

## Review Article

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# Overview of epidemiology and management hypertrophic cardiomyopathy among children

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## Abstract

Hypertrophic cardiomyopathy is the most common form of cardiomyopathy. It is a heterogeneous genetic cardiac muscle disorder characterized by inappropriate left ventricular hypertrophy, malalignment of the myocardial fibers, and myocardial fibrosis. Clinical pictures can vary from mild symptoms or asymptomatic to sudden cardiac death which is most common in young athletes. Diagnosis by echocardiography is the investigation of choice, electrocardiogram and magnetic resonance imaging have a diagnostic role. The study aimed to summarize the updated evidence regarding Epidemiology, pathophysiology, and treatment.

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## Introduction

Hypertrophic Cardiomyopathy (HCM) is the most common inherited heart disease in an autosomal dominant pattern with a prevalence of 1:500 in the general population. It is caused by pathogenic genetic variants in the sarcomere proteins, which is the commonest mutation [1].

Hypertrophic Cardiomyopathy (HCM) manifests in Left Ventricular (LV) hypertrophy, muscle hyper contractility, and fibrosis. Impaired relaxation, compliance of the Left Ventricle, Outflow Tract (LVOT) obstruction, and Mitral Regurgitation (MR) result in reduced exercise capacity, exertional dyspnea, and chest pain frequently experienced by the patients [2].

Hypertrophic Cardiomyopathy (HCM) is largely a clinical diagnosis mainly by echocardiography to identify left ventricular hypertrophy, Cardiac Magnetic Resonance imaging (CMR) is helpful when echocardiography is not clear. Suspicion for hypertrophic cardiomyopathy rises when left ventricle wall thickness is more than 15 mm or more than 13 mm if the family history is positive [3].

It is a highly treatable disease now with a lower morbidity and mortality rate. The transition from pharmacological management to interventional therapies has reduced mortality more than 10-fold from 6%/y to 0.5%/y currently (95% survival 10 years). Selective alternative percutaneous alcohol ablation to surgery, surgical septal myomectomy, pharmacological prevention of embolic stroke, and reduction of atrial fibrillation achieved significant progress in improving quality of life [4]. In addition to the risk stratification algorithm which can predict sudden death, prophylactic implantable defibrillators can prevent it. However, more acceptance and implementation of the established treatment advances in countries with great numbers of HCM which are encumbered by societal, cultural, and resource obstacles are essential to cover unmet needs and remaining challenges [5]. Furthermore, novel treatments under development aim to prevent and delay the onset of the disease which is the main goal of the treatment in patients with mutation carriers [5].

## Epidemiology

The prevalence of hypertrophic cardiomyopathy in the general population is 1 in 500. However, the incidence of HCM in children is lower, with an estimated rate of three to five cases per 1 million children [1]. Sudden Cardiac Death (SCD) is the most common adverse outcome in children with HCM, with an incidence of 1% to 7.2% per year [6].

In a 10-year Medicaid cohort study, 137 unique pediatric patients diagnosed with HCM were included. The cohort consisted of 64.2% males and 40.9% African Americans. Approximately 42.3% of patients were diagnosed with HCM within the first 24 months of life. The 10-year prevalence rate for pediatric HCM was 1.2 cases per 1,000,000, and the annual incidence rate in 2010 was 1.3 cases per 100,000. Among the patients who died (n=10), the cardiac-related mortality rate was 2.9%, with 70.0% of those deaths occurring in children aged 13 months or younger. Arrhythmia was diagnosed in 30.7% of the cohort, while heart failure and low birth weight were present in 12.4% and 8.8% of cases, respectively. Inborn errors of metabolism were found in 8.0% of the cohort studies, it was associated malformation syndromes in 13.1%, and neuromuscular disorders in 2.9%. Consequently, 75.9% of cases were classified as idiopathic HCM [7].

A study conducted in Kosovo included 43 children with HCM, ranging in age from 4 months to 9 years. Cardiac failure was the most common presenting feature, observed in almost half of the children. Transthoracic echocardiography revealed asymmetric hypertrophy in the left ventricle in 28 children and concentric hypertrophy in 15 children. Left ventricular ejection fraction was decreased in 21 children. Cardiac failure was managed with various combinations of medications such as diuretics,  $\beta$ -blockers, ACE inhibitors, and aspirin. Eight children died, four shortly after admission, and four who sought treatment abroad. Among the remaining 32 children, the average follow-up duration was 42 months. Surgical intervention was not performed due to resource limitations, and recovery was noted in 14 children who still required anti-heart failure medications. The mortality rate was higher among children with asymmetric HCM and those who presented with cardiac failure at admission [8].

Another study focused on Infants of Diabetic Mothers (IDMs) and found that among 32,993 IDMs, 0.6% had HCM [8]. Higher proportions of HCM were observed among Black and Hispanic children compared to those without HCM. IDMs with HCM had higher birth weights [8], higher in-hospital mortality rates, and greater odds of mortality compared to those without HCM [9].

A study analyzing data from 639 children diagnosed with HCM under the age of 12 and 568 children diagnosed between the ages of 12 and 16 showed that both age groups had a significant number of patients with a family history of HCM, heart failure symptoms, and prescribed cardiac medications. The median left ventricular wall thickness was high, and many patients had left ventricular outflow tract obstruction [10].

A multicenter study in Japan examined the long-term survival rate of pediatric HCM patients diagnosed before the age of 18, finding a good prognosis with a 20-year freedom from death rate of 80% [11]. The incidence, morbidity, and mortality are significantly higher in the first year of life, compared to the

rest of childhood [12].

In a specialized clinic, 874 patients were evaluated for inherited cardiac conditions, and high-throughput sequencing was performed on 41 genes related to these conditions. Disease-causing mutations in Sarcomere Protein (SP) genes were found in 43.8% of the patients. Patients with SP gene mutations were generally younger and have had a higher prevalence of family history of HCM and sudden cardiac death, exhibited asymmetric septal hypertrophy, and had greater maximum left ventricular wall thickness. They also had an increased incidence of cardiovascular death [13].

An observational study found that HCM is more common in males, occurs at a higher rate in infants, and is more prevalent in black individuals compared to whites or Hispanics [14]. Recent studies have found that HCM accounts for 42% of cardiomyopathy cases in childhood, with an annual mortality rate of around 1% [15].

Among 855 pediatric patients with HCM, 8.7% had inborn errors of metabolism, 15.5% had neuromuscular disorders, and 3.8% had malformation syndromes. The study also highlighted the genetic heterogeneity of pediatric HCM, with mutations identified in sarcomere protein genes in 44.8% of patients [16].

A study conducted in Nigeria examined children referred for echocardiographic evaluation and diagnosed with Acquired Heart Disease (AHD). The most common types of AHD were myocarditis/dilated cardiomyopathy, pericarditis, and rheumatic heart disease. HCM was identified in a small subset of patients, accounting for 5.5% of the cases. These children presented with symptoms such as dyspnea, chest pain, and palpitations [17].

## Pathophysiology

In the past, hypertrophic cardiomyopathy has been characterized by the occurrence of cardiac hypertrophy without significant hemodynamic stressors that could explain the extent of hypertrophy, as well as the absence of systemic disorders [18]. The pathophysiology of hypertrophic cardiomyopathy is primarily characterized by the involvement of specific processes that contribute to the development of heart dysfunction. These mechanisms encompass:

**Left Ventricular Outflow Tract Obstruction (LVOTO):** which pertains to the constriction of blood flow exiting the left ventricle. There are three potential levels of obstruction: valvular, sub-valvular, and supra-valvular. The presence of anatomic stenotic lesions can be observed over a continuum spanning from the left ventricle outflow tract to the descending aorta [19].

**Left ventricular systolic dysfunction:** normally, the left ventricular systolic function ranges from normal to hyperdynamic. Previous research has indicated that a range of 4% to 9% of patients experience systolic dysfunction, which is characterized by a left ventricular ejection fraction below 50%. The term used to refer to this condition is HCM with LV systolic dysfunction. Hypertrophic cardiomyopathy with left ventricular systolic dysfunction (HCM-LVSD) is commonly characterized by the presence of widespread myocardial fibrosis, alongside potential manifestations of left ventricular wall weakening and cavity expansion [20].

**Diastolic dysfunction:** The etiology of diastolic dysfunction and elevated Left Ventricular (LV) filling pressure is complex, involving many factors such as augmented LV mass leading to decreased chamber compliance, extended relaxation, ischemia, and myocardial fibrosis [21]. The coexistence of hypertrophy, disarray, and heightened interstitial fibrosis results in an augmented rigidity of the Left Ventricular (LV) wall. Consequently, the diastolic pressure-volume relationship undergoes a leftward shift and a modest upward displacement in comparison to the standard condition [21]. Patients diagnosed with hypertrophic cardiomyopathy who exhibit a restricted filling pattern are at an increased risk of experiencing unfavorable outcomes [22].

**Myocardial ischemia:** can serve as both a cause and a consequence of hypertrophic cardiomyopathy. When it acts as a cause, it induces fibrosis in the muscular wall, thereby reducing intra-ventricular capacity. This sequence of events ultimately culminates in the development of HCM. Likewise, the presence of microvascular ischemia in hypertrophic cardiomyopathy has been found to be correlated with symptoms such as chest discomfort, clinical decline, impaired diastolic function, and an unfavorable prognosis. An urgent and unresolved requirement in the field of hypertrophic cardiomyopathy pertains to the acquisition of a more comprehensive comprehension of the underlying processes that contribute to myocardial ischemia. There are several contributing elements, which include the following: An elevation in wall thickness leads to the occurrence of both a discrepancy between supply and demand, as well as an augmentation in the compression of the microcirculation during systole. The presence of left ventricular outflow tract obstruction leads to elevated intracavity pressures during ventricular systole. Furthermore, histologic analysis has demonstrated abnormalities in the microcirculatory vessels themselves [23].

## Management

**Initial pharmacologic therapy:** The pharmacological management of patients diagnosed with hypertrophic cardiomyopathy aims to provide relief from symptoms. Currently, there is no evidence suggesting that any medication can alter the natural progression of HCM. Therefore, asymptomatic patients do not require medication initiation [24].

For symptomatic patients, the approach to therapy depends on if the patient has outflow tract obstruction. The current clinical management of HCM primarily focuses on two main aspects: managing symptoms and assessing the risk of Sudden Cardiac Death (SCD) and implementing preventive measures [25].

Pharmacological therapy remains the mainstay of treatment for alleviating symptoms associated with HCM. This includes the use of  $\beta$ -adrenergic receptor blockers, which help to reduce heart rate, increase diastolic filling time, restore cardiac filling pressure, and reduce exercise-induced left ventricular outflow tract obstruction. Disopyramide may also be added to the treatment regimen to alleviate symptoms in patients with LVOTO, as it exerts a negative inotropic effect [26].

In cases where patients are unable to tolerate beta blockers, L-type calcium channel blockers may be considered as an alternative treatment option. Diuretics are generally not recommended for routine use in HCM management, although they may be judiciously employed to relieve congestive symptoms in specific patients [26].

In cases where additional medical therapy is chosen, the selection of treatment is personalized and may involve the use of

disopyramide combination therapy (disopyramide with a beta blocker or calcium channel blocker), or myosin inhibitor combination therapy (mavacamten plus beta blocker or calcium channel blocker) [3].

**Advanced surgical therapy:** Despite the administration of optimal medical therapy, patients who present with obstructive physiology and symptomatic manifestations may benefit from septal reduction therapy. This can be achieved through either septal myectomy or alcohol septal ablation [28]. In some rare cases, patients with advanced pathology may experience treatment-resistant symptoms and decompensation, which may necessitate the placement of a left ventricular assist device or cardiac transplantation. It is recommended that all patients who undergo either septal myectomy or alcohol septal ablation undergo an evaluation for the risk of sudden death and receive appropriate implantation of an implantable cardioverter-defibrillator for primary prevention [28].

**Atrial fibrillation and sudden cardiac death:** Throughout most of history, the risk of sudden arrhythmia-related death in young asymptomatic patients has been a prominent concern within the medical and patient communities regarding hypertrophic cardiomyopathy. However, the introduction of the transvenous Implantable Cardioverter-Defibrillator (ICD) to this patient population in 2000 has ultimately enabled the prevention of sudden death in HCM. ICDs have played a significant role in reducing HCM-related mortality by over 10-fold to 0.5% per year, with a 95% survival rate 10 years after diagnosis, which is consistent across all age groups [29].

Initial management of atrial fibrillation (AF) in patients with HCM is comparable to that of any patient with AF [30]. For asymptomatic patients or those with mild to moderate symptoms, initial therapy involves slowing the ventricular rate and initiating anticoagulation therapy. Beta blockers plus non-dihydropyridine calcium channel blockers, such as verapamil and diltiazem, are preferred as first-line agents in most patients, through intravenous preparations for rapid rate control. Digoxin should be avoided as a rate control agent in patients with HCM. In cases where patients exhibit severe symptoms or hemodynamic instability related to AF, urgent cardioversion should be performed [30].

## Conclusion

Hypertrophic cardiomyopathy is a genetic cardiac muscle disorder characterized by inappropriate left ventricular hypertrophy. It is the most common inherited heart disease with a prevalence of 1:500 in the general population. It is caused by pathogenic genetic variants in sarcomere proteins. HCM is diagnosed through echocardiography, electrocardiogram, and magnetic resonance imaging. The management focuses on symptom relief through pharmacologic and surgical therapy, and the use of implantable cardioverter defibrillators to prevent sudden cardiac death.

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