Does a big heart mean big trouble?

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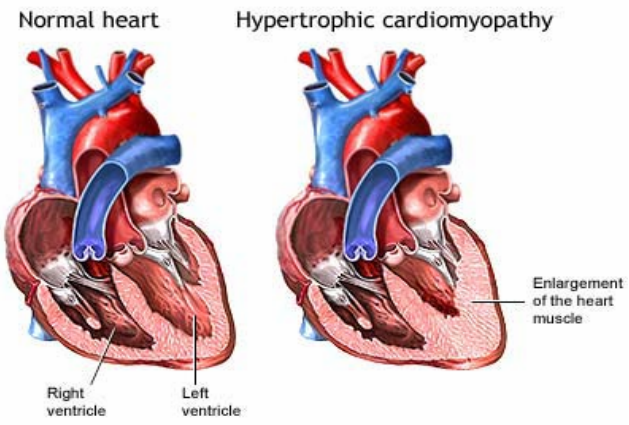
Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disease, occurring in 1 of 500 persons. It is defined as left ventricular hypertrophy (LVH) — Fig. 1—in the absence of an obvious cause. It is usually but not always asymmetric, involving primarily the ventricular septum, and is usually associated with disorganized cardiac muscle fibers. For the majority of patients, the course is relatively benign, although disease-related complications can develop at any point during its natural course. Knowing the risks of overall mortality and sudden death is important for identifying patients who are at risk for adverse events. This *Heartbeat* will address the two most serious consequences of HCM—left ventricular outflow tract (LVOT) obstruction and sudden cardiac death (SCD)—along with an evaluation and treatment plan.

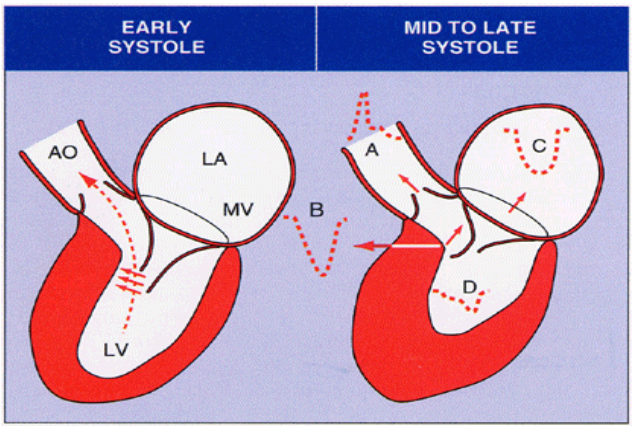
Figure 1. Big Heart



Obstruction

LVOT obstruction, manifested by a sub-aortic pressure gradient, occurs in approximately 25% of patients with HCM. This pressure gradient is apparently due to ventricular septal hypertrophy and anterior displacement of papillary muscles and mitral leaflets.[1] A unique feature of LVOT obstruction in HCM is its dynamic nature (Fig. 2).

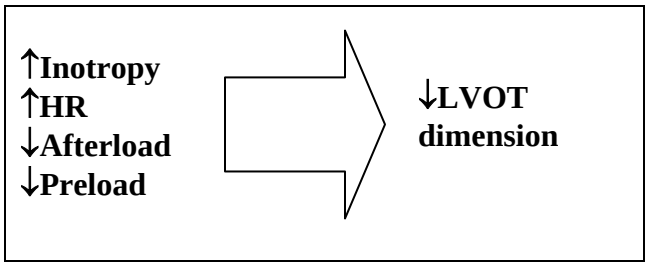
Figure 2.



AO – aorta, LV – left ventricle, LA – left atrium, MV – mitral valve

LVOT obstruction is a narrowing of the distance between the hypertrophied septum and anterior leaflet of the mitral valve (decreased LV volume or LVOT dimension), which is pulled anteriorly during systole (systolic anterior movement of the mitral valve). Further narrowing that intensifies the LVOT obstruction can be precipitated by multiple factors (Fig.3).

Figure 3. Factors that intensify LVOT obstruction



Clinical Presentation

Diastolic dysfunction is more common than systolic dysfunction due to multiple factors (LVH, interstitial fibrosis, myocardial ischemia, cardiac muscle disarray). This abnormality in diastolic relaxation results in increased left ventricular end-diastolic pressure, increased left atrial (LA) pressure, and increased pulmonary vascular resistance with resulting pulmonary congestion and *dyspnea—the most common symptom in HCM*. This occurs despite typically hyperdynamic LV systolic function.

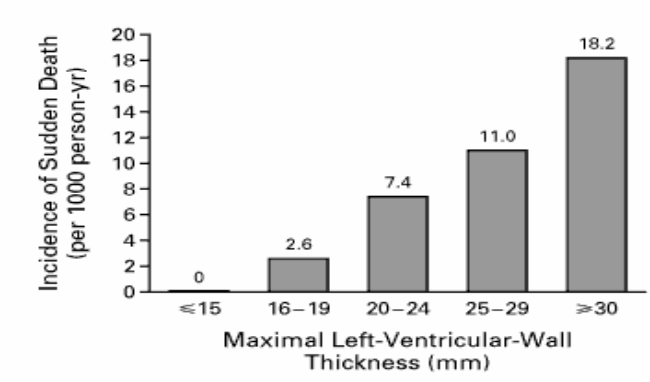
The clinical picture varies considerably. Many patients without obstruction are asymptomatic or minimally so, while those with obstruction present most commonly with dyspnea (>90%), anginal chest pain (25-30%), and unexplained syncope (15-25%). The physical exam may demonstrate the classic harsh crescendo-decrescendo systolic ejection murmur over the apex and left lower sternal border. (This murmur would be increased by anything that decreases LVOT dimension—increasing the obstruction).

Unfortunately, the first clinical manifestation of the disease in the mostly asymptomatic, young patients—under age 30—may be SCD, and identifying those at risk is <u>not</u> easy.

Sudden Cardiac Death

Identification and treatment of patients is important, since HCM is responsible for about one-third of all sudden deaths in young athletes. In attempting to risk-stratify patients with HCM, *the strongest predictor of risk for SCD is absolute left ventricular wall thickness* (LVWT). [2] (Fig 4)

Figure 4. Correlation of LVWT to Incidence of SCD



Many clinical features (Fig.5) have been associated with SCD, but most have low predictive accuracy. Features that more reliably identify high-risk patients include young age (<30), a family history of SCD, an abnormal blood pressure response to exercise (flat or hypotensive), and genetic abnormalities associated with an increased prevalence of SCD. Those with multiple risk factors have sufficient risk to warrant consideration for prophylactic therapy.[3] The incidence of SCD in HCM has been reported in some centers to be as high as 2-4% per year.

Figure 5. Risk factors for SCD

- LVH >20 mm.
- Flat/hypotensive response to exercise
- Demonstration of ischemia
- Young age (<30 years old)
- Family history of SCD
- Gene mutations prone to SCD
- Aborted SCD (personal history)
- Sustained VT or SVT (on EPS)
- Recurrent syncope in young
- Nonsustained VT (Holter monitoring)
- Bradyarrhythmias (occult conduction disease)

Initial Evaluation

Obtaining a *family history regarding HCM and/or SCD* is very important. Initial evaluation should include an *EKG*, and an *M-Mode 2D echocardiogram with Doppler color flow analysis* to assess for LVH, possible diastolic dysfunction, left atrial (LA) size, mitral regurgitation and LVOT obstruction. Echocardiography showing severe LVH, especially of the ventricular septum (asymmetric septal hypertrophy), without apparent cause, strongly suggests HCM.

Differentiating the normal effect of athletic training on the hearts of young athletes from potentially lethal HCM is important because intense exercise is contraindicated in HCM. It may increase the risk of SCD. Moreover, those with "normal" enlarged hearts won't be deprived from participating in active sports. Recent study results make this easier. The authors concluded that HCM should be considered strongly in any trained adolescent athlete with left ventricular wall thickness (LVWT) >12mm in a male and >11mm in a female with a small or normal sized

LV.[4] Only a small number of athletes exhibited a LVWT > 12mm, and all had LV chamber enlargement. However, the authors cautioned that this information should not be extrapolated to other ethnic or racial athletic populations (the study was done with mostly whites).

In another study, an LA size of $\geq$ 45 mm was associated with a substantial risk of subsequent atrial fibrillation (AF).[5] There was a 4-fold increase in the risk of HCM-related death of patients with AF (stroke or heart failure) when compared with matched control subjects in sinus rhythm—no association with sudden death. The overall incidence of AF in patients with HCM was 2% annually; with a 4-6 fold greater likelihood of developing AF compared with the general population.

Exercise stress testing can add diagnostic information regarding prognosis and LVOT obstruction. It should be performed in patients without obvious contraindications or risk factors for SCD. Another option is dipyridamole echo stress testing which has been shown to correlate directly with long-term prognosis.[6]

Treatment

LVOT Obstruction:

The medications listed in Table 1. can improve moderate to severe symptoms in 50% of HCM patients.[7] Slowing the heart rate or decreasing LV contractility improves diastolic function and decreases LVOT obstruction.

Table 1. Medications to improve symptoms

Medication	Benefit
β-Blockers	↓HR ↓ Contractility Improved ventricular filling ↑LVOT dimension
Non-dihydropyridine Calcium-blockers	↓HR ↓Contractility
Disopyramide	↓Inotropy ↓LVOT obstruction

Dual-chamber (DDD) pacing reduces symptoms and LVOT obstruction in some patients (question placebo effect). It is reasonable to consider a trial in those older than 65, who benefit more frequently, or those who are high-risk for more aggressive intervention.

There are several options if patients' symptoms are refractory to medications. These include myotomy-myectomy ("Morrow operation") and alcohol septal ablation. The indications, mortality and success rates are listed in Table 2. It should be noted that these procedures should only be used in patient's refractory to multiple drug regimens or DDD pacing and should be performed at an experienced center. Their complications and success rates have been shown to directly correlate with the experience of the surgeon or interventionalist.

Table 2. Interventions to Reduce LVOT Obstruction

Procedure	Indication	Mortality	Success
Myotomy-myectomy	Mod-severe LVOT obstruction refractory to medications	0-5%	90%
Ethanol septal ablation	NYHA class III-IV despite medications Septal thickness >1.8cm	0-4%	90%

SCD:

The studies using amiodarone in primary and secondary prevention of SCD in patients with HCM are mixed—not showing definitive benefit. Amiodarone may have some utility in reducing the frequency of AF.

Implantable cardioverter defibrillators (ICD) for prevention of SCD are a standard indication in high-risk patients per the new joint recommendations of the American Heart Association and American College of Cardiology.[8] A retrospective multicenter study of efficacy of ICD in prevention of SCD in patients with HCM demonstrated that the principal underlying arrhythmia of SCD is most likely ventricular fibrillation (VF) and ventricular tachycardia (VT). In these high-risk patients, ICDs were effective in termination of

these arrhythmias and improving outcomes.[9] *HCM patients identified as high risk for SCD should receive an ICD.*

Summary/Conclusions:

HCM is a complex disease whose most serious consequences are LVOT obstruction and SCD. Family history, symptoms, a suggestive murmur or an abnormal ECG should suggest an evaluation with M Mode 2D echocardiography with Doppler color flow analysis.

Measurement of LVWT via echocardiography is both the most useful diagnostic tool for HCM and the best means of determining risk for SCD. These measurements differentiate between athletic LVH (≤12mm and dilated LV)—no restrictions—and HCM (> 12 mm and normal or small LV)—cessation of sports recommended. So…not *all big hearts mean big trouble.* This new data can be applied immediately either to save a life or save a career of an adolescent athlete with a larger-than average heart.

Management of patients with HCM includes alleviation of symptoms, prevention of complications and reduction of SCD. Medications such as β-blockers (propanolol, metoprolol, atenolol), non-dihydropyridine calcium channel blockers (verapamil, diltiazem), and disopyramide may provide symptomatic relief by improving diastolic dysfunction. If patients are refractory to medication, consider DDD pacing, or surgical or alcohol septal ablation, to decrease LVOT obstruction.

There is no evidence that medications reduce the incidence or prevent SCD in patients with HCM. Current practice is to recommend cessation of participation in sports for young HCM patients.

An ICD is the standard of care when a patient is diagnosed with HCM and is found to be high-risk for SCD after appropriate risk stratification.

One future avenue in the treatment of HCM will be genetic testing. There is already evidence that certain genetic mutations associated with HCM carry a more malignant prognosis. How this information will impact treatment, a patient's ability to obtain insurance as well as other ethical dilemmas remains to be seen.

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