Hypertrophic cardiomyopathy: a practical approach to guideline directed management

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Hypertrophic cardiomyopathy, one of the most common genetic cardiovascular conditions, will be encountered by nearly every health-care provider regardless of specialty. In 2020, new hypertrophic cardiomyopathy management guidelines were published, updating and evolving preceding versions. This Seminar provides a concise review and practical guide to the updated recommendations for patients with hypertrophic cardiomyopathy.

Epidemiology

Hypertrophic cardiomyopathy is one of the most common genetic cardiovascular conditions, with an estimated prevalence of one in 200–500 adults (0·2–0·5%) in the general population worldwide; however, many patients might not be clinically apparent due to absence of signs or symptoms.[1,2] A writing committee, composed of cardiologists from North America, UK, and Australia, experienced with hypertrophic cardiomyopathy, published updated clinical management guidelines in November 2020 (panel),[3] which serves as the basis for this discussion. A practical definition is increased left ventricular wall thickness in the absence of abnormal loading conditions (eg, hypertension or aortic valve stenosis) capable of stimulating that magnitude of hypertrophy (figure 1).[3] We will not cover inherited syndromes in which left ventricular hypertrophy is only one of several components. Although generally understood to be an autosomal dominant condition, there is a slight predominance of men in clinically recognised cases.[4,5] Hypertrophic cardiomyopathy can be diagnosed at any age with incident cases described on prenatal evaluations, and into the fifth or sixth decade—in individuals with previously healthy left ventricular wall thickness.

Search strategy and selection criteria

This Seminar is derived from the authors work on the 2020 American Heart Association and American College of Cardiology guidelines for the management of patients with hypertrophic cardiomyopathy . This work includes an extensive evidence review, which included literature derived from research involving human participants, published in English, and indexed in MEDLINE (through PubMed), Embase, the Cochrane Library, the Agency for Healthcare Research and Quality, was conducted from Jan 1, 2010, to April 30, 2020. Key search words included: "hypertrophic cardiomyopathy", "coronary ischemia", "systole", "atrial fibrillation", "exercise", "stroke volume", "transplant", "magnetic resonance imaging", "sudden death", "sudden cardiac death", "left ventricular hypertrophy", "subvalvular stenosis", "echocardiography", "nuclear magnetic resonance imaging", "computed tomographic angiography", "genetic testing", and "diagnostic imaging."

Genetic basis

Over the last 30 years, major advances have been made in the identification of the genetic basis of hypertrophic cardiomyopathy. What was originally described as a tumour of the heart, is now defined as a disease of the sarcomere.[6–8] Hypertrophic cardiomyopathy is inherited as an autosomal dominant trait in most cases, with offspring having a 50% chance of inheriting the same disease-causing genetic variant. Hypertrophic cardiomyopathy is caused by variants in genes encoding the sarcomere proteins critical for contractile function. The two most common disease genes implicated are the *MYBPC3* and *MYH7* genes, accounting for 70–80% of all genotype-positive patients with hypertrophic cardiomyopathy. Several other sarcomere genes have been identified to cause hypertrophic cardiomyopathy, including *TNNI3, TNNT2, TPM1, ACTC1, MYL2,* and *MYL3*. Overall, a genetic cause is identified in 40–50% of people with hypertrophic cardiomyopathy tested for the common sarcomere-related genes, with higher rates in those with earlier age of onset of disease and an established family history of hypertrophic cardiomyopathy.[8]

Pathophysiology

The cardiac cycle (systole–diastole) involves binding of cardiomyocyte proteins actin and myosin, which then causes a conformation change in the myosin protein leading to the power stroke (systole). Uncoupling actin from myosin (diastole) is the energy consuming portion of the cardiac cycle. The molecular basis of hypertrophic cardiomyopathy appears to be enhanced actin–myosin interaction and binding such that the myocytes promote contraction and concurrently delay and impair relaxation.[9] It is not clear how this results in segmental hypertrophy, although focal shear or loading has been suggested.

In hypertrophic cardiomyopathy, the hypertrophy, while occurring in any pattern, is often asymmetric with some segments showing profound thickness and others that are completely within the normal range. Although unexplained left ventricular hypertrophy is the defining characteristic for clinically apparent (phenotypic) hypertrophic cardiomyopathy, abnormalities of the mitral valve apparatus are also quite common. These abnormalities include elongation and anterior positioning of the anterior mitral leaflet, hypertrophied and displaced

papillary muscles, and abnormal attachments of the chordae tendineae.[10,11] Taken together, these distorted anatomic features cause several functional problems including left ventricular outflow tract obstruction. The hypertrophy also causes increased left ventricular stiffness, which further compromises diastolic function over and above the cellular diastolic derangement caused by the enhanced actin–myosin interaction. In some patients, there is sufficient hypertrophy to compromise left ventricular chamber size and stroke volume.

One of the most well recognised functional abnormalities in hypertrophic cardiomyopathy is dynamic left ventricular outflow tract obstruction.[12] Although its presence is not required to make the diagnosis of hypertrophic cardiomyopathy, it is estimated that approximately 60–70% of patients have left ventricular outflow tract obstruction at rest or with physiologic provocation. This obstruction results from a combination of anatomic features, including the mitral valve abnormalities described here, and most notably, the hypertrophied septum which alters the blood flow vectors within the left ventricular cavity that forces blood to push the mitral leaflet into the left ventricular outflow tract during systole. This abnormality is also promoted by the mitral leaflet anatomy described in the previous paragraph. Left ventricular outflow tract obstruction can cause a substantial pressure gradient between the left ventricle and the aorta such that myocardial oxygen demand is augmented; at the same time there is decreased coronary perfusion pressure. The effect of the abnormal flow on the mitral valve also inhibits mitral leaflet coaptation such that mitral valve regurgitation results. As opposed to valvular aortic stenosis, or a subaortic membrane that is considered fixed, the dynamic nature of the obstruction is highly dependent on left ventricular loading conditions and contractility.[13,14] Increases in contractility, decreases in preload (eg, dehydration or relative hypovalaemia), and decreases in afterload (eg, systemic vascular resistance) all augment the obstruction. Notably, all three of these occur when an individual transitions from a resting to an active state (eg, standing up or walking). Many patients might have latent outflow tract obstruction (no gradient at rest but readily apparent during upright effort). Consequently, symptoms with effort rather than rest and symptoms that vary from day to day are common in patients with obstructive hypertrophic cardiomyopathy.

Atrial fibrillation occurs in up to 25% of patients with hypertrophic cardiomyopathy, probably resulting from the diastolic dysfunction or mitral regurgitation, or both.[8,15,16] Atrial fibrillation can be particularly symptomatic in hypertrophic cardiomyopathy as the loss of atrial contribution to left ventricular filling, as well as the increase in heart rate both represent decreased left ventricular preload that can augment the outflow tract obstruction. Management of atrial fibrillation broadly encompasses pharmacological therapies such as β blockers, anticoagulation, and in some patients, the need for atrial fibrillation ablation. The risk of atrial fibrillation-related stroke is higher in patients with hypertrophic cardiomyopathy, approximately 3% per year (which is the equivalent to a CHA_2DS_2-VASc score of 3 in the general population) such that anticoagulation is usually indicated independently of this scoring tool.[17]

Ventricular arrhythmias are also seen in hypertrophic cardiomyopathy and sudden cardiac death is reported to occur in approximately 1% of patients.[18] Although the mechanisms are poorly understood, contributing factors probably include increased myocardial oxygen demand (increased muscle mass and increased work related to

***Panel:* Top takeaways from the 2020 American Heart Association and American College of Cardiology guidelines for the management of patients with hypertrophic cardiomyopathy**

- Importance of shared decision making
- Defined roles for hypertrophic cardiomyopathy specialty centres and primary cardiology teams
- Revised recommendations for screening children and adolescents in families with hypertrophic cardiomyopathy
- Growing role of cardiac MRI imaging
- Evolved sudden cardiac death risk assessment including paediatric patients
- Refined roles for septal myectomy and septal ablation
- More definition on management of heart failure
- New recommendations on exercise as part of a healthy lifestyle

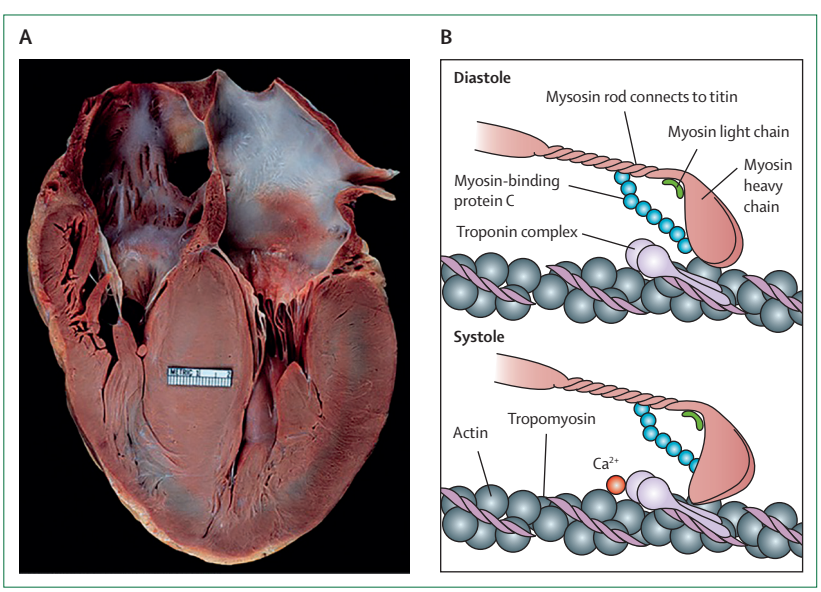

Figure 1: **Pathologic specimen of hypertrophic cardiomyopathy**
(A) Gross pathology specimen of heart with hypertrophic cardiomyopathy. (B) Depiction of cardiac sarcomere protein interactions in systole and diastole. Reproduced from Fuster and colleagues by permission of McGraw-Hill Education.

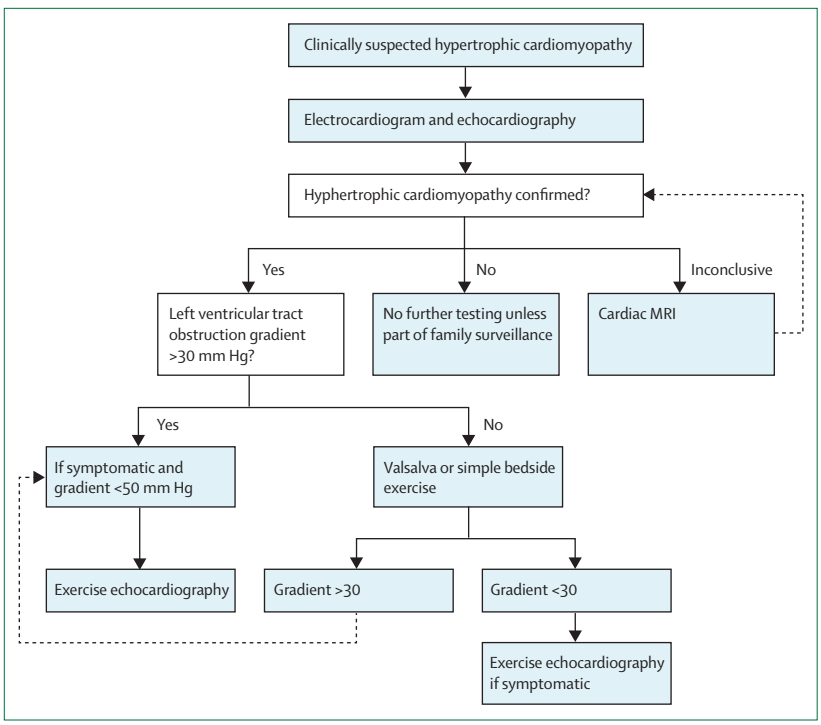

Figure 2: **Recommended diagnostic evaluation for patients with clinically suspected hypertrophic cardiomyopathy**

outflow obstruction), decreased myocardial oxygen supply (less dense capillary network), which together can result in ischaemia. Additionally, many patients with hypertrophic cardiomyopathy have intramyocardial fibrosis which can lead to electrical inhomogeneity. Sudden cardiac death risk assessment incorporating some of these factors (or surrogates of these markers) as well as markers of disease severity are an important part of the management of hypertrophic cardiomyopathy as discussed here.[3]

Evaluation

Clinical presentation

Patients with hypertrophic cardiomyopathy typically come to recognition in one of three ways: evaluation of variable effort-related symptoms (dyspnoea, angina, or syncope and presyncope), as part of systematic family screening when hypertrophic cardiomyopathy is already recognised in the family, or incidentally as a result of testing done during evaluation of another medical condition.

Baseline testing

The most common initial tests for patients suspected of having hypertrophic cardiomyopathy are electrocardiography (normal in up to 5% of patients) and echocardiography, which is the primary imaging modality to make the diagnosis and characterise the haemodynamic status (figure 2).[3] Cardiac MRI is used to supplement echocardiography if the resultant images are inconclusive or of suboptimal quality. Practically, hypertrophic cardiomyopathy is considered to be present when the left ventricular wall thickness, in any segment, is greater than or equal to 15 mm (>13 mm in the presence of a definitive family history of hypertrophic cardiomyopathy), or a wall thickness Z score is greater than 2·5 (>2 in the presence of a definitive family history) in children and adolescents (left ventricular outflow tract obstruction is not required to make the diagnosis of hypertrophic cardiomyopathy). Importantly, there must not be another clinical syndrome or condition present that is capable of producing the magnitude of hypertrophy observed. For example, aortic stenosis or uncontrolled hypertension could result in hypertrophy of less than 20 mm, but are very unlikely to cause wall thickness greater than 20 mm. Similarly, if other systemic conditions (eg, amyloid or Fabry) are suspected, cardiac MRI and blood testing should be considered. For individuals in whom hypertrophy is borderline on echocardiography, cardiac MRI can be useful as it can better visualise all of the cardiac segments and can also identify characteristic patterns of fibrosis aiding in both diagnostic clarity and sudden cardiac death risk assessment.

For those who are diagnosed with hypertrophic cardiomyopathy, ambulatory electrocardiographic monitoring of at least 24 h duration is recommended as part of risk assessment. Exercise testing can be helpful in assessing the patient's functional capacity and detecting latent outflow obstruction (with exercise echocardiography).

Genetic testing and family screening

Genetic testing is crucial to the diagnosis and management of hypertrophic cardiomyopathy in patients and their families.[7,19,20] Currently, the most common setting where genetic testing is used is in cascade genetic testing after a genetic diagnosis is made in the proband, who is often the first to present with disease in the family and has a clear clinical phenotype. Once a genetic diagnosis is established in the family, cascade genetic testing of the specific disease-causing variant can be offered to first-degree relatives, and subsequently other relatives who could be at risk of disease. Those relatives who do not carry the disease-causing variant can be released from lifelong clinical surveillance. Those who do carry the disease-causing variant will be recommended to undergo regular clinical surveillance done at intervals depending on the underlying disease, age, and severity of clinical disease.[3] This ability to target clinical surveillance to those relatives at risk of developing disease is the key utility of cardiac genetic testing in hypertrophic cardiomyopathy.

Genetic testing might also clarify an underlying diagnosis that could be atypical in phenotype characteristics. A clinical suspicion based on phenotype evaluation of an atypical form of hypertrophic cardiomyopathy (so-called hypertrophic cardiomyopathy phenocopies) could result in disease-causing variants in

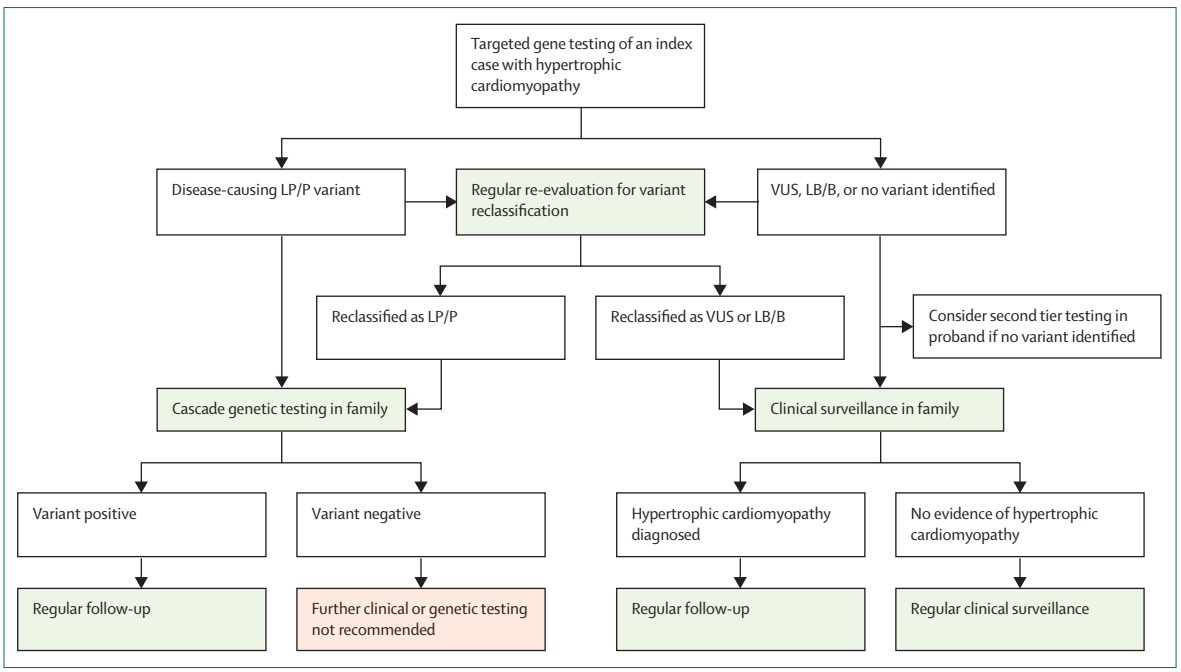

Figure 3: **Family screening for patients with hypertrophic cardiomyopathy**
Reproduced from Ommen and colleagues[3] the by permission of American Heart Association and the American College of Cardiology Foundation. LP/P=likely pathogenic/pathogenic. LB/B= likely benign/benign. VUS=variants of uncertain significance.

PRKAG2 (glycogen storage disease), *LAMP2* (Danon disease), *GLA* (Fabry disease), and disease genes related to RASopathies. In some of these diseases, the genetic test result could alter the management and therapy options, such as enzyme replacement therapy in patients with Fabry disease or more aggressive clinical management of young male patients with Danon disease. In hypertrophic cardiomyopathy, genotype is also related to overall prognosis in patient subgroups, with patients with hypertrophic cardiomyopathy who carry a disease-causing sarcomere variant having a worse prognosis than those who do not carry a disease-causing sarcomere variant.[8,21]

The utility of cardiac genetic testing extends to the next generation in terms of reproduction decisions. If the disease-causing variant is known in the family, this information can provide additional options for couples seeking to have children. Reproductive genetic counselling can clarify the risk of transmission of disease, as well as discussing potential reproductive options such as preimplantation genetic diagnosis, prenatal genetic screening, and postnatal genetic testing. This diagnosis involves in-vitro fertilisation; however, before implantation, embryos are tested for the disease-causing variant and only those not carrying the variant are implanted. This means that the child will not carry the disease-causing variant and be free from hypertrophic cardiomyopathy.

Family screening of first-degree relatives of patients with hypertrophic cardiomyopathy is recommended in all families.[3] There are two screening algorithms that can be used (figure 3). For families that wish to use genetic testing, the proband is the first to be tested, as described here. If a pathogenic (or likely pathogenic) hypertrophic cardiomyopathy-associated variant is identified, then cascade genetic testing, starting with the first-degree relatives (parents, siblings, and children) is the next step. If the family chooses not to pursue genetic testing, or if the testing does not reveal a pathogenic or probable pathogenic variant, then the family must use the clinical screening algorithm, which employs electrocardiography and echocardiography, on a periodic basis, in all first-degree relatives. For adult relatives, the screening commences as soon as the proband is initially identified and is repeated every 3–5 years. For children and adolescents, screening can start at any age but no later than the onset of puberty. It seems prudent to initiate screening immediately in families that have a history of childhood hypertrophic cardiomyopathy, or particularly malignant clinical expressions of hypertrophic cardiomyopathy, such as severe left ventricular hypertrophy or sudden cardiac death. This screening is repeated every 1–3 years until they cross into the adult screening surveillance frequency.

Management

Sudden cardiac death risk assessment

Periodic assessment of the individual patient's risk for sudden cardiac death is an important, and a relatively challenging aspect of hypertrophic cardiomyopathy management (figure 4). Although many clinical features have been proposed as potential ways to identify those patients at increased risk, the current practice relies on:

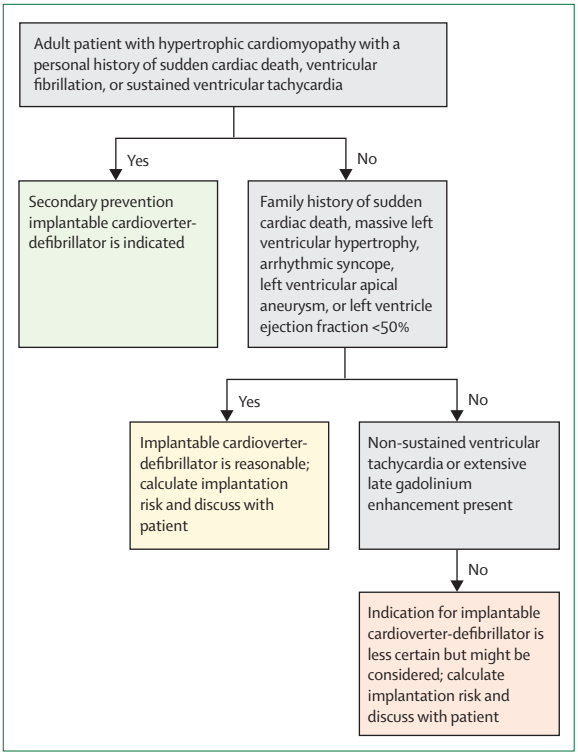

Figure 4: **Sudden death risk assessment for patients with hypertrophic cardiomyopathy and indications for implantable cardioverter-defibrillator**
Reproduced from Ommen and colleagues[3] by permission of American Heart Association and the American College of Cardiology Foundation.

personal history of sudden cardiac death or sustained ventricular arrhythmias; maximum left ventricular wall thickness; arrhythmia-related syncope; family history of sudden cardiac death; non-sustained ventricular tachycardia; decreased left ventricular ejection fraction (<50%); left ventricular apical aneurysm; and extensive myocardial fibrosis as identified on cardiac MRI (>15–20%).[3]

Additionally, a risk calculator has been developed to help quantify the magnitude of risk for the individual patient.[22] This risk calculator uses a subset of the above variables and also considers age, left atrial size, and outflow tract gradients. Some providers have used the calculated risk estimate as the principle determinant of whether an implantable cardioverter-defibrillator is indicated.[23] Others have suggested that the risk markers individually help identify patients at increased risk and that the calculated risk estimate helps communicate to the patient the extent of that risk.[3] Using this combination, in an open dialogue, helps the patient make a fully informed decision about whether they want to pursue implantable cardioverter-defibrillator placement.

The risk markers differ in children (with more weight given to non-sustained ventricular tachycardia, syncope, and massive hypertrophy), as does the complexity of device implant in individuals with smaller stature.[3] Risk estimate calculators have also been developed for paediatric patients, but have not yet gained wide clinical use.[24,25]

Initial therapies

Pharmacological management of patients with hypertrophic cardiomyopathy has a goal of symptom relief. To date, no medication has been shown to alter the natural history of hypertrophic cardiomyopathy, so asymptomatic patients do not need to start medications simply because they carry a hypertrophic cardiomyopathy diagnosis. For symptomatic patients, the principles of therapy depend on whether the patient has outflow tract obstruction or not.

For patients with resting or provoked gradients greater than 50 mm Hg, optimising contractility, afterload, and preload are important. Ensuring that the patient is maintaining adequate fluid intake and trying to eliminate high dose diuretics or pure vasodilators is an important consideration. β blockers are generally considered the first drug therapy. Verapamil or diltiazem are substituted if the β blockers are ineffective or intolerable.[3] The success of therapy is judged by the patient's symptom status, not based on the left ventricular outflow tract obstruction gradient.

For patients that do not have significant outflow tract obstruction, β blockers and the calcium channel blockers can still be used, but they can also benefit from approaches to heart failure with preserved ejection fraction. This subset of patients can be challenging to treat.

Advanced therapies

Some patients do not attain satisfactory improvements in quality of life with β blockers, verapamil, or diltiazem. For such patients, the next options include adding disopyramide, a potent negative inotrope, or relief of the obstruction via mechanical thinning of the septum (septal reduction therapy): surgical septal myectomy or percutaneous septal ablation.[3] Disopyramide offers a non-invasive next step, but comes at the cost of common side-effects (albeit reversible) and less efficacy. Both invasive options should be performed at experienced centres as outcomes are significantly better such that long-term survival can be normalised as compared with the general population. Percutaneous septal ablation offers a non-surgical approach with less pain and shorter hospital stays but with slightly lower effectiveness as compared with surgery, including a 10% reintervention rate. It is best suited for patients with modest gradients and hypertrophy and those who prefer the non-surgical approach after a balanced discussion of the options. Surgical myectomy has been performed since the late 1950s, has the highest efficacy (90–95%) and very low complications (death and stroke in about 0·5%). Myectomy is clearly favoured in patients who have other cardiac surgical indications, in those with very thick, or very thin wall thickness, in patients with very severe gradients (eg, >80 mm Hg),

and for those who prefer this option after a balanced discussion.

Some patients develop severe heart failure symptoms. When this occurs, particularly among those without significant outflow tract obstruction (non-obstructive hypertrophic cardiomyopathy), then patients are generally treated according to heart failure management guidelines, including options for cardiac resynchronisation, ventricular assist devices, or cardiac transplantation. One notable difference is that patients with hypertrophic cardiomyopathy, who have enhanced actin–myosin interactions at the cellular level, and elevated ejection fraction owing to the small left ventricular chamber, are considered to cross into heart failure with reduced ejection when ejection fraction is less than 50% (rather than <35% in other cardiomyopathies). Early referral for those with reduced ejection fraction for consideration of advanced heart failure therapies including transplantation might be indicated.

Controversies and research needs

There are now data to support that standard recommendations for healthy activity levels are also realised in patients with hypertrophic cardiomyopathy.[26] However, there are historic data suggesting that at the highest level of intensity, hypertrophic cardiomyopathy is over-represented in elite athletes who die suddenly.[27] Conversely, studies focused only on patients with hypertrophic cardiomyopathy have not shown excess events based on effort intensity or participation.[28] Taken together, these findings probably mean that although risk is elevated, that risk (as compared to other patients with hypertrophic cardiomyopathy) is relatively small, but unquantifiable at this time. There remains controversy on whether patients with hypertrophic cardiomyopathy should be excluded from competitive athletics a priori, or whether informed patients can make individual choices.[3]

At the time of writing there has been intense work on novel drug therapy directed at the molecular aspects of hypertrophic cardiomyopathy. Current pharmacological treatments for hypertrophic cardiomyopathy such as β blockers, are non-specific and can be ineffective. The EXPLORER-HCM Study recently reported the benefits of a novel, first-in-class, reversible allosteric inhibitor of cardiac specific myosin, mavacamten (MYK-461), as a targeted treatment for symptomatic, obstructive hypertrophic cardiomyopathy.[29] This small molecule is a unique treatment, as it specifically targets the mechanics of myosin-actin cross-bridge formation, and is likely to impact the way we treat patients with obstructive hypertrophic cardiomyopathy. The initial trial data show positive results, but longer term efficacy and safety data are needed.

Contributors

Both authors searched the literature, mutually drafted this Seminar, reviewed, edited, and agreed upon the submission of the final report.

Declaration of interests

We declare no competing interests.

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