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POSITION STATEMENT

Update on the Diagnosis and Management of Hypertrophic Cardiomyopathy☆

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This standard of practice document briefly outlines the current approach to the diagnosis and management of hypertrophic cardiomyopathy (HCM). The supporting levels of evidence are reported in both the *American Heart Association* HCM guidelines [1] and the *European Society of Cardiology* HCM guidelines [2]. There is also a detailed recent review of HCM for further reference [3]. Since the last CSANZ HCM guidelines in 2011, the main changes relate to emerging sudden death risk factors such as the amount of myocardial fibrosis, the development of an HCM Risk Score, and more careful consideration of cascade genetic testing in asymptomatic relatives without an HCM phenotype.

Clinical Characteristics of HCM

Definition and Prevalence

Hypertrophic cardiomyopathy (HCM) is a primary cardiac disorder characterised by hypertrophy, usually of the left ventricle, in the absence of other loading conditions, such as aortic stenosis, hypertension or thyroid disease. Although previously thought of as a rare disorder, recent population-based clinical studies suggest the prevalence of the condition to be as high as 1 in 200 in the general population [4] making HCM the commonest known cardiovascular genetic disorder known.

Clinical Presentation

Hypertrophic cardiomyopathy is inherited as an autosomal dominant disorder with variable penetrance. This means affected individuals are heterozygous and offspring of affected individuals have a 50% risk of inheriting the gene mutation, with males and females equally at risk. Patients with HCM can range in presentation from minimal or no symptoms and have a benign, asymptomatic course, to the development of the most serious complications including heart failure and sudden death. HCM is a common structural cause of sudden cardiac death in individuals aged less than 35 years, including competitive athletes. The pathophysiology of HCM is complex and is reflected in the diversity of clinical features. Individuals with HCM can have a variety of symptoms including chest pain, which may be typical of angina, symptoms related to pulmonary congestion, i.e. dyspnoea, fatigue, orthopnea, and paroxysmal nocturnal dyspnoea, impaired consciousness, i.e. syncopal and presyncopal episodes, and palpitations [3].

Clinical Diagnosis

Clinical examination features of HCM include the characteristic ''jerky'' rapidly rising pulse and prominent left ventricular impulse, and an apical systolic murmur, which increases with the Valsalva manoeuvre and is related to dynamic obstruction. There is frequently a fourth heart sound. The 12-lead electrocardiogram (ECG) may show abnormalities including voltage criteria for left ventricular hypertrophy, T-wave inversion and Q waves. The echocardiogram remains the investigation which most reliably confirms the diagnosis of HCM and which provides detailed information about the distribution and severity of hypertrophy, the left ventricular cavity size, assessment of left ventricular systolic and diastolic function, left ventricular outflow tract obstruction and mitral regurgitation. Hypertrophic cardiomyopathy is usually recognised by a maximal left ventricular wall thickness ≥15 mm in adults (13–14 mm is considered borderline,

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unless there is a definite family history of HCM). Other investigations that may be helpful in confirming the diagnosis or in establishing "risk of sudden death" profile include exercise testing (with or without echocardiography or myocardial perfusion scanning), ambulatory Holter monitoring, and a history of cardiac events in other family members.

When considering the diagnosis of HCM, a number of "HCM phenocopies" may also need to be considered, particularly when the hypertrophy is more concentric rather than asymmetric. These include infiltrative disroders such as Fabry disease and amyloidosis, as well as glycgoen and lysosomal storage diseases.

Most recently, cardiac magnetic resonance (CMR) imaging has emerged as an important investigation in further defining the extent and severity of both cardiac hypertrophy and fibrosis. The diagnostic criteria for HCM remain the same as for echocardiography, i.e. maximal left ventricular wall thickness ≥15 mm in adults. The main advantages of CMR imaging over echocardiography relate to quantification of fibrosis using LGE, as well as assessment of areas of the heart not as well imaged by echocardiography, namely apical HCM. Rarely, cardiac biopsies are obtained and may show the classical histopathological features of HCM, including myofibre disarray, myocyte hypertrophy and interstitial fibrosis, although such findings are usually not identified until post-mortem.

Risk Stratification for Sudden Cardiac Death

The issue from the clinicians' perspective is how does one determine who is at highest risk of sudden death. The table below summarises the current factors considered important in evaluating which individuals with HCM are at highest risk of sudden death. Most clinicians would recommend ICD therapy if any one of the five major risk factors is present, although recent debate has focussed on whether at least two risk factors are required. The other risk factors listed in Table 1 have been shown in studies in smaller cohorts of patients to play an incremental role in evaluating risk of sudden death, including recent early evidence that the amount of late gadolinium enhancement (LGE >15% of left ventricular myocardium) on CMR imaging may also be an important risk factor. Clearly, many patients have some of the minor risk factors and so the decision regarding prophylactic ICD therapy is difficult. In this case, a combination of clinical judgement and the desires of the individual patient need to be considered.

Most recently, the HCM Risk Score [5] has been established which calculates risk based on a number of variables in addition to the risk factors outlined in Table 1, including LVOT gradient, left atrial size, and age at evaluation. This risk prediction model then calculates the 5-year risk of sudden cardiac death (low <4%, intermediate 4–6%, high >6%). This risk prediction model is currently undergoing validation in other independent HCM cohorts.

Table 1 Risk Stratification for Sudden Cardiac Death in HCM.

Major Risk Factors	Previous cardiac arrest/ventricular tachycardia (secondary prevention)
	Family history of premature sudden cardiac death[#]
	Left ventricular wall thickness ≥30 mm
	Previous episodes of documented NSVT (≥3 beats, rate ≥120 bpm)
	Unexplained syncope
Other Risk Factors	Abnormal blood pressure response to exercise[*]
	Evidence of myocardial ischaemia
	LVOT obstruction (≥30 mmHg at rest, or with provocation)
	Late gadolinium enhancement on CMR imaging
	Age at presentation (before age 21 years)
	Increased left atrial size

Abbreviations: HCM = Hypertrophic cardiomyopathy; MR = cardiac magnetic resonance; bpm = beats per minute; LVOT = left ventricular outflow tract obstruction; NSVT = non-sustained ventricular tachycardia.
[#]Includes a family history of sudden cardiac death at any age if definitely caused by HCM.
[*]Abnormal blood pressure response to exercise is defined as an increase in systolic BP <20 mmHg, no rise, or a fall in BP >20 mmHg during exercise, or a disproportionate fall in blood pressure immediately post-exercise.

Genetic Testing in HCM

HCM Disease Genes

Familial HCM is a genetically heterogeneous disorder, meaning a mutation in more than one gene can lead to the same condition. At least 11 causative genes have been identified to date, which primarily encode sarcomere, or sarcomere-related proteins, and include the cardiac β-myosin heavy chain (*MYH7*), myosin binding protein C (*MYBPC3*), cardiac troponin T, tropomyosin, cardiac troponin I, essential and regulatory myosin light chain, and more recently, titin and actinin-2 genes [6]. A single mutation in any of these genes will lead to HCM. Most recently, *multiple mutations* in the one individual (i.e. two or three gene mutations) have been identified, and these individuals may develop clinically more severe disease [7,8].

Genetic Testing

Genetic testing for HCM is used to identify the disease-causing gene mutation. This genetic information can be used for cascade genetic testing in at-risk family members, and can therefore facilitate earlier management of at-risk members and avoid lifetime clinical surveillance in those family members who have a negative predictive genetic test [9]. Genetic testing may also assist in making future reproductive decisions, since a known gene mutation in the family can be used in preimplantation genetic diagnosis

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