

# Hypertrophic Cardiomyopathy

## What is hypertrophic cardiomyopathy?

Hypertrophic cardiomyopathy is a primary disease of the heart muscle (myocardium) characterised by hypertrophy (an increase in the thickness) of the left ventricle, associated with an overactive left ventricle and a small left ventricular chamber. Although any region of the left ventricle can be involved, hypertrophy frequently involves the septum (the wall between the left and the right chamber of the heart), which results in an obstruction in the outflow tract of the left ventricle.

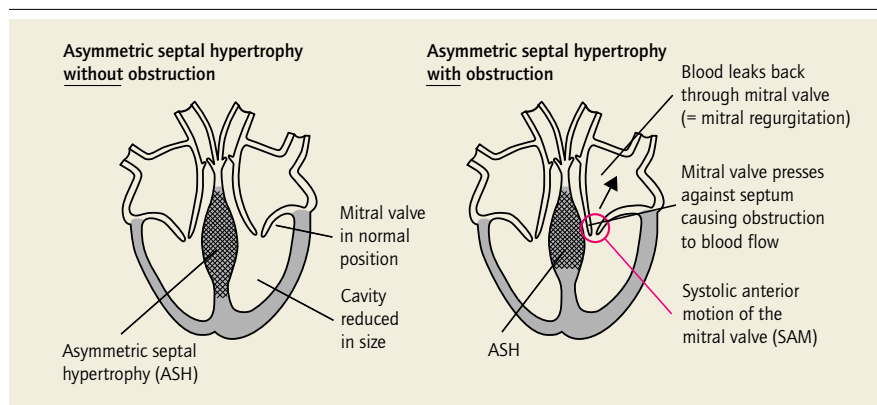


The condition was first described in 1958. It is a relatively common genetic cause of sudden death, particularly in young active males. Syncope (short periods of fainting) or sudden death in these subjects may occur due to arrhythmias or from an obstruction due to ventricular wall thickening and blockage of the blood flow. As dehydration can trigger a syncopal event, it is often athletes who suffer from sudden death while running, cycling or playing football.

The hypertrophy of the heart muscle cells (myocytes) continues in a silent manner for many years and may lead ultimately to

an end-stage, dilated cardiomyopathic state. Depending upon the time frame, the affected heart can appear entirely normal, markedly hypertrophic or even dilated, which makes the diagnosis difficult.

There is no particular symptom or complaint which is unique in hypertrophic cardiomyopathy. Exercise capacity may be limited by breathlessness and fatigue. Chest pain may be usually brought on by exertion and relieved by rest. People may also experience palpitations, which is an uncomfortable awareness of the heart beat. Peo-



ple with the condition may experience light-headedness, dizziness and more seriously, blackouts. Episodes may occur in association with exercise, with palpitations or without any apparent provocation.

Clinical diagnosis is made most reliably by echocardiography. Severe ventricular wall thickening can be noted. A normal left ventricular measures up to 12mm, while thicknesses of more than 30mm are not unusual in severe cases of the disease. Hypertrophic cardiomyopathy remains difficult to diagnose unless gross pathological abnormalities are found in echocardiography or *post mortem*. At autopsy, hypertrophied myocytes with bizarre shapes, chaotic cellular alignment, and gross cellular disarray in the left ventricle can be seen under the microscope.

### Who does hypertrophic cardiomyopathy affect?

It is estimated that one in 500 people (0.2 per cent of the general population) carry the genetic mutation for hypertrophic cardiomyopathy. This is equivalent to some 800,000 carriers in Europe. Fortunately, the prevalence of the disease is lower. Of the 2,000 individuals per million subjects expected to be affected, 200 are expected to develop dilation and heart failure. Other people with the hypertrophic cardiomyopathy mutation will not show signs of the disease during their lives. The mortality rate for individuals with the disease is four per cent per year. Sudden death is the most common cause.

The relevance of the patient's clinical history is high, given that around 70 per cent of cases of hypertrophic cardiomyopathy are familial and inherited as autosomal dominant traits, with 50 per cent of their relatives expected to be carrying the genes. There is no gender bias. The disease has widely variable prevalence. Although inheritance is autosomal dominant, a family history of syncope or sudden death may be lacking.

At least ten different genes encoding the cardiac muscular tissue (sarcomere) have been implicated in the condition. Over 150 mutations found in the proteins of the sarcomere have been reported since the first genetic cause was identified in 1990. Within the gene-encoding for the heavy chain of the protein beta-myosin (MYH7), numerous "malignant" mutations have been described. These particular mutations are considered to be associated with a poor clinical prognosis, including progression to end-stage heart failure or sudden death, a higher manifestation of the disease, and extreme wall thickness of the left heart ventricle.

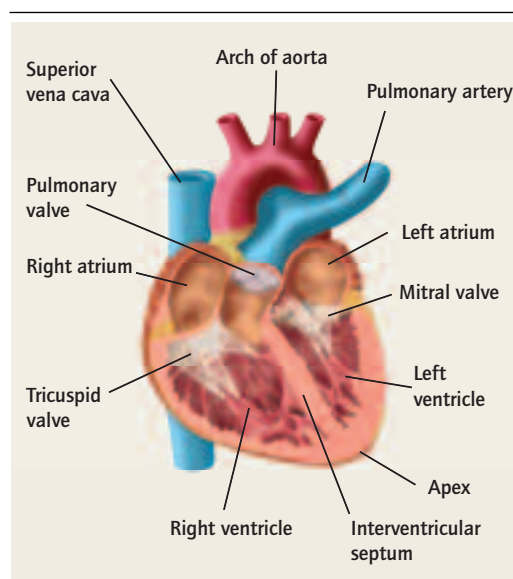
### Present treatments

There are no formal guidelines for treating asymptomatic patients with hypertrophic cardiomyopathy. In those patients with symptoms, medications that reduce the outflow obstruction remain the mainstay of therapy. Such medications include beta-blocking medicines which also increase ventricular compliance. Whether early administration of beta-blocking medication will modify the disease is under investigation.

Another option is calcium channel blockers, which improve diastolic relaxation and decrease the outflow gradient due to reduction of the contractility of cardiac muscle. The use of anti-arrhythmic medication is reserved for life-threatening ventricular arrhythmias. In symptomatic patients, the outflow obstruction may be reduced by surgical procedures or by catheter-based interventions.

Sudden death is thought to occur due to a primary electrical abnormality by ventricular arrhythmias. A clinical study of patients in whom defibrillators were implanted showed that nearly 25 per cent experienced ventricular arrhythmias over a three-year follow-up period. In those patients deemed at high-risk for an arrhythmic event, an implantable cardioverter defibrillator (ICD) may be the option to avert sudden death.

**Hypertrophic cardiomyopathy is a disease of the heart muscle. It can cause sudden death, particularly in young, active men. Medicines can prevent a fatal outcome. Further research is being carried out in the search for better treatments.**



Heart

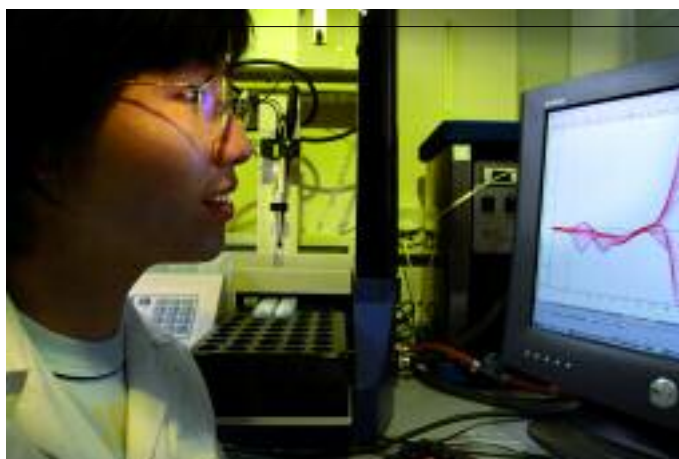
### What's in the development pipeline?

Researchers are studying angiotensin 2 (A-2), which modulates cell growth and cardiac function. There is also evidence that the renin-angiotensin system may be active in cardiac cells, and the hypertrophic action of A-2 could therefore be mediated by locally produced hormone.

Animal studies have demonstrated that inhibition of angiotensin-converting-enzyme (ACE) and A-2 receptor blockade can reduce cardiac hypertrophy and improve diastolic function of the left ventricle. In several phase 2/3 clinical studies investigators are examining the abilities of ACE inhibiting compounds and A-2 blocking agents to cause regression of ventricular hypertrophy.

Scientists are evaluating the contribution of Insulin-Like Growth Factor-I (IGF-I) and its binding protein to increased left ventricular mass in hypertrophic cardiomyopathy.

Left ventricular diastolic dysfunction and arrhythmias are believed to be in part due to myocardial fibrosis. Therefore, investigators are examining an anti-fibrotic molecule to improve diastolic function and exercise performance in a phase 2 clinical trial.



Other efforts are directed at identifying disease genes, collecting large, informative gene-families for linkage, and starting genotyping of series of patients.

### The longer-term future

In hypertrophic cardiomyopathy, the genetic make-up of an individual is clinically relevant. The identification of the disease-gene mutation implies that the mutation carriers may develop the disease at some time during the course of their life. In future, the emphasis will be to decipher the disease's molecular pathogenesis and to develop pharmacological interventions to prevent, attenuate or reverse the course of the disease.

The existing experimental data in animal models have established the possible reversibility of cardiac signs and show a way to test the potential beneficial effects of medicines. Thus far, two potential targets have emerged, namely, (i) signalling molecules RhoA and Rac 1, which are considered essential for cardiac hypertrophic response; and (ii) the renin-angiotensin-aldosterone system. Given the slow evolution of the disease in humans, collaborations among investigators will be necessary to perform large-scale trials to test the potential beneficial effects of HMG-CoA reductase inhibitors and blockers of the renin-angiotensin-aldosterone system.

Screening will become crucial. Advances in molecular genetics and biology will lead to an early diagnosis of mutation carriers, risk stratification and ultimately, development of better therapies based on blockade or activation of specific pathways involved in the pathogenesis of the disease.

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