

## Pediatric Hypertrophic Cardiomyopathy (HCM, Hypertrophic Obstructive Cardiomyopathy) — Diagnosis and Treatment

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**Hypertrophic cardiomyopathy (HCM) is the preferred term for both, what was earlier classified as an obstructive and non-obstructive type of HCM. HCM manifests as otherwise unexplained thickening of the left ventricular (LV) myocardium, left ventricle outflow tract (LVOT) obstruction and mitral valve's systolic anterior motion (SAM). TTE is recommended as the best modality choice to make a clinical diagnosis of the disease. Treatment of pediatric HCM patients is based on long-term care and close observation, adequate medical or surgical treatment of symptoms, prompt identification and treatment of those at risk for sudden death, and on-going screening of at-risk family members.**



## Overview

Hypertrophic cardiomyopathy in children is defined as the **primary genetic disorder of sarcomeric proteins within the cardiac myocyte**. Patients with hypertrophic cardiomyopathy have **asymmetric myocardial hypertrophy** that is inappropriate to their age or high blood pressure if present. Due to the common involvement of the interventricular septum, outflow tract obstruction is a common finding in patients with hypertrophic cardiomyopathy.

## Epidemiology of Pediatric Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) being the **most common inherited cardiac disease** affects 1 out of 500 persons with no geographic specificity and is also a chronic illness with lifestyle restrictions for the patient. However, significant mismatch comparing to the occurrence rate of diagnosed HCM patients in daily cardiology practice implies a significant number of asymptomatic, undiagnosed or short life expectancy patients. It must be stressed that **patients may have the HCM genotype without the phenotypic manifestations of HCM**.

Hypertrophic cardiomyopathy affects both the pediatric and adult population, making important differences regarding etiology and outcome essential to recognize on time, as survival rate, in high percent, results from the percentage of recognized and adequately treated cause of disease.

## Etiology of Pediatric Hypertrophic Cardiomyopathy

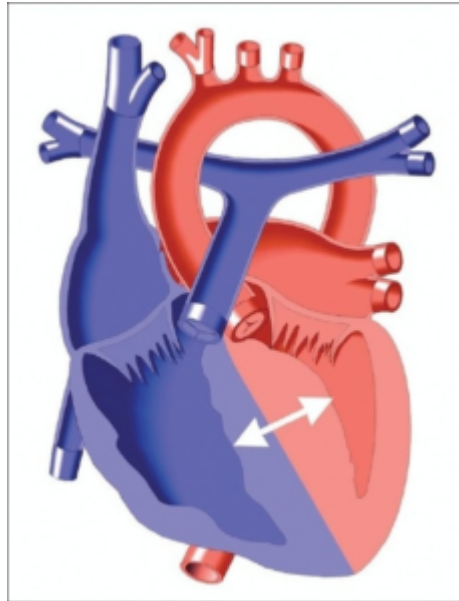
Different genes have been linked to hypertrophic cardiomyopathy. The **15 genes that have been implicated with hypertrophic cardiomyopathy have been found to encode myosin heavy chain, actin, titin, myosin-binding protein, and tropomyosin**.

The exact genetic cause of pediatric hypertrophic cardiomyopathy can be identified in approximately 50 to 80% of the cases. This means that other cases of hypertrophic cardiomyopathy might be attributed to other genetic mutations that are not yet known.

Children with inborn errors of metabolism, Noonan syndrome and neuromuscular disorders might develop hypertrophic cardiomyopathy as a complication and not as a primary disorder. Glycogen storage disorders, namely, defects in the protein kinase gamma-2 and the lysosomal-associated membrane protein 2 have been also linked to a familial hypertrophic cardiomyopathy in children.

## Pathophysiology of Pediatric Hypertrophic Cardiomyopathy

HCM is a **primary cardiac disorder**, actually a consequence of proven or suspected defects of cardiac myocytes' sarcomeric proteins.



**Image:** "HCM is characterized by LV hypertrophy not due to another cardiac or systemic disease, hyperdynamic systolic function and impaired heart relaxation, with or without obstruction to blood flow across the left ventricular outflow tract." by Frazier A, Hunt EA, Holmes K. License: [CC-BY 2.0](#)

HCM's hallmark is inappropriate and frequently asymmetric myocardial hypertrophy in the absence of known provoking hypertrophic stimulus, but the pathophysiology of the disease is a complex one, with multiple interrelated abnormalities.

The most important being **left ventricle outlet obstruction**, accompanied by **mitral regurgitation**, frequently accompanied by **diastolic dysfunction**, as well as **arrhythmias** and **consequent myocardial ischemia**.

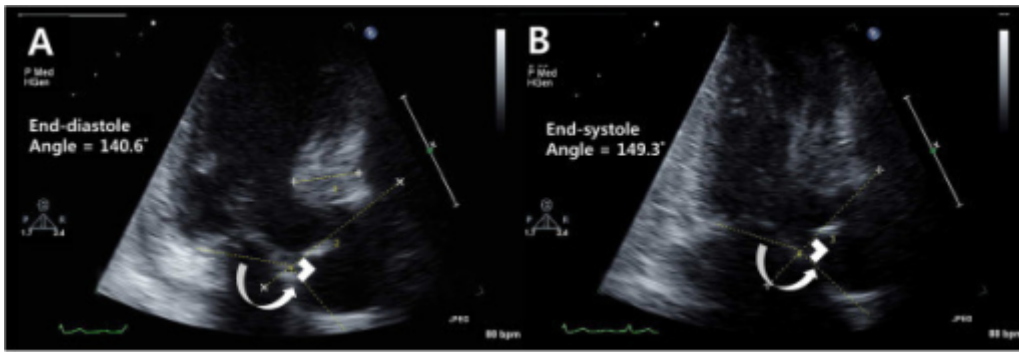
Clinical differentiation of types with or without obstruction is important due to different therapeutic approach being implemented.

## LVOTO (Left Ventricular Outflow Tract Obstruction)

First researchers of HCM noticed that the left ventricle's contractility, as well as changes in load of the ventricle, are factors that subsequently have a **significant impact on functional subvalvular left ventricle outflow tract gradient**.

The significance of LVOTO gradient in clinical settings through the controversial issue is accepted nowadays following the various studies results that showed the existence of genuine mechanical obstruction occurring on the **outflow tract**.

An important fact to stress is that it is not the value of the mean left ventricle outflow gradient itself that is considered the key factor in choosing the adequate management of the condition, but the rapid left ventricle outflow gradient's peak. As a natural consequence of prior explanation, gradient as a term is reserved for rapidly occurring peaks of the gradient.



**Image:** "Assessment of geometry-associated left ventricular outflow tract obstruction. Measurements of basal septal wall thickness at end-diastole, the angle between the ascending aorta and the plane of the mitral valvular orifice at both end-diastole (A) and end-systole (B) from 3-chamber view images." by Cha JJ, Chung H, Yoon YW, Yoon JH, Kim JY, Min PK, Lee BK, Hong BK, Rim SJ, Kwon HM, Choi EY. License: [CC-BY 4.0](https://creativecommons.org/licenses/by/4.0/)

**Obstructions have been observed in rest or under physiological provocation** and studies have shown that (numeric values are calculated in mm Hg):

- Roughly 33% of patients will have an obstruction (definition: gradient above the value of 30).
- Roughly 33% of patients have gradients that are provoked by the basal level (physiological) activity – (below the value of 30 when resting, and above the value of 30 when physiological activities are performed).
- Roughly 33% of patients will have a non-obstructive form at rest (basal) or when there is provoking factor included (gradient lower than 30 mm Hg).

**N.B.** Marked gradients above the level of 50 mm Hg (both in resting condition or induced by provoking factors) are being thought as a baseline for considering invasive treatment plans, in the cases where there's no adequate control of symptoms with given medications.

**Obstruction leads to raising in left ventricle systolic pressure**, that induces lengthening of ventricular relaxation, the rise of left ventricle diastolic pressure, subsequently to mitral regurgitation, myocardial ischemia and finally the fall in cardiac output. Outflow obstruction occurs as a result of an interaction of anterior motion of the mitral valve during systole and septal contact.

Large left ventricle outflow tract gradients may be generated, in the presence of a minor obstruction, or without any, in certain scenarios namely extensive physical strain, during **Valsalva maneuver** or as a consequence of certain medication intake.

Significant spontaneous LVOTO gradient's variations occur throughout a day depending on activities or dependent on consummated alcohol or eaten food. It is also a common clinical scenario that worsening of symptoms happens in the period after a meal.

## Diastolic Dysfunction

Multifactorially induced dysfunction in diastole is seen as a **significant pathophysiological defect in HCM patients**, with the impact both on the chamber rigidity and the relaxation time of ventricle.

**Ventricular relaxation impairment is a consequence of:**

- LVOTO leading to ventricular overload during the systole.
- Non-uniformity of the ventricular cycle's volume.
- Intracellular calcium's defect reuptake that leads to slower

- Chamber stiffness is a consequence of severe hypertrophy of the myocardium.

The detected ventricular relaxation associated condition is **decreased the volume of blood during the systole of left atria** and consequent decrease in filling of the ventricle during diastole, all clinically manifested as ischemia of myocardium, potentially followed by chest pain and dyspnea.

**Exercise can trigger this scenario**, as well as drugs stimulation, stress or similar leading to an elevated level of catecholamine.

## Myocardial Ischemia

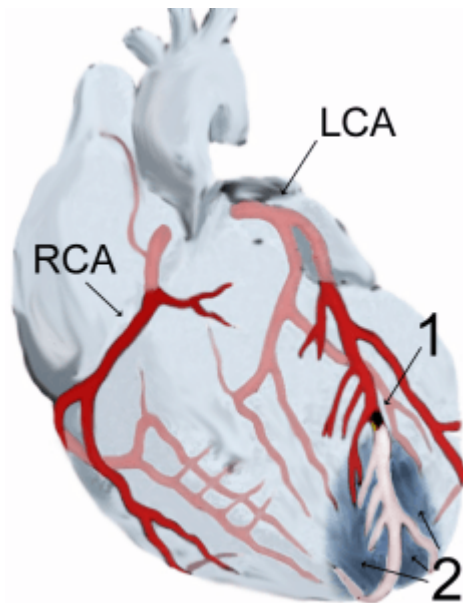


Image: "Myocardial Infarction" by J. Heuser.  
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Although severe myocardial ischemia with all its clinical outcomes occasionally occurs in patients with hypertrophic cardiomyopathy, these conditions are **caused by the uneven ratio of blood supply to the myocardium** and the demand for it. The cause is not in the degenerative atherosclerotic changes of hearts vessels.

LV hypertrophy increases oxygen demand causes, causes lower than sufficient blood supply of the coronary arteries; part of the reason being thicker than expected wall of intramural arterioles because of medial hypertrophy due to luminal narrowing.

## Autonomic Dysfunction

This is the **failure to increase and/or sustain the level of arterial blood pressure**; while physical activity is undertaken may be the consequence of:

- The dynamic LVOTO obstruction.
- Systemic vasodilatation during physical activity.

**Approximately 1/4 of all HCM patients have an exercise-induced pathological response of arterial blood pressure with the following criteria is fulfilled:**

- Failure of arterial blood pressure during systole to elevate more than 20 (mm Hg).
- Blood pressure during systole not decreasing.

This finding is frequently found in poorer prognosis cases.

One of the potential answers to that may be that fail in autonomic regulation as seen in these patients, including the inability of systolic pressure to decrease accompanied by a slow heart rate present a pathological reflexive answer to obstruction.

## Mitral Regurgitation

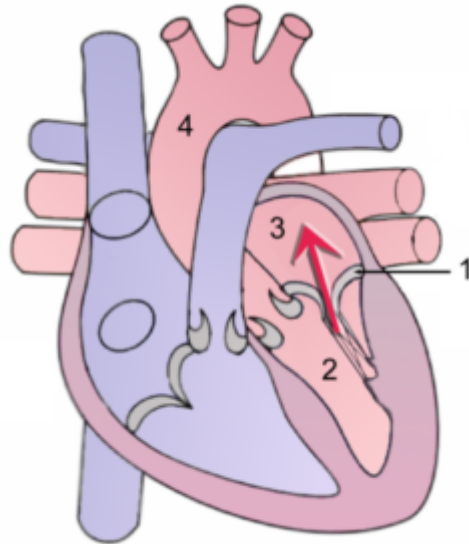


Image: "Mitral Regurgitation." License: [CC-BY 2.5](https://creativecommons.org/licenses/by/2.5/)

MR is a **common finding in LVOTO obstruction patients** and is considered to have a primary role in the etiology of symptoms of dyspnea. However, if the following events, namely eject-obstruct-leak pattern, as presented in this order, are looked at, then MR is actually a response phenomenon.

MR is **caused by the damage occurring on the mitral valve complex**, mainly as the systolic anterior motion of the mitral valve's that occurred after left ventricle outflow tract obstruction.

The mitral regurgitation jet flow has its peak during the middle and last part of the ventricular systole with lateral and posterior direction. The influence on both mitral regurgitation level, as well as the level of obstruction of LVOTO, is proportional and subjected to a difference in ventricular volume and level of contraction.

Additional, mitral valves disease per se, such as prolapse, has to be identified as this finding has a great impact on the choice of potential treatments.

## Diagnosis of Pediatric Hypertrophic Cardiomyopathy

The HCM diagnosis is made with imaging of the heart, **nowadays two methods being an option:**

1. 2-dimensional echocardiography conventionally.
2. Cardiac MRI increasingly.

**To fulfill the criteria for morphologic diagnosis, the following is needed:**

- In adults, the existence of a non-dilated and otherwise unexplained thickening of the myocardium of left ventricular (measuring in mm 15 or above) or the proportional numeric calculated on the basis of child's body surface.
- In children, the definition of Hypertrophied LV wall is a ratio to the general population's Z-score (in standard deviations it should be 2 or 3).

**Commercially available genetic testing is useful for:**

- When a patient has suspicious genetics - to confirm/rule out the definitive diagnosis.
- Identification of affected HCM's relatives.

**A large sub-group of patients, however, does not fit under morphologic criteria, being:**

Ones with HCM and genetic confirmation regardless of the degree of wall thickness.

Subclinical HCM occurring in relatives (sarcomere mutations carriers ) not accompanied by LV hypertrophy - the sub-group is known as "genotype positive/phenotype negative"

Myriad of patterns of thickened left ventricle wall that is reported both, in about 33% of, patients having a minor left ventricle's wall area changed leading to the normal overall result of LV mass when it's being calculated.

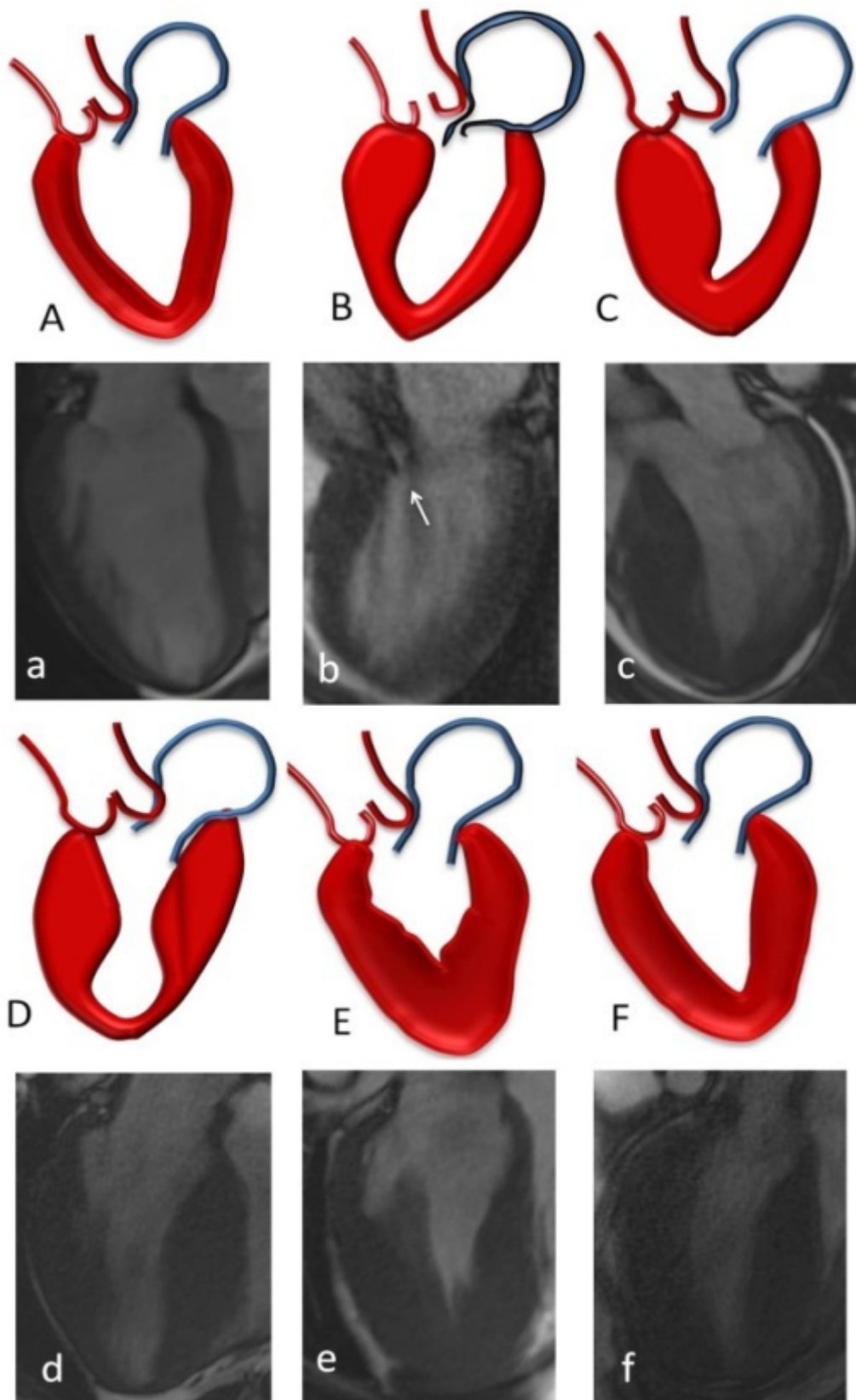


Image: "Left ventricular patterns in HCM, each drawing is accompanied by its corresponding image, (A, a) normal LV, (B, b) sigmoid septum showing SAM of mitral valve (white arrow), (C, c) reversed septal contour, note that there is no signs of LVOT, (D, d) mid-ventricular hypertrophy, (E, e) Apical HCM, (F, f) symmetric HCM." by Noureldin RA, Liu S, Nacif MS, Judge DP, Halushka MK, Abraham TP, Ho C, Bluemke DA. License: [CC-BY 2.0](https://creativecommons.org/licenses/by/2.0/)



# Investigations of Pediatric Hypertrophic Cardiomyopathy

## Imaging

### 1. Echocardiography

- **TTE (transthoracic echocardiogram) is the first-line investigation** of choice in all patients in whom HCM is suspected.
- **TTE as an aid for screening protocol for relatives of HCM patients** that do not genotype negative.
- **TTE screening in 1 to 1.5 years period for children whose parents have HCM**, first exam conducted before puberty or earlier (when plans for serious sports engagement arise or the signs of early puberty arise).
- **Control TTE for the diagnostic staging of patients with HCM** having clinical status changes or new cardiovascular events.
- A transesophageal echocardiogram (TEE) used during surgical procedures.
- **Contrast TTE or TEE during interventional procedures** for monitoring of the intervention.

### 2. Stress Testing

- **Treadmill exercise** testing is used for classifying of the function related and therapy response related degree.
- Stress testing accompanied by ECG and blood pressure monitoring for SCD risk stratification.
- HCM patients having a rapid peak of LVOTO gradient equal or below 50 mm Hg, procedure's use is in detecting and quantifying LVOTO obstruction during physical activity

### 3. Cardiac Magnetic Resonance

**Patients with suspected HCM** in cases of inconclusive echocardiography.

**Patients with previously known HCM** if additional information could lead to a different type of treatment or indicate invasive treatment options, additional information needed in a wide range of situations such as failure of from echocardiography to precisely address anatomical details of the mitral valve or the papillary muscles, as well as detailed perception of hypertrophy not of LV (including the affected areas and the scale of disease).

In cases of inconclusive echocardiography when defining potential aneurysm, and in cases of hypertrophy that includes the apical region of LV.

## Concomitant Coronary Disease Evaluation

**Coronary arteriography (both invasive or CT angiography)** in these patients, who are experiencing chest discomfort, and are clinically sorted out as a medium to high-risk patients regarding the existence of coronary artery disease, given that additional information would change further treatment.

**Computed tomographic angiography (CTA)** for assessing coronary anatomy in HCM patients, with a low likelihood of CAD and experiencing chest discomfort.

**SPECT or PET perfusion scans** in the assessment of conditions that are related to coronary arteries consequences as the negative test is excellent in excluding the diagnosis.

## Differential diagnosis of Pediatric Hypertrophic Cardiomyopathy

Differential diagnosis regarding other cardiac conditions having left ventricle hypertrophy arises in:

**Physiological left ventricle hypertrophy as in an athlete's heart** (an uncommon clinical scenario that happening in borderline hypertrophy of the left ventricle wall).

**Joint appearance of systemic hypertension in senior patients** having hypertrophy of the left ventricle, when genetic testing resolves the dilemma.

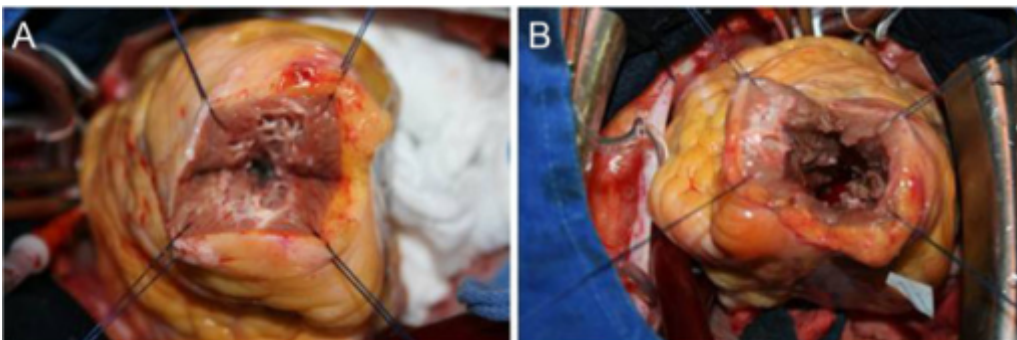
**Left ventricle hypertrophy found in metabolic or storage diseases or multisystem disorders**, in babies, children and young adults. There are many diseases that may be encountered like Fabry disease, Noonan syndrome, and Pompe disease.

From systemic hypertension or from dilated cardiomyopathy when hypertrophy is present in the end stage.

## Management of Pediatric Hypertrophic Cardiomyopathy

Patients with confirmed ventricular arrhythmias on Holter monitoring should receive amiodarone. [Beta-blockers](#) can be also used in the management of hypertrophic cardiomyopathy.

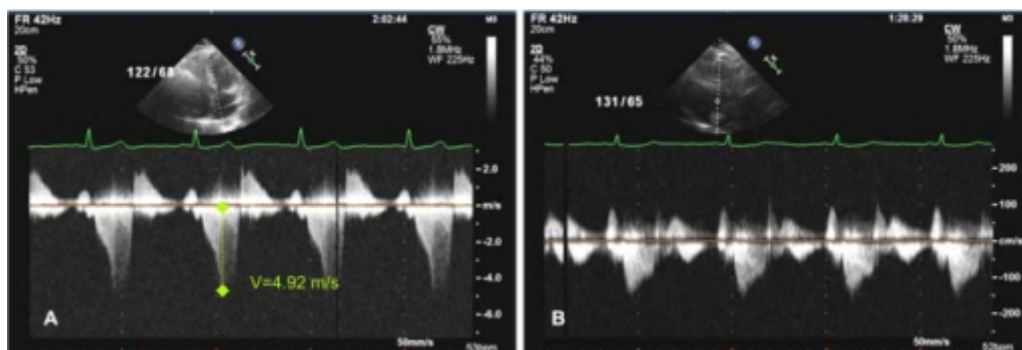
**Surgical or catheter-based treatment** of outflow tract obstruction in hypertrophic cardiomyopathy has been found to have similar efficacy. Surgical intervention is reserved for patients who have an outflow gradient of more than 50 mm Hg. A **left ventricular myectomy** is the surgical procedure of choice and is known to be associated with excellent symptomatic relief. Unfortunately, surgical treatment has not been found to be associated with a reduction in the risk of sudden cardiac death.



**Image:** "Intraoperative photographs illustrating the transapical approach. (A) The patient's apical hypertrophy before myectomy. (B) Augmentation of the left ventricular cavity after myectomy." by Scudeler TL, Rezende PC, Oikawa FT, da Costa LM, Hueb AC, Hueb W. License: [CC BY 4.0](#)

**Catheter-based alcohol septal ablation (ASA)** of the left ventricle has been used for

the treatment of outflow tract obstruction in patients with hypertrophic cardiomyopathy. The efficacy of the procedure is similar to surgical intervention, but with lower side effects.



**Image:** “Transthoracic echocardiogram in hypertrophic obstructive cardiomyopathy: continuous-wave Doppler across the LVOT (A) before ASA indicating severe obstruction with a dynamic gradient of 96 mmHg and (B) 6 months after ASA with a resolution of the obstruction.” by El Masry H, Breall JA. License: [CC-BY 2.5](https://creativecommons.org/licenses/by/2.5/)

Finally, patients who have frequent ventricular arrhythmias should undergo the **placement of a pacemaker**. Usually, patients with an implanted pacemaker also need an **implantable cardioverter defibrillator** to deliver a small shock whenever they go into ventricular fibrillation. Implantable cardioverter-defibrillators have been shown to decrease the risk of sudden cardiac death significantly.

## Asymptomatic Patients

**Healthy lifestyle** for patients with HCM promotion is a reasonable recommendation (such as low-intensity aerobic exercise).

## Symptomatic Patients

### Pharmacologic Management

In adult patients, **beta-blocking drugs as a first-line therapy** for curing the signs and symptoms of coronary ischemia on the ground of existing or non-existent obstruction. When low dose beta-blockers are not effective in symptoms control, raising the dose to achieve heart rate 60 to 65 beats per minute is advised (until the maximal dose of beta-blockers is reached).

**Verapamil therapy** (to start-up in minimal doses and titrate) when patients are not responsive to beta-blocking drugs.

**PA pure vasoconstricting drug such as intravenous phenylephrine** in the management of hypotensive crisis when obstructive HCM patients do not respond to IV fluid administration.

### Invasive Therapies

The experienced operator should **perform a reduction of the size of the septum**. The treatment is reserved for adequate patients, given that severe symptoms did not react to extensive drug therapy and obstruction of the LVOTO is present.

### Eligible patients if all of the following is present

**Clinical:** NYHA functional classes III or IV classification for assessment of symptoms,

loss/or near loss of consciousness symptoms in the physical strain that reduce the quality of everyday activities given that adequate drug treatment has been prescribed.

**Hemodynamic:** Dynamic LVOTO gradient, equal to or above 50 mm Hg in basal metabolism or on minor provocation and mitral valve dysfunction.

**Anatomic:** Individual operator's judgment of relevant anatomy of the heart.

## References

<http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/cardiology/hypertrophic-cardiomyopathy/>

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