will develop progressive enlargement of the left ventricle (148). Interestingly, members within the same family, presumably carrying the *same genetic mutation*, can present either with HCM or dilated cardiomyopathy (147). Whether modifying genes or environmental stresses are responsible for such disparate presentations is not known. Recently it has been shown that *different mutations in the same gene* (actin) lead either to familial dilated (149) or hypertrophic (110) cardiomyopathy. The mutations in the HCM were in proximity to a myosin binding site, suggesting they would interfere with actin-myosin interactions and affect force *generation* within the sarcomere (110). In contrast, the mutations in the dilated cardiomyopathy occurred in the immobilized end of actin, a region that interacts with anchoring proteins within the Z band linking the myocyte to the extracellular matrix; hence, dilated cardiomyopathy may result from alteration of force *transmission* (149). Consistent with this hypothesis is the demonstration that mutations of other proteins involved in anchoring the myocyte to the extracellular matrix [dystrophin (150) and desmin (151)] lead to human dilated cardiomyopathy (151).

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