



# CardioCase

of the Month

## Hypertrophic Cardiomyopathy

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### CardioCase presentation

#### Presley's check-up



Presley, 37, discovered he had a heart murmur at the age of 16 and based on transthoracic echocardiography (TTE), he was subsequently diagnosed as having hypertrophic cardiomyopathy (HCM).

He was asymptomatic from a cardiac standpoint for almost 10 years and had no evidence of significant resting gradient across the left ventricular outflow tract (LVOT).

However, on subsequent follow-up, he described infrequent episodes of fast palpitations, each lasting for 3 seconds to 5 seconds with no associated presyncope or syncope. He had a 24 Holter monitor test that failed to document any significant ventricular or supraventricular dysrhythmias. A repeat TTE demonstrated the presence of a 70 mmHg to 80 mmHg gradient across the LVOT and consequently, he was started on 120 mg of slow release verapamil, q.i.d.. Because of the persistence of the gradient, 50 mg of atenolol was added.

At the time of his last check-up he explained that he continued to have no significant cardiac symptoms apart from the previously mentioned palpitations.

Aside from grade III/VI systolic murmur at the left lower sternal border that increased with the Valsalva maneuver, his physical examination was unremarkable. A repeat ECG at this time showed the following:

- asymmetric septal hypertrophy (ASH) with 24 mm septal thickness,
- 87 mmHg gradient across the LVOT and
- mild systolic anterior motion of the anterior mitral leaflet (SAM) with no significant mitral regurgitation and normal biventricular systolic function (Figure 1 and Figure 2).

During a treadmill exercise test, he completed 13 minutes on Bruce protocol and achieved 15 METs with no ischemic changes or dysrhythmia. However, the test showed flat BP response to exercise, with a maximum BP of 120 mmHg from a baseline of 108 mmHg.

**Presley's check-up continued on page 20.**

#### About the authors...

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2. Diastolic dysfunction associated with increased filling pressures resulting from impaired LV relaxation and filling of a hypertrophied and noncompliant LV
3. Impaired coronary vasodilator reserve and myocardial ischemia
4. Supraventricular and ventricular tachyarrhythmias (e.g., atrial fibrillation [AF] and ventricular tachycardia or fibrillation)

### Natural history and clinical presentation of HCM

The clinical course of HCM typically varies and patients may remain stable over long periods of time, with a significant proportion achieving normal longevity.<sup>1</sup> Although adverse clinical consequences—including premature death—are well documented, a more balanced perspective regarding prognosis has recently evolved.<sup>1-2</sup> The risks of HCM have been previously overestimated by dependence on reports from tertiary referral centers (mortality rates up to 6% annually). More recent studies conducted in the past 10 years from less selected regional or community-based HCM patient cohorts, cite much lower overall annual mortality rates of approximately 1%, not dissimilar to that expected in the general adult population.<sup>1</sup>

Therefore, HCM may be associated with important symptoms and premature death, but often with no or relatively mild disability and without the need for major therapeutic interventions.

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Table 1

#### Risk factors for sudden death in HCM

##### Major risk factors:

- Cardiac arrest (ventricular fibrillation)
- Spontaneous sustained ventricular tachycardia
- Family history of sudden death

##### Minor risk factors:

- Unexplained syncope
- Left ventricular wall thickness > 30 mm
- Abnormal BP during exercise
- Non-sustained ventricular tachycardia
- LVOT obstruction (gradient > 30 mmHg)
- Microvascular obstruction
- High-risk genetic defect

Patients who experience symptoms as a consequence of HCM have a clinical course that evolves along one or more pathways:

- a) Progressive heart failure with exertional dyspnea
- b) Fatigue and chest pain
- c) Occasional evolution to end-stage phase
- d) AF
- e) Sudden death (some high-risk subsets associated with an annual mortality rate of 5%).<sup>3</sup>

Sudden death frequently occurs as the initial disease presentation, often in asymptomatic or mildly symptomatic young patients. It remains the most common mode of demise, the most devastating and the most unpredictable complication of HCM. Although high-risk patients constitute only a minority of the overall disease spectrum, historically a major investigative focus has been on the clinical identification of this important patient subset by acknowledged risk factors (Figure 3). Even though considerable data is available on stratification of risk and a large measure of understanding has been achieved, criteria for precise identification of all high-risk patients by clinical risk markers are not complete. A substantial minority of those HCM patients who suddenly die have no or only one risk factor.

### Diagnostic evaluation

HCM may be suspected on the basis of abnormalities found on cardiac examination or ECG. Classic findings include a systolic ejection murmur that becomes increasingly loud during maneuvers and decreases

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during preload (such as a change in the patient's position from squatting to standing) with evidence of LV hypertrophy on ECG.

Confirmation of the diagnosis of HCM continues to be customarily based on transthoracic two-dimensional echocardiographic recognition of the disease phenotype, with LV hypertrophy (wall thickness > 15 mm), unassociated with ventricular cavity enlargement. However, genotype–phenotype correlations in family members have demonstrated that virtually any LV wall thickness (including normal) is compatible with the presence of a mutant HCM gene. Maximum LV wall thickness shows a particularly wide range, extending up to 60 mm and is the most substantial indicator in any cardiac disease. Mean LV wall thickness in a population of HCM patients is 21 mm to 22 mm, far exceeding, on average, that observed in systemic hypertension or aortic valve stenosis.

The degree of LV outflow tract obstruction is assessed by continuous-wave Doppler echocardiography at rest, or with physiologic provocation under exercise conditions, by virtue of the characteristic midsystolic peaking waveform. Mitral regurgitation, usually mild-to-moderate in degree, accompanies outflow obstruction with the regurgitant jet typically directed posteriorly. Flow

duration, maximum velocity and Doppler spectral configuration differentiate the mitral regurgitation jet from that of LV outflow. Markedly impaired myocardial relaxation, due to hypertrophied myocardium, is characteristic.

Once the diagnosis is made, the patient's family history (with special attention to HCM or sudden death) should be carefully obtained. All first-degree family members should undergo periodic screening with echocardiography every five years to test for this autosomal dominant disorder, since hypertrophy may not be appreciable until the sixth to seventh decade of life. Annual screening is recommended for adolescents 12 years to 18 years of age.

In the future, the diagnosis of HCM may be based on the identification of mutations in the genes encoding the sarcomeric proteins, but this technique is not currently the standard of care. Patients should undergo an evaluation that includes a 48-hour Holter monitor and exercise test which provides prognostic information. All patients should be offered instructions for prophylaxis against infective endocarditis and should be advised to avoid dehydration and strenuous exertion (*i.e.*, intense physical activity involving bursts of exertion or repeated isometric exercise).

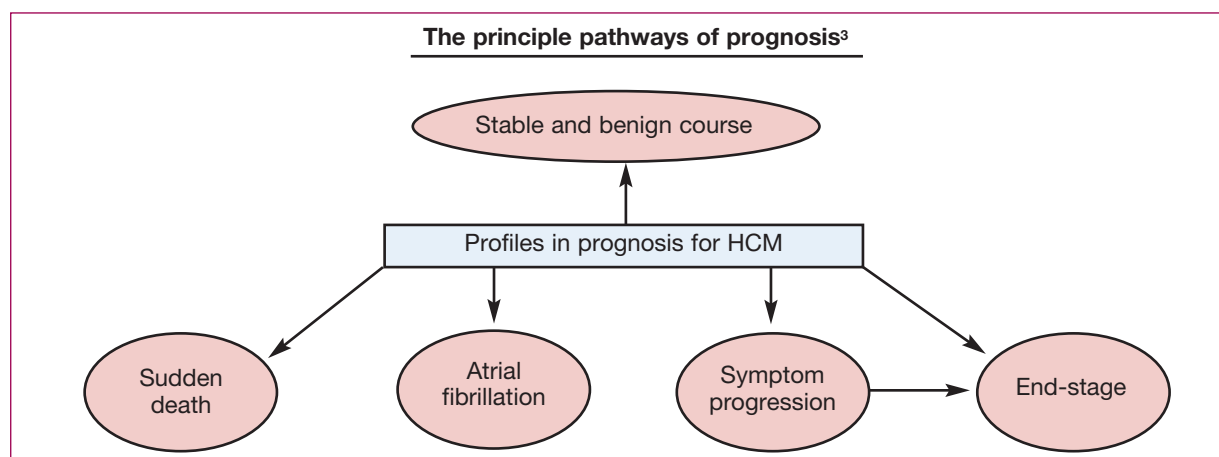


Figure 3. The principle pathways of prognosis, including disease progression, in the broad clinical spectrum of HCM. Widths of the respective arrows approximate the frequency with which each pathway occurs in HCM.

Table 2

## Pharmacologic therapy for patients with HCM

Drugs	Decreased resting gradient	Decreased exercise gradient	Improve diastolic function	Daily dose	Endpoint of adjustment	Side-effects
<b>β-blockers (atenolol, metoprolol, propranolol)</b>	+	+++	+	50 mg to 600 mg	Resting heart rate < 60 bpm to 70 bpm	- Bradycardia - Hypotension - Fatigue - Bronchospasm
<b>CCB (verapamil)</b>	+	+++	++	240 mg to 480 mg	Resting heart rate < 60 bpm to 70 bpm	- Bradycardia - Hypotension - Constipation
<b>Disopyramide</b>	++	+++	+	100 mg to 600 mg	Relief of symptoms	- Anticholinergic effects - QT prolongation

CCB: Calcium channel blocker    +: Mild effect    ++: Moderate effect    +++: Large effect

### Patients at increased risk for sudden death

The identification of patients at increased risk for sudden death (in whom implantation of an implantable cardioverter defibrillator [ICD] should be considered) is an important part of the evaluation. An increased risk of sudden death runs in families and “malignant” genetic mutations have been identified. Yet currently, the clinical value of genetic screening is unknown and clinical risk factors should be used for assessment.

The following are predictors of sudden death:

- a history of out-of-hospital cardiac arrest,
- documented, sustained ventricular tachycardia or fibrillation, along with
- a family history that includes sudden death among first-degree relatives with HCM.<sup>3</sup>

The presence of other risk factors (Table 1) may as much as double the risk of sudden death, but a single risk factor has low predictive value (< 2%), in part because event rates are low.

Electrophysiological studies are not considered useful for identifying patients at risk for sudden death, since ventricular arrhythmias are commonly provoked at the time of an electrophysiological study and are of low predictive value.<sup>4</sup>

The implantation of an ICD is the treatment of choice to prevent sudden death. In any individual

patient, an overall assessment of major and minor risk factors and coexisting conditions should be used to determine whether use of an ICD is indicated.

The high negative predictive value of these clinical markers (> 90 %) suggests that the absence of risk factors can be used to identify patients in whom the likelihood of sudden death is low.

### Pharmacologic therapy

The first-line approach to the relief of a patient's symptoms of HCM is pharmacologic therapy designed to block the effects of catecholamines that exacerbate the outflow tract obstruction and to slow the heart rate so that diastolic filling is enhanced (Table 2). β-blockers are generally the initial choice for patients with symptomatic hypertrophic obstructive cardiomyopathy and are initially effective in 60% to 80% of patients. For patients whose symptoms are not controlled with a β-blocker, verapamil or disopyramide can be used alone or in combination.

### Non-pharmacologic options

#### Surgical septal myectomy

Throughout the past 40 years, based on the experience of many centers worldwide, the ventricular septal myectomy operation (Morrow procedure) has been established as the primary

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**Table 3**  
**Comparative features of non-pharmacologic therapies**

	Dual-chamber pacing	Septal ablation	Myectomy
<b>Mortality</b>	< 1%	< 2% to 3%	< 2% to 3%
<b>Residual gradient</b>	< 40 mmHg	< 20 mmHg	< 10 mmHg
<b>Effectiveness</b>	10% to 40%	70% to 80%	90%
<b>Follow up</b>	> 10 years	> 40 years	< 5 years
<b>Complication-type</b>	Infection or perforation	a) Complete heart block b) Ventricular septal defect c) Large MI	a) Complete heart block b) Ventricular septal defect c) Aortic regurgitation
<b>Complication</b>	< 2%	a) 5% to 8% b) Unknown c) Unknown	a) < 3% b) < 1% c) < 1%
<b>Time to gradient resolution</b>	4 weeks	8 weeks to 12 weeks	Immediate


therapeutic option for adults and children with obstructive HCM (gradient 50 mmHg at rest or with physiologic [exercise] provocation) and severe drug-refractory symptoms. These patients represent a small (< 5%)<sup>2</sup> although important subset of the overall HCM population.

Surgical myectomy is performed through an aortotomy and involves resection of a small amount of muscle from the proximal ventricular septum, extending from near the base of the aortic valve to beyond the distal margins of mitral leaflets and the point of obstruction due to mitral septal contact. With surgery, the LVOT is enlarged and the mechanical impedance to LV ejection and mitral regurgitation is usually abolished.

Surgical normalization of LV pressures leads to the relief of heart failure symptoms and to functional limitation in the majority of patients. Therefore, it represents a reversible form of heart failure. Operative mortality is now low (1%) in most major centers (Table 3).

### Septal ablation

Catheter-based alcohol ablation has emerged in the past five years to six years as a potential alternative to surgical septal myectomy in selected

patients. This technique involves the introduction of 1 mm to 3 mm of absolute alcohol into a target septal perforator branch of the left anterior descending coronary artery to produce a transmural MI within the proximal ventricular septum. Septal ablation mimics myectomy by reducing septal thickness and excursion and by also enlarging the LVOT, thereby lessening systolic anterior motion and mitral regurgitation. A major unresolved concern raised with respect to alcohol ablation is the potential long-term risk for arrhythmia-related events (including sudden death) directly attributable to the septal infarction. 

### References

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