Hypertrophic cardiomyopathy: from gene to bedside

SAMI FIROOZI, JULIA RAHMAN, WILLIAM J MCKENNA

Abstract

Hypertrophic cardiomyopathy (HCM) is the commonest inherited cardiovascular disorder with a prevalence of one in 500 in the general population. It is believed to be a disease of the cardiac sarcomere and is caused by a variety of mutations in genes responsible for sarcomeric contractile proteins. It is characterised macroscopically by myocardial hypertrophy and microscopically by myocyte fibrosis and disarray.

Most patients tend to present with functional limitation and symptoms such as palpitation, chest pain or syncope. The underlying mechanisms involved are complex, multiple and not yet fully understood. Further clarification of these mechanisms may enable improvements in current symptom control or the development of new avenues of therapy.

A small but significant proportion of patients suffer sudden cardiac death and this can be the initial presentation of the condition. In fact, HCM is the commonest cause of sudden death among individuals below the age of 30 years. The identification of this high-risk cohort remains the most important aspect of HCM management, particularly in light of growing evidence of the effectiveness of prophylactic strategies.

Key words: hypertrophic cardiomyopathy, genetics, management.

Background

Hypertrophic cardiomyopathy (HCM) is a genetic disease of the sarcomeric contractile proteins.[1] It is characterised by left ventricular hypertrophy (LVH) in the absence of a discernable cause such as hypertension or aortic stenosis. Its genetic, morphological and clinical features show marked heterogeneity. Pathologic descriptions of HCM were first reported in the mid 19th century[2,3] yet it remained – until publications by Brock[4] and Teare[5] 40 years ago – regarded as a separate clinical and pathological entity. Despite better understanding of the genetics of HCM, much controversy remains regarding its pathophysiology, diagnosis and treatment. This article aims to provide an up-to-date review of current evidence concerning its optimal management.

Department of Cardiological Sciences, St George's Hospital Medical School, Cranmer Terrace, London, SW17 0RE.
Sami Firoozi, BHF Research Fellow
Julia Rahman, Cardiology Senior House Officer
William J McKenna, BHF Professor of Molecular Cardiovascular Sciences
Correspondence to: Dr S Firoozi
(email: sfiroozi@sghms.ac.uk)

Table 1. Sarcomeric contractile protein mutations causing hypertrophic cardiomyopathy

Sarcomeric protein	Mutation site
Beta myosin heavy chain	Chromosome 14
Troponin T	Chromosome 1
Myosin binding protein C	Chromosome 11
α-Tropomyosin	Chromosome 15
Ventricular myosin essential light chain	Chromosome 3
Ventricular myosin regulatory light chain	Chromosome 12
Troponin I	Chromosome 19
Actin	Chromosome 15
ANP-kinase	Chromosome 7

Epidemiology

It is generally accepted that the prevalence of HCM stands at about 0.2% (or 1 in 500), a figure that is higher than previously thought.[6] It is the commonest genetically transmitted cardiac disease and occurs in all racial groups although most published work has taken place in Japan, Europe and the USA.

Genetics

Hypertrophic cardiomyopathy exhibits autosomal dominant inheritance in the majority of cases with several mutations in genes encoding cardiac sarcomeric proteins (table 1). Mutations in the γ2 subunit of the ANP kinase gene have been identified in families with HCM and Wolff-Parkinson-White syndrome and/or atrioventricular block.[7] A further mutation has also been described in the cardiac troponin-I gene.[8] The mechanism by which specific mutations result in disease is incompletely understood.[9] Phenotypic expression of the disease is extremely variable, even in family members carrying identical mutations suggesting the influence of other genetic, age-related and environmental factors in the genotype-phenotype relationship. One example of this is the ACE gene polymorphism where the DD polymorphism is commoner in patients from families where the

phenotype is more malignant with a high prevalence of premature sudden death.

Anatomic abnormalities

Hypertrophic cardiomyopathy is defined clinically as LVH without identifiable cause and pathologically by myocardial fibre disarray and small vessel disease.[10] By far the commonest (70%) pattern of LVH is asymmetrical septal hypertrophy (ASH), which involves myocardial thickening within the interventricular septum out of proportion to the posterior or free wall of the left ventricle.[11] Other typical patterns of hypertrophy include concentric (25%) and apical hypertrophy (<5%). Right ventricular hypertrophy in isolation is rare but is seen in association with LVH in up to one-third of patients. The microscopic architecture is classically disordered since hypertrophic myocytes are seen to form whorls around foci of connective tissue. Myocyte orientation is disturbed and individual cells take on bizarre shapes and are arranged in chaotic patterns – 'disarray'.[12] Other characteristic features include the 'small vessel disease' of HCM resulting from subendocardial thickening and medial hypertrophy of the intramyocardial arterioles. This remodelling process probably gives rise to the myocardial ischaemia and replacement fibrosis seen in HCM.[13]

Pathophysiology

Outflow tract obstruction

Patients with HCM can be broadly divided into obstructive and non-obstructive groups. Obstructive HCM involves impedance to the outflow of blood at the left ventricular outflow tract (LVOT). The obstruction can either be latent (provocable), labile (variable) or persistent (present at rest). In the non-obstructive form, there is no obstruction at rest or on provocation. The obstruction in HCM is due to the systolic anterior motion of the anterior mitral valve caused by Venturi forces operating as a consequence of the rapid ejection of blood through a narrowed LVOT. Complete systolic anterior motion results in contact between the mitral valve leaflet and interventricular septum and gives rise to a subaortic pressure gradient across the outflow tract.

Diastolic dysfunction

Most patients with HCM have abnormalities of diastolic function that include slow and prolonged isovolumic relaxation, a decreased rate of rapid LV filling and increased chamber stiffness.[14] As well as mitral inflow, pulmonary vein Doppler studies and myocardial tissue velocity imaging (Tissue Doppler) offer further means of assessing diastolic function; they may also be useful in differentiating physiological from pathological hypertrophy. The mechanisms of dysfunction vary between patients but factors include myocardial hypertrophy, ischaemia, fibrosis, and regional asynchrony.

Myocardial ischaemia

Patients with HCM have reduced coronary flow reserve and myocardial ischaemia has been repeatedly demonstrated during pacing and pharmacological stress. It is possible that ischaemia leads to chest pain and dyspnoea in many individuals and has been suggested as the trigger for fatal arrhythmias.[15] ST-segment changes are common during exercise and ambulatory ECG,[16] yet clinical evaluation of patients with chest pain remains problematic due to the resting ECG changes.

Clinical profile

Natural history

Ventricular hypertrophy is usually seen during periods of rapid somatic growth – especially in the first year of life and during adolescence.[17] In some patients, however, clinical presentation is delayed until middle or old age (>40 years). This 'late onset' phenotype has been shown to be particularly associated with mutations in the gene for myosin binding protein C.[18,19] Although these patients do not experience sudden death at a young age due to delayed disease expression, the clinical course following clinical presentation appears to be similar to other HCM patients and no less benign.

The natural history of HCM is typically variable. Most individuals undergo a slow progression of symptoms with a decline in exercise capacity. A minority of patients do, however, rapidly deteriorate with wall thinning, LV dilatation along with systolic impairment ('dilated HCM') and develop congestive cardiac failure.

Sudden death is an important feature of HCM; it can occur at any age but is rare in the first decade.[20] HCM has an overall annual mortality of 2%, reaching a maximum of 4-6% during childhood and adolescence.[21]

Presentation

The majority of patients with HCM remain asymptomatic throughout life and are diagnosed either incidentally or during family evaluation. Some patients, however, develop symptoms such as chest pain, dyspnoea, palpitation and syncope. Whilst orthopnoea and nocturnal dyspnoea are relatively rare, the onset of atrial fibrillation (AF) often leads to a marked deterioration in symptoms. Furthermore, it should be noted that sudden death might be the first clinical manifestation of the disorder.

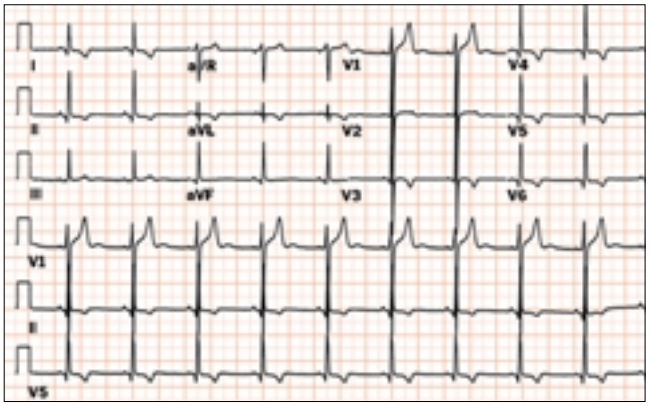
In most cases, physical examination is entirely normal but in patients with obstruction, abnormalities of the pulse character and an outflow tract murmur may be evident. In some cases, the murmur may be exacerbated on preload and afterload reduction.

Electrocardiogram

At least 80% of patients with HCM have an abnormal electrocardiogram (ECG),[22] although no changes are absolutely diagnostic. Abnormal QRS morphology including deep S-waves, LVH voltage criteria and repolarisation changes are frequently seen (figure 1). ECG evidence of left atrial enlargement is also a recognised finding. Other features of the abnormal ECG include pathological Q-waves, usually seen in the inferolateral leads, and giant negative T-waves (figure 2) typically in cases of apical hypertrophy.[23]

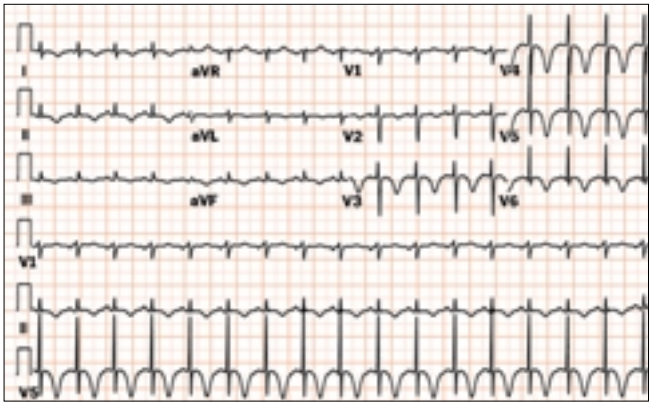
The ECG is an important diagnostic tool, particularly in cases of HCM where the morphological features are subtle and thus

Figure 1. Electrocardiogram changes in a patient with hypertrophic cardiomyopathy including voltage criteria for LVH, T-wave inversion and Q-waves



Key: LVH = left ventricular hypertrophy

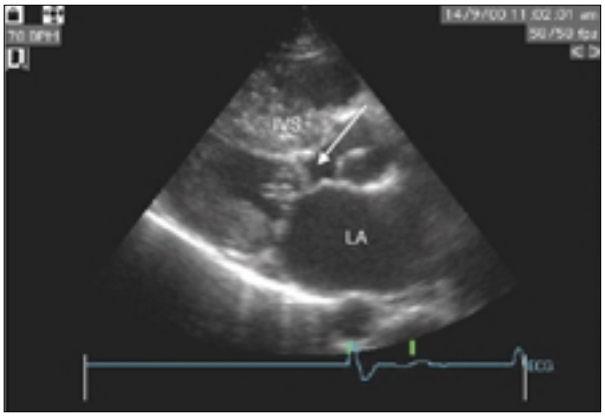
Figure 2. An electrocardiogram of an HCM patient with giant inverted T-waves



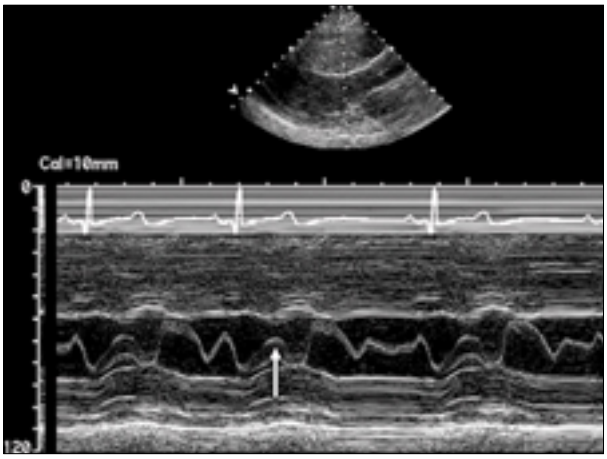
Key: HCM = hypertrophic cardiomyopathy

Figure 3. **a** shows a two-dimensional parasternal long axis view illustrating asymmetrical septal hypertrophy
b shows an M-mode trace illustrating severe septal hypertrophy and systolic anterior motion of the mitral valve

a



b



the echocardiogram may be equivocal or normal. The presence of ECG changes in association with a positive family evaluation may lead to the diagnosis where echocardiography may have resulted in false negatives. Similarly, the differentiation of HCM from other causes of myocardial hypertrophy (e.g. athlete's heart) by echocardiography alone may be problematic as other distinguishing structural features may be absent. In these cases, however, ECG changes may enable the distinction to be made, as certain changes are highly suggestive of HCM.

Echocardiography

The two-dimensional echocardiogram is the most important form of investigation in HCM. Diagnostic criteria vary but a left ventricular wall thickness exceeding two standard deviations from the mean when corrected for age, sex and height is generally diagnostic in the absence of any associated cardiac or systemic cause. The distribution and extent of hypertrophy can be assessed using long and short axis views (figure 3).[24] The left ventricular cavity is typically small and is associated with normal or supra-normal systolic function. As a result, there may be systolic obliteration of the left ventricular cavity. Often, there is left atrial enlargement reflecting elevated end-diastolic pressures.

Echocardiography can also detect the degree of mitral valve abnormalities including systolic anterior motion and mitral regurgitation. The presence and magnitude of outflow tract obstruction can be measured using Doppler echocardiography. Doppler can also be used to assess diastolic dysfunction by looking at mitral valve inflow indices; more sophisticated modalities, such as pulmonary venous Doppler and myocardial tissue velocities, may be used to look for abnormal patterns of relaxation.

Cardiopulmonary exercise

The majority of patients with HCM report exercise limitation and

decreased functional capacity.[25] The most common and practical method of assessing functional capacity is the New York Heart Association (NYHA) classification. Unfortunately, this type of subjective assessment has important shortcomings. A patient's perception of a 'normal' exercise capacity may be adapted to a sedentary life and so they may be labelled incorrectly as 'asymptomatic'. Conversely, some patients over-report symptoms yet have a perfectly satisfactory exercise capacity when assessed objectively. Prospective studies have shown that the majority of patients with HCM have objective evidence of functional limitation when assessed using cardiopulmonary exercise testing with over 90% of patients having peak oxygen consumption measures under the normal predicted value.[26,27]

Differential diagnosis

In adults, unexplained LVH is sufficient for a diagnosis of HCM, but some individuals do not fulfil conventional diagnostic criteria. In particular, difficulties arise amongst the paediatric population, highly trained athletes and in hypertension. Minor ECG and echocardiographic abnormalities assume much greater significance in the context of an affected family than in the general population due to the dominant pattern of inheritance. A number of rare neuromuscular and metabolic syndromes overlap with the 'idiopathic' form of HCM and should be considered in the differential diagnosis.

Hypertension

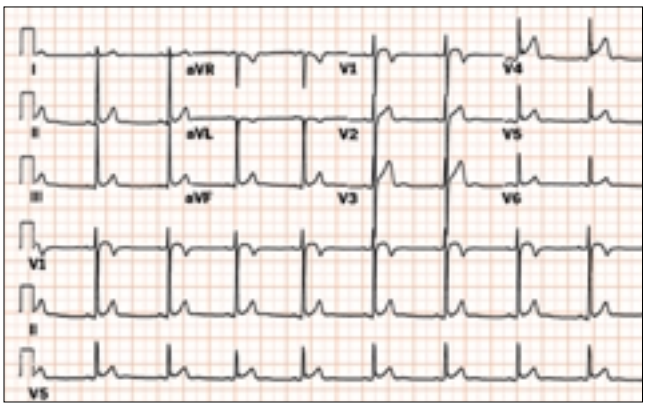
Left ventricular hypertrophy occurs in up to 50% of hypertensive patients, the extent of which is determined by factors including sex, race and severity of hypertension.[28] As a general rule, HCM involves a greater degree of hypertrophy than hypertension. When faced with a wall thickness of over 2 cm, especially in Caucasians, one must always consider a diagnosis of HCM.[29] Asymmetrical hypertrophy occurs more often in HCM, whereas concentric LVH is seen more often in hypertension, and whilst systolic anterior motion is associated with both conditions, the combination of systolic anterior motion, outflow tract obstruction and asymmetrical septal hypertrophy indicates a diagnosis of HCM. This pattern and many other patterns of echocardiographic abnormality are not highly specific markers.[30]

Athlete's heart

Hypertrophic cardiomyopathy is the commonest cause of sudden death in athletes below the age of 35 years.[31] Regular intensive physical exercise can lead to cardiovascular adaptations referred to as the 'athletic heart syndrome'.[32] Although this includes mild increases in left ventricular wall thickness, some HCM patients have a wall thickness in the same range (12–15mm; 'the grey zone') and yet remain at risk of sudden death.[33,34] This distinction is crucially important as continued participation in competitive sports for a young HCM patient may be life-threatening, whereas a mistaken diagnosis of HCM in a normal athlete may unnecessarily deprive them of their career and possible livelihood with financial, social and psychological consequences.

A diagnosis of HCM in an adult elite athlete is extremely likely when LV wall thickness exceeds 16 mm in men or 14 mm in women,[35] especially when combined with a family history of HCM and/or sudden death. The ECG of 'athlete's heart' characteristically shows evidence of LVH, sinus bradycardia, sinus arrhythmia and mild repolarisation changes (figure 4) but the coexistence of marked repolarisation abnormalities with mild hypertrophy is highly suggestive of HCM. Echocardiographic features supporting a diagnosis of HCM include a small LV cavity (athletes tend to have an enlarged LV cavity), left atrial enlargement, abnormal diastolic function and outflow gradients.[36] In cases where the distinction between physiological adaptation of athlete's heart and pathological hypertrophy of HCM is not clear on the basis of ECG and echocardiography, cardiopulmonary exercise testing can offer valuable information and help in the differentiation. Whereas the vast majority of patients with HCM have impairment of functional capacity reflected by sub-normal exercise indices, athletes will have supra-normal exercise indices reflecting their supreme cardiovascular fitness.

Figure 4. An electrocardiogram of an endurance athlete showing sinus bradycardia, voltage criteria for LVH and early repolarisation changes



Key: LVH = left ventricular hypertrophy

Noonan's syndrome

This is a primary genetic disorder where the phenotype can range from that similar to Turner's syndrome to very subtle somatic abnormalities. Twenty-five percent have LVH;[37] systolic anterior motion may be present but only in the face of severe hypertrophy. A further association is of right ventricular outflow tract obstruction.

Friedreich's ataxia

Friedreich's ataxia is an autosomal-recessive disorder where cardiac involvement occurs in over 90% of cases and can result in HCM. It can lead to symptoms prior to neurological deficits becoming clinically apparent.[38]

Mitochondrial cytopathy

Mutations in mitochondrial DNA have recently been found to be

associated with HCM with certain genotypes being linked to particular patterns of hypertrophy.[39] Data regarding its similarity to HCM are limited.

Lentiginosis

Rarely, HCM is linked with the autosomal-dominant cardiocutaneous LEOPARD syndrome (Lentigenes, ECG abnormalities, Ocular hypertension, Pulmonary stenosis, Abnormal genitalia, Retardation of growth, sensorineural Deafness).[40]

Stratification of risk

Whilst sudden death is a relatively rare event in HCM, its occurrence in young asymptomatic individuals has a disproportionately strong impact on the affected family and wider community. The identification of such patients is the most important aspect of disease management, and risk stratification in HCM remains a challenge, despite extensive research. Its clinical importance is based on the principle that if sudden death can be avoided, the prognosis for most patients is relatively favourable.

Studies show that ventricular arrhythmias are the most common cause of death occurring either as a primary event or secondary to various triggers including paroxysmal AF, myocardial ischaemia, diastolic dysfunction and hypotension.[41]

Risk factors for sudden death

The clinical heterogeneity of HCM makes risk assessment difficult. Certain features have been shown to be associated with an increased risk of sudden death (table 2).[1,42-44] It must be noted that the presence of obstruction *per se* does not seem to affect risk significantly, though data sets do not include sufficient numbers of patients with large gradients (>100 mmHg). Further studies have revealed that a young age at diagnosis and massive LVH (>30 mm)[45] may also adversely affect risk. These variables have a low positive predictive accuracy and whilst they cannot be used to identify patients needing prophylaxis, their high negative predictive accuracy can be helpful in detecting which patients are of low risk.

Management of the high-risk patient

The relative importance of these risk factors is still not clear and the point at which prophylactic intervention should be administered depends on the level of risk perceived as acceptable. In general, patients with two or more risk factors are deemed 'at risk'. The aim is to prevent triggers for sudden death or life-threatening arrhythmias. Two main options exist – amiodarone and an implantable cardioverter defibrillator (ICD)[46,47] – though precise clinical criteria to choose between the two therapies have not yet been defined. Choice is further influenced by cost, availability and cultural differences in treatment strategies.

Low-dose amiodarone has been shown to decrease the incidence of sudden death in patients with non-sustained ventricular tachycardia[48] and in high-risk children.[49] These results are based on a non-randomised study and are limited by the small size of the populations involved and the relatively low incidence of sudden death. Concerns have also been expressed over the use of amiodarone in young children. Amiodarone therapy may also have a role as a bridge to more definitive therapy with the ICD.

Table 2. Clinical risk factors for sudden death

- Previous cardiac arrest or sustained ventricular tachycardia (VT)
- Family history of premature sudden death
- Non-sustained ventricular tachycardia on ambulatory ECG monitoring
- Unexplained syncope
- Abnormal exercise blood pressure response
- Severe left ventricular hypertrophy (wall thickness >30 mm)

The ICD has pacing abilities and the potential to abort potentially fatal arrhythmias and prevent sudden death,[50] but it is associated with various complications, is costly and has significant socio-economic implications in terms of effects on insurance and employment. The use of ICD in children is also not straightforward due to body size. Patients need to be aware of all the risks and benefits associated with either treatment to enable them to make fully informed decisions. It is also important to emphasise that, even in high-risk groups, sudden death remains a relatively rare occurrence.

The long-term efficacy of prophylactic strategies in high-risk groups is still unknown and whilst we await further data, we must remember that most patients fall outside this group and need reassurance about prognosis rather than aggressive intervention.

Family evaluation

The identification of potentially affected family members is an essential and often neglected aspect of HCM management. The aim of family evaluation is to identify affected individuals, who can then go on to be assessed with regards to risk of sudden death. The importance of family evaluation is underscored by the fact that sudden death can be the initial mode of presentation of HCM. Affected individuals who are deemed to be at risk can be offered prophylactic therapy, whilst those not at risk can be reassured.

Evaluation of family members involves clinical assessment, ECG and echocardiography. Genetic testing is not universally available, but with further development it will enable more reliable and conclusive diagnosis to be made. Furthermore, gene testing will negate the need for repetitive family evaluation and will enable the detection of high-risk mutations, which are at a subclinical stage or are clinically subtle.

Symptomatic therapy

Obstructive HCM

Medical therapy

Beta blockers and verapamil have long been used empirically as first line treatments in HCM to control symptoms. Beta blockers reduce heart rate and prolong diastole, increasing passive ven-

tricular filling.[51] They also improve myocardial ischaemia and decrease outflow tract obstruction. Evidence has shown that up to 70% of patients show symptomatic improvement yet high doses are often required and side effects may be limiting. Verapamil improves ventricular filling and may also reduce myocardial oxygen demand[52] but its effects are unpredictable. In rare cases it may precipitate acute haemodynamic collapse in patients with large outflow gradients or severely compromised diastolic dysfunction.

Disopyramide is also effective in alleviating obstruction and relieving symptoms by virtue of its negative inotropic properties.[53] Some clinicians advocate its use as first-line treatment for obstructive HCM though its clinical and haemodynamic properties have been shown to decrease with time. Disopyramide also accelerates AV node conduction and merits caution when used alone, especially in patients with atrial fibrillation. One useful strategy is to use disopyramide in conjunction with agents that slow AV conduction.

Surgical therapy

Invasive intervention is only required for patients with significant (>50 mmHg) outflow obstruction and symptoms refractory to pharmacological therapy.[54] Surgery aims to widen the LV outflow tract, thereby abolishing systolic anterior motion and outflow obstruction. The operation usually achieves a reduction in outflow gradient in 95% of cases and subjective long-term symptomatic improvement in most cases.[55] The operation also carries an acceptably low mortality of 1–2% in experienced centres. Recognised complications, including ventricular septal defect and heart block, have become less frequent with the use of modified surgical technique and peri-operative transoesophageal echocardiography.[56] Furthermore, intrinsic abnormalities of the mitral valve can also be corrected by means of mitral valve repair or replacement.[57]

Transcoronary alcohol septal ablation

This interventional catheter-based technique involves the injection of a small quantity of pure alcohol into the first septal perforator branch of the left anterior descending artery - a 'chemical myectomy'.[58] The aim is to cause a small, controlled infarct with resultant fibrosis, which leads to widening of the outflow tract and gradient reduction. Both subjective and objective symptomatic improvements have been reported whilst complete heart block has been identified as the most frequent complication.[59-61] Data are, however, restricted to preliminary studies and further randomised trials are required to assess its long-term effects.

Pacemaker therapy

Over the past 15 years, uncontrolled studies have shown that AV sequential pacing is able to decrease or eliminate outflow obstruction in some patients with HCM.[62,63] This effect is thought to be due to paradoxical septal motion and widening of the LVOT to thereby relieve the obstruction. Though early reports are promising, reported symptomatic benefit is unaccompanied by objective evidence of improved exercise capacity, and may be due to a placebo effect.[64] Its long-term efficacy remains unknown and the lack of reliable markers for positive responders limits its utility.

Key messages

- Hypertrophic cardiomyopathy is caused by mutations in sarcomeric contractile protein genes
- Symptom control can be achieved either pharmacologically or by more invasive therapies
- Initial disease presentation may be with sudden death and the period of highest risk is during adolescence and young adulthood
- Risk stratification enables identification of at-risk individuals, which enables targeting of prophylactic measures
- Clinical evaluation of first-degree relatives is an important part of disease management
- Genetic testing in the future will enable more reliable and rapid identification of affected and high-risk individuals

Non-obstructive HCM

The majority of HCM patients do not have outflow tract obstruction. For this group, the therapeutic options are more limited. Calcium antagonists are preferred when systolic function is normal.[65] Verapamil is particularly useful in patients with exertional angina. Its mechanism of action is unclear though LV relaxation and exercise tolerance are improved.[66] If calcium antagonists are not tolerated, reducing the heart rate with beta blockers may relieve ischaemia and prolong ventricular relaxation. If patients develop symptoms of pulmonary congestion, diuretics may be added although their injudicious use can be dangerous in patients with severe diastolic impairment.

Management of supraventricular arrhythmia

Atrial fibrillation is seen in up to 25% of all HCM patients and is the arrhythmia most commonly associated with adverse clinical effects such as thromboembolism, heart failure and death.[67] Cardioversion should be used where possible and where not possible, control of ventricular rate is sufficient to improve symptoms in most patients. Anticoagulation should be considered if AF is sustained or recurs frequently. Treatment for other supraventricular arrhythmias is not indicated unless they are sustained or associated with symptoms.

Summary

Hypertrophic cardiomyopathy exhibits diversity in terms of its genetic aetiology and clinical picture. The management of the

condition revolves around symptom control and the identification of at-risk individuals and sudden death prevention. Better understanding of the genotype-phenotype relationship and disease mechanisms will enable improvements in the above.

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