Hypertrophic obstructive cardiomyopathy

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Hypertrophic obstructive cardiomyopathy is an inherited myocardial disease defined by cardiac hypertrophy (wall thickness ≥15 mm) that is not explained by abnormal loading conditions, and left ventricular obstruction greater than or equal to 30 mm Hg. Typical symptoms include dyspnoea, chest pain, palpitations, and syncope. The diagnosis is usually suspected on clinical examination and confirmed by imaging. Some patients are at increased risk of sudden cardiac death, heart failure, and atrial fibrillation. Patients with an increased risk of sudden cardiac death undergo cardioverter-defibrillator implantation; in patients with severe symptoms related to ventricular obstruction, septal reduction therapy (myectomy or alcohol septal ablation) is recommended. Life-long anticoagulation is indicated after the first episode of atrial fibrillation.

Introduction

Hypertrophic cardiomyopathy is characterised by the presence of increased left ventricular wall thickness that is not explained by abnormal loading conditions (such as hypertension or valvular disease).[1,2] The definition is clinical: it makes no a priori assumptions regarding aetiology or pathology, and it is both practical and appropriate for everyday clinical practice. The distinction between primary and secondary myocardial disorders has been abandoned because of overlap between aetiological factors and because of increasing recognition of underlying causes.[3]

Obstruction of the left ventricular outflow tract (LVOTO) is a major hallmark of hypertrophic cardiomyopathy and underlies the first historical pathological description in 1868 by Vulpian, reported as idiopathic hypertrophic subaortic stenosis,[4] as well as the more modern description in the 1950s by Brock and Teare.[5,6] The obstruction, defined as a maximal left ventricular gradient greater than or equal to 30 mm Hg at rest or with provocation, is present in approximately two-thirds of patients with hypertrophic cardiomyopathy, and constitutes diagnosis of hypertrophic obstructive cardiomyopathy.

In this Seminar we review essential knowledge of hypertrophic cardiomyopathy that is necessary for a basic understanding of this field, with a specific focus on treatments for hypertrophic obstructive cardiomyopathy. The evidence for clinical management of hypertrophic cardiomyopathy and hypertrophic obstructive cardiomyopathy is based predominantly on observational cohort studies and analyses of registries rather than on randomised controlled trials. Therefore, a major goal of this Seminar is to provide a balanced overview and update of hypertrophic obstructive cardiomyopathy, highlighting both recently published findings and current controversies.

Epidemiology

The prevalence of unexplained left ventricle hypertrophy is estimated by several global studies (in the USA, Europe, Asia, and east Africa) to be about one in 500 adults (0·2%) in the general population.[7] In children the true prevalence is unknown, but population-based registries reported an incidence of 0·3–0·5 per 100 000.[8,9]

Most studies observe a lower incidence in children than in adults and also a small male preponderance that could be related to a particular natural history of this genetic disease, with age-related and earlier onset in men than in women.[10] Genetic studies performed in families with hypertrophic cardiomyopathy, or in the general population, also led to the identification of mutation carriers with no phenotypic expression (ie, at the preclinical stage), or of unknown clinical status, which could suggest a higher prevalence of hypertrophic cardiomyopathy than previously estimated.[7,11]

Causes

Hypertrophic cardiomyopathy is a genetic disease in almost all cases,[12,13] with acquired disease (table 1, panel) occurring only very rarely or in patients with a particular presentation, such as in amyloid light-chain or senile amyloidosis. Most genetic causes are related to mutations in sarcomeric proteins, but non-sarcomeric genetic mutations are observed in a substantial proportion of patients, especially in children.

Sarcomeric causes

About 35–60% of patients with hypertrophic cardio-myopathy carry a pathogenic mutation in sarcomeric protein genes with an autosomal dominant inheritance (table 1)[14,15] and are more frequently identified in the context of familial forms, greater wall thickness, and reverse curve hypertrophy.[15,16] Most mutations are heterozygous missense or truncating mutations and are observed in genes encoding myosin heavy chain, cardiac muscle β isoform (*MYH7*), cardiac myosin binding

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	Gene	Locus	Associated phenotype	Gene frequency (%) or inheritance
Sarcomeric genes: thick filament				
Beta myosin heavy chain	MYH7	14q11.2	..	20–30%
Regulatory myosin light chain	MYL2	12q23-q24	..	2–4%
Essential myosin light chain	MYL3	3p21.3	..	1–2%
Sarcomeric genes: intermediate filament				
Cardiac myosin-binding protein C	MYBPC3	11p11.2	..	30–40%
Sarcomeric genes: thin filament				
Cardiac muscle troponin T	TNNT2	1q32.1	..	5–10%
Cardiac troponin I	TNNI3	19q13.4	..	4–8%
α-tropomyosin	TPM1	15q22.1	..	<1%
α-cardiac actin	ACTC1	15q11q14	..	<1%
Non-sarcomeric genes				
α-galactosidase A	GLA	..	Fabry disease	X-linked; 1–2% of men
Transthyretin	TTR	..	Amyloidosis	Dominant; 1–10%
Lysosome-associated membrane glycoprotein 2	LAMP2	..	Danon disease	Dominant; rare
AMP-activated protein kinase subunit gamma 2	PRKAG2	..	Wolff-Parkinson-White syndrome	Dominant; rare
Four and a half LIM domains protein 1	FHL1	..	FHL1-related diseases	X-linked; rare
Lysosomal alpha-glucosidase	GAA	..	Pompe disease	Recessive; rare
Tyrosine-protein phosphatase, non-receptor type 11	PTPN11	..	Noonan disease	Dominant; rare
Frataxin	FXN	..	Friedreich disease	Recessive; rare
Mitochondrial DNA genes	..	..	Mitochondrial diseases such as MELAS and MERFF	Mitochondrial; rare

Table 1: **Main causes of hypertrophic cardiomyopathy**

Panel: **Other main causes of hypertrophic cardiomyopathy**

Non-genetic causes
- Amyloid light-chain or senile transthyretin amyloidosis
- Neonate of diabetic mother
- Drug-induced (tacrolimus, steroid)

Differential diagnosis
- Hypertension* and phaechromocytoma
- Aortic valve stenosis*
- Athlete's heart
- Obesity*

*excluded by the definition of hypertrophic cardiomyopathy

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protein C (*MYBPC3*), or cardiac muscle troponin T (*TNNT2*). Several studies[10,17–22] report an age-related penetrance, since left ventricle hypertrophy might not develop until the third decade or beyond, and in rare cases can be incomplete (with no cardiac expression at advanced age). Apart from the large genetic heterogeneity, phenotypic heterogeneity is also obvious both between and within families, which suggests a complex genotype-phenotype relations. Although results of early investigations suggested an association between increased risk of sudden cardiac death or an early-onset phenotype with some genes or mutations (especially some mutations in *TNNT2* or *MYH7* genes),[15–18,21] no clear and consistent correlations have been seen for most mutations. However, several studies show that some patients could have a complex genotype with multiple mutations, with a more severe or earlier disease onset, related to a gene-dosage effect.[14,23–27] It was also suggested that patients with a sarcomere mutation had an increased risk of cardiovascular events, especially heart failure, in comparison with patients who had negative results from genetic testing and no sarcomere mutation.[28–30]

Non-sarcomeric causes
Non-sarcomeric genetic causes of disease have been observed in about 25% of children with hypertrophic cardiomyopathy in a US paediatric registry,[31] mainly related to inborn errors of metabolism (eg, Pompe disease), malformation syndromes (e,g, Noonan syndrome), and neuromuscular disorders (eg, Friedreich ataxia). In adults, the proportion of non-sarcomeric causes of hypertrophic cardiomyopathy is lower but includes metabolic storage diseases such as Danon disease (*LAMP2* gene), Fabry disease (*GLA* gene), left ventricle hypertrophy associated with Wolff-Parkinson-White syndrome (*PRKAG2* gene), familial amyloidosis (*TTR* gene), and mitochondrial cardiomyopathies. Recognition of these

particular diseases is especially important because of the specific management, and sometimes treatments, that could be proposed.[32]

Pathophysiology

Most patients have an asymmetric pattern of left ventricle hypertrophy that affects mainly the interventricular septum, although other patterns, including apical or concentric hypertrophy, can be observed.[33,34] Microscopically, there is myocyte and myofibrillar disarray, increase in interstitial connective tissue, areas of replacement fibrosis, and medial hypertrophy of small coronary arteries.[35–37] Diastolic dysfunction is commonly observed along with preserved ejection fraction.

Intraventricular obstruction usually occurs at the left ventricular outflow tract, but can be midventricular. The obstruction at the left ventricular outflow tract is caused by systolic anterior motion of the mitral apparatus towards the hypertrophied septum (figure 1). The drag forces across the mitral valve pull the leaflets anteriorly to the basal septum and lead to both LVOTO and malcoaptation of the mitral leaflets, resulting in mitral regurgitation. Midventricular obstruction is caused by hypertrophied papillary muscles and midventricular hypertrophy (figure 2). The left ventricular obstruction is dynamic and the degree of obstruction depends largely on loading conditions and cardiac contractility. Therefore, physiological and pharmacological manoeuvres that decrease left ventricular volume (Valsalva manoeuvre, vasodilatation caused by nitrates, or standing from squatting to an upright position) or increase contractility (dobutamine) are associated with augmentation of obstruction. The left ventricular obstruction can be found in one-third of patients at rest and in one-third of patients during exercise or provocative manoeuvres (so-called latent obstruction). Exceptionally, right ventricular obstruction is detected in patients with an extremely thick interventricular septum.

Primary abnormalities of the mitral apparatus are also commonly observed and include leaflet elongation, valve dysplasia or prolapse, chordal elongation, papillary muscle hypertrophy or bifidity, and abnormal origins or insertions of the papillary muscles.[38,39]

Efforts have been made to understand the consequences of sarcomeric mutations, especially missense *MYH7* mutations, through various in-vitro, ex-vivo, or animal model experiments. The mechanisms by which mutations lead to the cardiac phenotype are still a matter of discussion but studies consistently suggest a hypercontractile model that involves an increase in ATPase activity, actin sliding velocity, calcium sensitivity, and finally, increase of sarcomeric force generation.[40–42] Other studies, however, had different findings and suggested a hypocontractile model with lower force generation[43,44] and hypertrophy as an adaptive secondary process.[45] Some authors emphasised early elevated sarcoplasmic calcium concentration during diastole[46] or
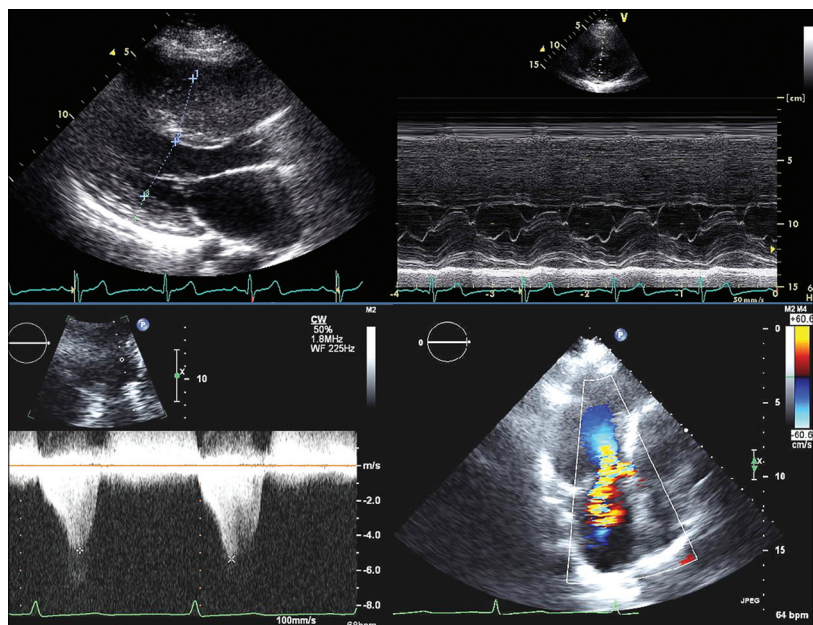

Figure 1: **Echocardiography of hypertrophic obstructive cardiomyopathy**
Findings of echocardiography are integral to the evaluation of patients with hypertrophic cardiomyopathy. Upper panel shows anatomical findings of increased wall thickness. Both 2D echocardiography and M-mode echocardiography can be used to estimate the level of outflow tract obstruction caused by systolic anterior motion of mitral apparatus. Bottom panel shows Doppler findings. Lower left panel shows continuous wave Doppler used to quantitate degree of obstruction; colour flow imaging (lower right panel), shows turbulent flow in the outflow tract and associated posteriorly directed jet of mitral regurgitation observed in the setting of systolic anterior motion.
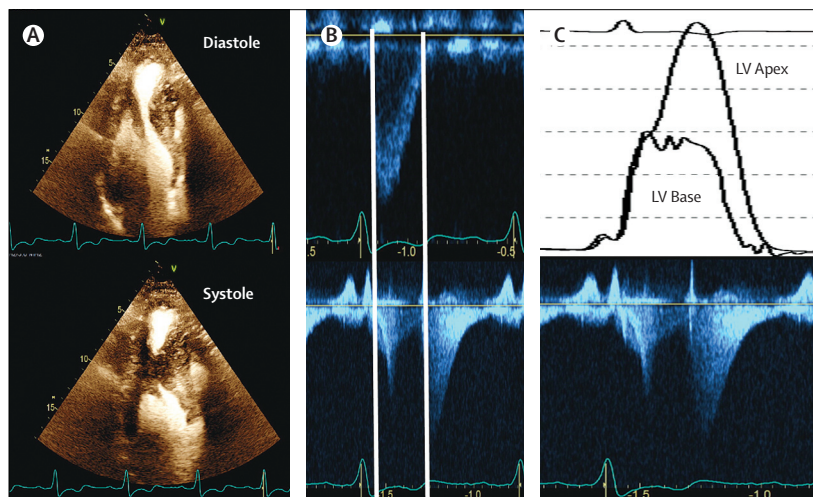

Figure 2: **Midventricular obstruction in a patient with apical hypertrophic cardiomyopathy**
Panel A shows contrast-enhanced 2D echocardiography in diastole (upper) and systole (lower), clearly illustrating the presence of midventricular obstruction. Panel B shows pulsed-wave Doppler (upper) through the left ventricular outflow tract, superimposed upon the continuous wave Doppler (lower), and illustrates the timing of midventricular obstruction in systole and the apical-to-base flow in early diastole. Panel C shows the invasive haemodynamic tracings superimposed on the same continuous wave Doppler signal.

abnormal ATP use and bioenergetic homeostasis.[47] Appropriate understanding of signalling pathways and pathophysiological mechanisms is crucial to develop new specific treatment in hypertrophic cardiomyopathy, and some preliminary data regarding new treatments are very encouraging.[42,48]
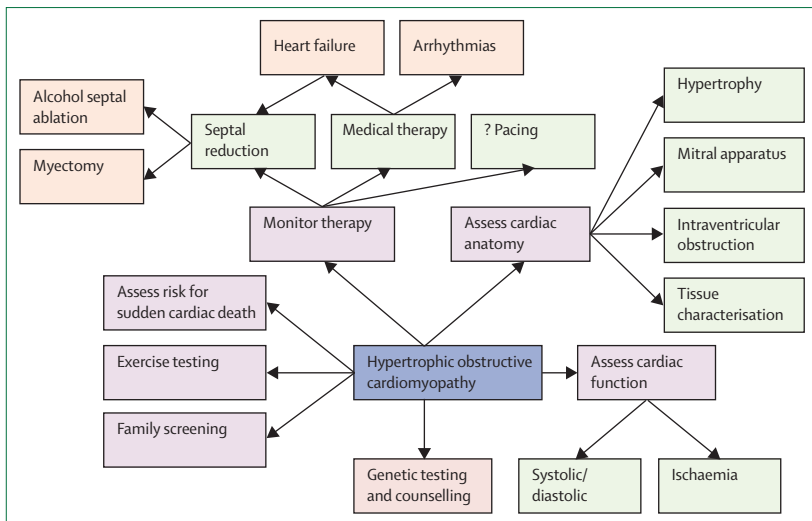
Figure 3: Evaluation strategy and goals of therapy in hypertrophic obstructive cardiomyopathy

Clinical presentation

Most patients remain asymptomatic or mildly symptomatic throughout life, whereas others have dyspnoea, exercise intolerance, chest pain, palpitations, presyncope, and syncope. These symptoms are uncommon in children and young adults. Therefore, sudden cardiac death might be the initial presentation in unfortunate young individuals. The frequency of exercise intolerance, dyspnoea, and palpitations increases with age.

Clinical diagnosis

The main diagnostic and therapeutic tasks of clinicians are summarised in figure 3. The classic auscultatory finding is a systolic ejection murmur that is best heard between the apex and left sternal border, which increases with any manoeuvre that decreases preload or afterload. The left ventricular obstruction is typically coupled with the murmur of mitral regurgitation at the apex and axilla.

An electrocardiograph (ECG) should be performed in all patients, since it is the most sensitive routine diagnostic test in the setting of hypertrophic cardiomyopathy, and with only 5–10% of patients having a normal ECG at the time of presentation.[49] Electrocardiographic abnormalities include P wave abnormalities, prominent septal Q waves—typically seen in the inferior and lateral leads—repolarisation abnormalities, and left axis deviation. In some instances, giant deeply inverted T waves in the precordial leads might suggest the midventricular or apical variant of hypertrophic cardiomyopathy. Although it is a sensitive test, the ECG lacks specificity, and therefore a normal ECG should prompt further diagnostic evaluation, usually with imaging. Ambulatory (24–48 hour) ECG monitoring has an important role in risk stratification. It can be useful in the capture of ventricular arrhythmias as part of the risk assessment process, or in the evaluation

of symptoms of palpitations, when it could capture either a ventricular or a supraventricular arrhythmia, including paroxysmal atrial fibrillation.[1]

Pathological hypertrophy is considered in the presence of unexplained wall thickness of 15 mm or more.[1] In patients with an established diagnosis of hypertrophic cardiomyopathy, lower cutoff values can be used when screening first-degree relatives, with an absolute wall thickness of 13–14 mm being suggestive of the diagnosis.[1] Two-dimensional (2D) echocardiography is regarded as the initial step in evaluation of hypertrophy (figure 1). Detection of chamber characteristics, including the presence of apical pouches, could be aided by the use of intravenous contrast agents to enhance endocardial definition (figure 2). However, echocardiography is dependent on available acoustic windows for performance of the examination, and can be limited by constraints of lateral resolution. In these instances, cardiac magnetic resonance could be considered as either a second approach in the setting of a non-diagnostic echocardiographic examination, or as an alternative initial imaging investigation. Indeed, cardiac magnetic resonance is more sensitive than echocardiography in the detection of segmental wall abnormalities.[50,51]

In echocardiography (figure 1), both M-mode and 2D-imaging help delineate systolic anterior motion. With systolic anterior motion of the mitral apparatus, the mitral regurgitant jet will predictably be posteriorly directed. In the presence of a central or anteriorly directed jet, consideration must be given to a primary mitral apparatus abnormality as a co-contributor to the mitral regurgitation. This influences treatment, since resolution of left ventricular obstruction will not resolve mitral regurgitation in the setting of primary mitral valve disease.

Continuous wave Doppler is used to estimate the maximum instantaneous left ventricular gradient, which typically occurs in late systole and has a characteristic late-peaking, dagger-shaped profile (figure 1). All patients should perform the Valsalva manoeuvre to elicit latent obstruction; if the test is negative, amyl nitrite inhalation or sublingual application of isosorbide dinitrate can be used. A thorough assessment of the ventricular apex to delineate the presence of an apical aneurysm is especially important, and in this regard, contrast echocardiography could be useful to define the 2D characteristics of apical aneurysm. Doppler interrogation, including colour flow imaging, complements this assessment. However, cardiac magnetic resonance is superior to echocardiography with contrast for left ventricular apical assessment, specifically in the evaluation of apical pouches across the spectrum of hypertrophic cardiomyopathy.[52,53]

Assessment of myocardial tissue abnormalities is best done with cardiac magnetic resonance (figure 4). In hypertrophic cardiomyopathy, interstitial fibrosis is common and seen in, on average, two-thirds of patients with a range of 33–86% across studies.[54–56] In cardiac

magnetic resonance imaging, delayed imaging is used to assess for late gadolinium enhancement (LGE), which is taken as a sign of abnormalities of the extracellular milieu, and more specifically is assumed to represent fibrotic change.[56–60] Typically the pattern with LGE is variable and presents as a patchy, mid-myocardial abnormality with a predilection for sites of abnormal hypertrophy and right ventricular septal insertion. The findings with LGE strongly and independently predict adverse outcome.[55,56,61,62] Quantification with LGE as a surrogate of the amount of fibrosis has garnered interest, especially in the setting of risk stratification of patients for device therapies. However, LGE is challenging from a technical standpoint, with variability in sequences that measure LGE, thresholds for detection with LGE, and timing of post-contrast imaging. The largest meta-analysis of prognosis studies available at the time of guideline publication in the USA and Europe shows a trend towards increased risk of sudden cardiac death or aborted sudden cardiac death with LGE.[63] A follow-up meta-analysis that included two subsequent studies indicated a significant association between myocardial fibrosis, as suggested by LGE on cardiac magnetic resonance, and sudden cardiac death or aborted sudden cardiac death.[64] The extent of LGE appears to correlate with the combined risk of sudden mortality events.[56,65] However, absence of an accepted methodological standard and histopathological validation of LGE quantification in hypertrophic cardiomyopathy, in addition to technical variability in LGE imaging, challenge the clinical interpretation of LGE quantification in standard practice. A more qualitative approach that focuses on the extent, location, and severity of LGE might be more practical and could assist in management, especially in equivocal cases. LGE is of substantial importance in the natural history and progression of adverse effects in hypertrophic cardiomyopathy, but controversy remains regarding the optimal approach to quantification and its relationship to sudden mortality events. This should prompt further investigation of how measurement of LGE can be best merged with current risk stratification pathways for the individual patient.

With echocardiography and cardiac magnetic resonance, assessment of left ventricular ejection fraction can be misleading, since small cavity size can result in a normal or supranormal left ventricular ejection fraction, even in the presence of abnormalities in systolic function. In this regard, Doppler myocardial strain imaging and 2D speckle-tracking echocardiography can elaborate on myocardial abnormalities that contribute to systolic dysfunction.[38] Cardiac magnetic resonance provides information about chamber volumes and left ventricular ejection fraction, similar to echocardiography. Myocardial tagging using cardiac magnetic resonance can also be useful in the assessment of regional function; however, this technique is not widely used.[66,67] Assessment of left ventricular filling pressures remains a challenge, because
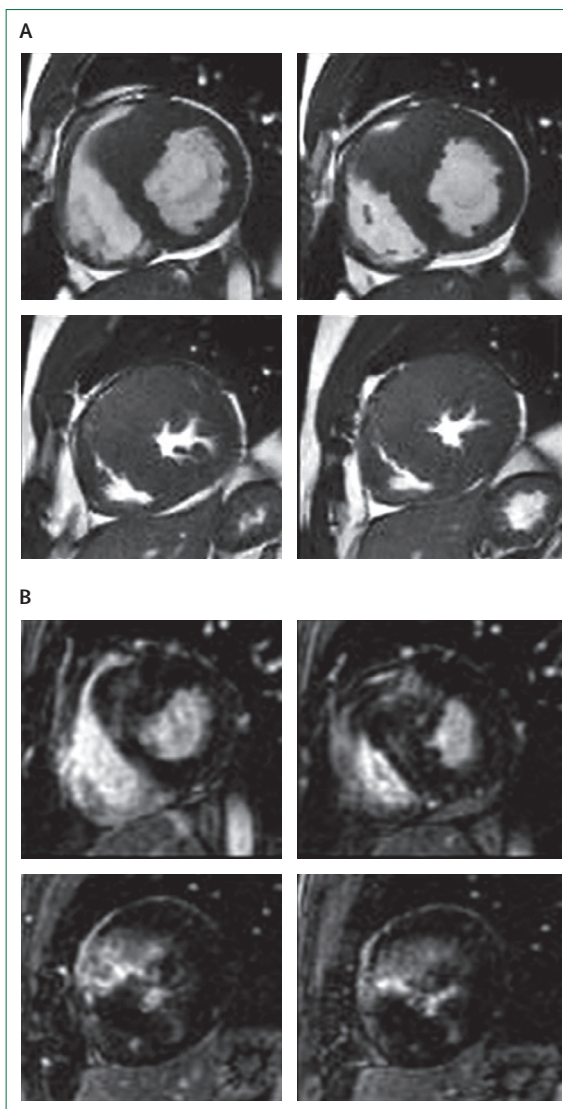

Figure 4: **Cardiac magnetic resonance with late gadolinium enhancement in a patient with hypertrophic obstructive cardiomyopathy**
Steady state free precession (A) sequences are used to assess morphology and function, and A is in the short axis imaging plane. Note the severe septal hypertrophy extending to involve the right ventricular side of the septum. Myocardial delayed enhancement sequence (B) taken at similar levels in the short axis imaging plane shows areas of abnormal delayed enhancement, consistent with fibrotic change and therefore an increased risk of poor cardiovascular outcome.

there is no single variable that has been validated as completely accurate in measuring this factor in hypertrophic cardiomyopathy.[38] Despite these challenges, a comprehensive echocardiographic examination that takes into consideration both 2D and Doppler profiles and timing intervals can be used to aid non-invasively in the practical assessment of diastolic function.[38]

Myocardial ischaemia in the absence of epicardial coronary artery disease is a common finding in hypertrophic cardiomyopathy.[68,69] Perfusion abnormalities have been associated with a poor

prognosis in hypertrophic cardiomyopathy[70] and conversely, the relief of obstruction has been associated with improvement or normalisation of perfusion defects.[71] Positron emission tomography (PET) is the most reliable non-invasive quantitative measure of myocardial ischaemia in hypertrophic cardiomyopathy.[38,72] Abnormalities in perfusion after pharmacological vasodilation are seen, using PET, in the absence of epicardial coronary artery disease and are similarly associated with an adverse prognosis,[73,74] suggesting microcirculatory abnormalities that could be involved in pathogenesis. Direct imaging of the coronary arteries is traditionally achieved with invasive angiography; however, cardiac CT could offer a novel approach to coronary artery imaging. Cardiac CT is more sensitive than invasive angiography in detecting abnormalities of coronary arterial course, such as myocardial bridging,[75] and could have a role in the pre-assessment phase before planned septal reduction therapy.

Exercise testing is a safe and important part of the clinical evaluation of patients with hypertrophic cardiomyopathy.[76] There are essentially four areas of the evaluation in which exercise testing adds incremental value to patient care. The first is in the assessment of stress-induced left ventricular obstruction, when such a gradient is not present at rest. This becomes important especially in the patient with symptoms of hypertrophic cardiomyopathy. The second is the determination of the blood pressure response to exercise, in which an abnormal response could portend an increased risk of sudden cardiac death. Third is in the assessment for concomitant coronary artery disease and, perhaps more importantly, for provocable ventricular arrhythmias, which have been associated with adverse clinical outcomes.[77] Provocable ventricular arrhythmia is an uncommon finding in symptom-limited exercise testing; however, when ventricular arrhythmias are observed they portend an increased risk of sudden cardiac death.[77] A simple treadmill test suffices for the assessment of blood pressure response to exercise; in patients with hypertrophic obstructive cardiomyopathy, however, the exercise test needs to be coupled with echocardiography.[76] The fourth benefit, in asymptomatic or mildly symptomatic patients, exercise stress testing provides risk stratification, with a low event rate in patients achieving greater than 100% predicted metabolic equivalents.[78]

Genetic testing and counselling

Integration of genetic testing into clinical practice is a relatively recent advance. Genetic testing and counselling require professionals trained to manage the various medical and non-medical implications of a genetic disease.[1,2,12,79] Two indications for genetic testing in a patient with hypertrophic cardiomyopathy (the index patient or proband) are highly recommended.[1,2]

The main reason for the identification of a pathogenic mutation in a patient is to facilitate family screening and identify first-degree relatives at risk of developing hypertrophic cardiomyopathy. When a pathogenic mutation has been identified in the proband of the family then predictive genetic testing is proposed for first-degree relatives. Relatives who do not carry the mutation can be discharged from follow-up, whereas those who carry the mutation should undergo a regular cardiac examination (at least ECG and echocardiography). Indeed, clinical long-term follow-up of relatives is mandatory because late-onset cardiac expression is observed in a significant proportion of patients, even after 30 years of age.[19–22,80] Management of gene-positive, phenotype-negative individuals (the preclinical stage of hypertropic cardiomyopathy) has emerged as a new challenge, with observations indicating that they might exhibit ECG abnormalities and mild morphological or functional abnormalities, including left ventricle remodelling, tissue Doppler abnormalities, myocardial crypts or fibrosis, mitral leaflet elongation, and abnormal collagen biomarkers.[39,81–87] The natural history of this preclinical stage is uncertain, with very rare reports of sudden cardiac death before obvious left ventricle hypertrophy,[88–90] and most data suggest a benign evolution during this stage.[22,91,92] Decisions about abstaining from competitive sports by these individuals should be discussed on a case-by-case basis, according to full cardiac examination, type of sport activity, underlying genes and mutations, and family history.[1,93,94] Sports activities are usually permitted, but regular cardiac examination is mandatory.

The second reason for genetic testing is to perform additional diagnostic investigations in a patient with atypical clinical features of hypertrophic cardiomyopathy, raising the suspicion of non-sarcomeric genetic cause. Appropriate recognition of these diseases, such as lysosomal or metabolic disorders, is a major goal since their management could be different, with specific therapeutics (eg, enzyme replacement therapy in Pompe or Fabry disease), different complications (eg, conduction defects in PRKAG2 disease), different evolution (eg, rapid systolic dysfunction in Danon disease) or different mode of inheritance (eg, Fabry and Danon disease are X-linked).[32] Other situations might benefit from genetic testing, but with a lower level of evidence or more difficulties in its interpretation, such as equivocal diagnosis of hypertrophic cardiomyopathy[93] or prognostic stratification.[9,15–18,91] In a very limited number of cases, genetic testing can be discussed for reproductive issues, such as prenatal testing or preimplantation diagnosis.[95,96]

Genetic analyses should be done by a certified diagnostic laboratory, since the interpretation of genetic results and management of the implications require specific expertise.[12,79] This requirement is emphasised by advances in molecular sequencing technologies and use of next-generation sequencing in clinical practice.[97] This technology represents a major advance in the ability to rapidly analyse a large panel of hypertrophic cardiomyopathy-related genes.[98–101] However, the technology

also identifies a considerable number of sequence variants of unknown clinical significance, which leads to major challenges in determining the clinical relevance of some next-generation sequencing results.[97,102,103]

Treatment

The natural history of hypertrophic cardiomyopathy and hypertrophic obstructive cardiomyopathy can be influenced by several therapeutic strategies. These include medicines to control symptoms, septal reduction therapies, treatments for heart failure and arrhythmias, primary and secondary prevention of sudden cardiac death with the use of an implantable cardioverter-defibrillator (ICD), and cardiac transplantation for the end-stage, so-called burned-out phase, of the disease. By contrast with ischaemic heart disease, there is a paucity of randomised clinical trials of pharmacological treatments in hypertrophic cardiomyopathy, and treatment strategies are largely based on observational data and empiricism.

Medical therapy

Medical therapy is the primary measure for controlling symptoms, which typically manifest as chest pain, dyspnoea, palpitations, or a combination of these symptoms. Maximum tolerated doses of non-vasodilating β blockers or verapamil (rarely coupled with β blockers) are used to decrease heart rate, prolong diastole, reduce left ventricular obstruction during exercise, and improve myocardial oxygen supply-demand relationships. Notably verapamil can, rarely, lead to vasodilation resulting in an increase of left ventricular obstruction and subsequent worsening of clinical status. As such, its use is not recommended in patients with marked obstruction or elevated pulmonary artery pressures.[104] Therefore, non-vasodilating β blockers are usually the first-choice therapy in symptomatic hypertrophic obstructive cardiomyopathy patients and should be titrated up to achieve resting heart rate of 50–60 beats per minute.[104,105] Current understanding suggests that medical therapy has minimal effect, if any, on the natural progression of morphological and physiological abnormalities in hypertrophic obstructive cardiomyopathy. Intuitively, these drugs might also be considered for treatment of asymptomatic or mildly symptomatic patients with extremely high resting or provoked obstruction, but there are no controlled data to support or refute this prophylactic therapeutic approach.

If medical therapy with non-vasodilating β blockers or verapamil is unsuccessful, disopyramide or cibenzoline can be considered.[106] These Class IA antiarrhythmic drugs have negative inotropic effects and can decrease resting and provoked left ventricular obstruction.[107] If disopyramide is used, β blockers or verapamil need to be continued to prevent rapid atrioventricular conduction, especially in patients with atrial fibrillation. However, some patients might have anticholinergic side-effects (constipation, urinary retention) or hypoglycaemia.[106]
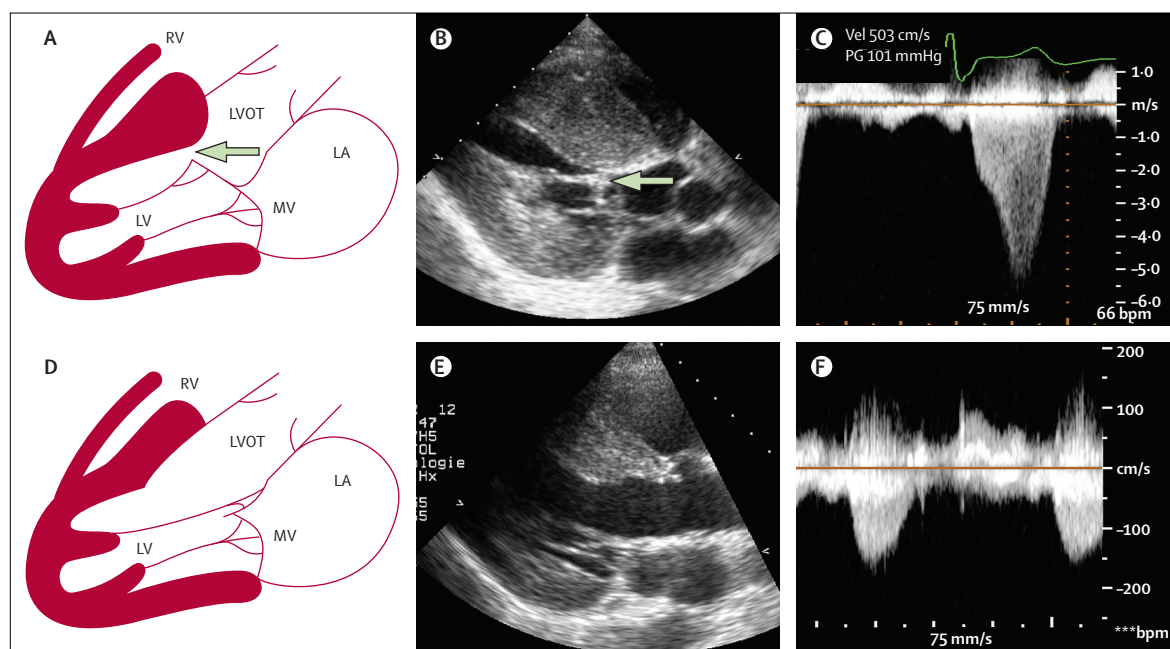

Figure 5: Scheme of septal reduction therapy
(A) Left ventricular outflow obstruction (arrow) created by hypertrophied basal septum and systolic anterior motion; (B) transthoracic echocardiography with systolic anterior motion (arrow); (C) continuous wave Doppler imaging of dynamic LVOTO; (D) schematic finding after septal reduction; (E) transthoracic echocardiography after septal reduction procedure; (F) absence of LVOTO in continuous wave Doppler imaging after septal reduction therapy. LA=left atrium. LV=left ventricle. LVOT=left ventricular outflow tract. LVOTO=obstruction of the left ventricular outflow tract. MV=mitral valve. RV=right ventricle.

When patients suffer from congestive symptoms despite traditional treatment with non-vasodilating β blockers or verapamil, low-dose loop or thiazide diuretics can be given with caution to improve exertional dyspnoea and swelling of the legs.

Traditional medical therapy is often effective in relieving chest pain, dyspnoea, and syncope during exertion. Unfortunately, there is no evidence for any improvement in survival, or protection from future heart failure or arrhythmias. Several pharmacological interventions have also been studied, mainly in animal models, to attenuate or reverse left ventricle hypertrophy and fibrosis.[108,109] Although some of these interventions showed potentially beneficial effects, solid evidence of a clinical effect remains to be established.

Septal reduction therapy

Severe and highly symptomatic left ventricular obstruction needs effective mechanical relief in the form of septal reduction therapy (figure 5). Candidates for this treatment are patients who remain symptomatic despite taking the appropriate drug therapy. Interventional or surgical therapy might also be considered in patients who are at high risk of sudden cardiac death and suffer from substantial obstruction. It was observed that relief of left ventricular obstruction could improve the post-procedural risk profile, which might be associated with a lower risk of sudden cardiac death[110,111] but additional studies are required to validate or refute these findings.

Surgical myectomy has been the gold standard treatment for most patients with intractable symptoms for decades.[112] Reduction of LVOTO is usually achieved by removal of 5–10 g of myocardium from the basal interventricular septum. More extensive operations include resection of the hypertrophied myocardium in the middle or even apical segment of the interventricular septum, plication of mitral valve leaflets, removal of thickened secondary chordae or mobilisation and reorientation of papillary muscles (the so-called RPR procedure—resection of the myocardium, plication of the anterior leaflet, release of the papillary muscle).[113–116] Results of long-term surgical studies show a permanent decrease or even abolishment of LVOTO, reduction of mitral regurgitation, and postoperative NYHA class 1 or 2 in 70–95% of treated patients.[114,115,117] Furthermore, results of some studies even suggest that longevity of post-myectomy life is similar to the sex-matched and age-matched general population.[114,115]

Alcohol septal ablation was introduced as an alternative to surgical myectomy in the mid-1990s.[118] The technique involves injection of a small amount (1–3 mL) of desiccated alcohol[119] into an appropriate septal branch, which results in myocardial necrosis, scarring, and subsequent septal shrinking.[110,118,120–123] The procedure is followed by a widening of the left ventricular outflow tract with a decrease of obstruction, a reduction of left ventricle hypertrophy, and symptomatic relief.[110,120–123] Recently, it has been shown that a larger volume of alcohol is slightly more effective in decreasing the left ventricular outflow tract gradient, but it is also associated with a higher occurrence of peri-procedural complete heart block. Therefore, doses of alcohol between 1·5 and 2·5 mL seem to be well balanced in terms of safety and efficacy for most patients.[124] Since the right bundle-branch block occurs in approximately half of patients treated with alcohol septal ablation, the risk of complete heart block after this treatment is highest in patients with pre-existing left bundle-branch block; conversely, most patients after myectomy develop the left bundle-branch block. The long-term results from a multinational alcohol septal ablation registry show that 89% of patients, after alcohol septal ablation, are in NYHA class 1 or 2, the mean decrease of LVOTO was 76%, and the 30-day mortality rate was 1%.[123] Additionally, despite initial fears, late left ventricular dysfunction or a higher rate of sudden cardiac death have not been observed, and several studies have observed that patients post-alcohol septal ablation had a long-term survival comparable with that of the sex-matched and age-matched general population.[120–122]

Both septal reduction treatments, when done in dedicated centres, are considered safe and effective. However, recent data from the Nationwide Inpatient Sample database suggest that a real-world mortality rate associated with myectomy (or surgery that involves myectomy) might even be 5·9%,[125] which contradicts the low myectomy-related mortality rates (about 1%) presented by the best high-volume North American centres.[114,115,117,126] These contradictory results are probably not unique in the progressive evolution of medicine, and it should be recognised that the more complex the therapeutic goals, the bigger the gap between the results of procedures achieved in dedicated centres and community hospitals.[123] Therefore, the procedure-related mortality rate of 0·4% for septal reduction therapy, achieved in experienced interventional or surgical hypertrophic cardiomyopathy centres, should be considered a potential outcome of optimum therapy rather than the result of routine clinical practice in less-specialised hospitals.[123,126,127] Notably, both septal reduction treatments are associated with complications including complete heart block with subsequent implantation of a permanent pacemaker (10–12% of patients after alcohol septal ablation and 1–9% after myectomy).[114,124,125,128] Therefore, septal reduction therapy should be performed in dedicated hypertrophic cardiomyopathy centres that achieve a procedure-related mortality rate less than or equal to 1% (the so-called 1% rule). This strategy will assure future patients' accessibility to the best therapy based on long-term experience. Importantly, providing that procedure-related mortality is fairly low, optimum septal reduction therapy could be offered to patients with less limiting symptoms, or to patients with extremely high LVOTO and only mild symptoms. However, such a strategy requires continued rigorous investigation to confirm its validity. Currently, patients with only mild basal hypertrophy and long mitral

leaflets or redundant chordae; extreme septal hypertrophy, significant papillary muscle abnormalities, or both; and left ventricular mid-cavity obstruction, are considered good candidates for myectomy. Patients with less complex left ventricular pathology and hypertrophy localised mainly in the basal septum, with appropriate septal perforator anatomy, could be better suited to alcohol septal ablation. The haemodynamic goal is the same for both therapies, and the residual left ventricular gradient should be less than 30 mm Hg.[129,130]

The decision to pursue septal reduction therapy must be made in an informed setting. Lessons can be taken from the emerging transcatheter strategies for treatment of aortic valve stenosis, in which therapeutic decision-making takes place in the setting of a heart-care team, comprised of the patient, clinical cardiologist, interventional cardiologist, and cardiovascular surgeon. If such an approach, inclusive of all disciplines, is advocated in a setting where a high level of expertise and appropriate morbidity and mortality statistics are available, then the optimum approach that serves the needs of the patient will probably be found.

Special therapeutic considerations

Atrioventricular pacing with a short AV interval might be considered in older patients with intractable symptoms who are high risk for, or unwilling to undergo, septal reduction therapy, or in patients with only mild septal hypertrophy.[1,2] The proposed mechanism of benefit is related to alterations in the activation sequence of the interventricular septum and possibly the effects of ventricular remodelling.[2,131] However, evidence supporting this therapy is only modest and three randomised studies suggested just borderline effects of dual chamber pacing on left ventricular obstruction,[132–134] whereas a long-term cohort study suggested a beneficial late effect.[135]

Patients who have heart failure, despite the absence of significant obstruction (residual pressure gradient <30 mm Hg), are treated with angiotensin-converting-enzyme inhibitors, diuretics, and mineralocorticoid receptor antagonists.[1] Cardiac resynchronisation therapy might be considered in patients with a successfully treated obstruction, QRS duration greater than 120 ms and left bundle-branch block.[1,136] If progressive left ventricular dysfunction is accompanied by severe heart failure (the burned-out phase), heart transplantation has to be considered as the only definitive therapeutic option.[137]

Patients with hypertrophic obstructive cardiomyopathy are at increased risk of atrial fibrillation, which can occur even in patients without any clinical symptoms.[138,139] Standard medical therapy, including β blockers, verapamil, amiodarone or electrical cardioversion, is used in these patients. However, the most important therapeutic measure is life-long anticoagulation treatment in all patients who experience a first episode of atrial fibrillation. Unlike the risk assessment strategies used for atrial fibrillation in the general population, the CHA2DS2-VASc score does not correlate well with clinical outcomes in the setting of hypertrophic cardiomyopathy,[140] and therefore should not be used in decision making with regard to the need for anticoagulation in this group of patients. Additionally, permanent anticoagulation might be considered in patients with sinus rhythm and an enlarged left atrial dimension. This recommendation has only an empirical basis, but the annual incidence of stroke or embolic events has been reported as about 1%, and higher age and a left atrial dimension of 48 mm or more have been identifed as independent predictors of embolic events, even in patients without documented atrial fibrillation.[141] The elevated thromboembolic risk related to atrial fibrillation has led to the recommendation for anticoagulation with warfarin in patients with atrial fibrillation. The role of the oral direct thrombin inhibitors (dabigatran) or direct factor Xa inhibitors (rivaroxaban, apixaban) in patients with hypertrophic obstructive cardiomyopathy and atrial fibrillation remains to be ascertained.[142]

On the basis of data that show a low probability of infective endocarditis in patients with hypertrophic obstructive cardiomyopathy,[143] antibiotic prophylaxis is not generally recommended.[1,2] However, the risk of obstruction-related endocardial lesions, especially in the left ventricular outflow tract, still exists[144] and all infections should be carefully managed in patients with left ventricular obstruction. Theoretically, the risk of having infective endocarditis in symptomatic patients with hypertrophic obstructive cardiomyopathy might be increased, in view of the haemodynamic compromise that usually occurs from damage to the mitral valve.

Although most patients with hypertrophic cardiomyopathy die at rest or during a mild physical activity, strenuous exercise and competitive sport should be avoided because of the risk of sudden cardiac death.[145] This recommendation is not dependent on the severity of LVOTO, symptoms, or previously performed septal reduction treatments.[94] However, recreational physical activities are advisable and should be tailored to each patient according to their own risk profile.[1,145]

Most patients with hypertrophic obstructive cardio-myopathy tolerate pregnancy well, but severe LVOTO, heart failure, arrhythmias, and medication taken in the pre-pregnancy period have been identified as risk factors of adverse cardiovascular events during pregnancy.[1,2,146] These events occur most frequently at the beginning of the third trimester, which coincides with the period of the highest circulating blood volume.[146] Symptomatic women are treated with β blockers. Caesarean section in this setting is rarely required and is reserved for those with severe progressive disease during the course of the pregnancy; asymptomatic women are permitted to go into spontaneous labour.[1]

	European model	North American model
Secondary prevention	Sustained ventricular tachycardia; resuscitation for ventricular fibrillation. ICD is recommended in all patients.	Sustained ventricular tachycardia; resuscitation for ventricular fibrillation. ICD is recommended in all patients.
Primary prevention	Family history of sudden death; unexplained syncope; maximum left ventricular wall thickness; non-sustained ventricular tachycardia; age; left atrial diameter; left ventricular outflow gradient (rest or Valsalva). 5-year risk <4%, ICD is not indicated; 5-year risk ≥4–6%, ICD is considered; 5-year risk >6%, ICD is recommended.	Family history of sudden death in a 1st degree relative; unexplained syncope; maximum left ventricular thickness ≥30 mm; non-sustained ventricular tachycardia; abnormal blood pressure response during exercise (decrease or failure to increase systolic blood pressure by at least 20 mm Hg during exercise test). When 1 or more risk factors are present, ICD might be reasonable (Class IIa). The role of risk modifiers, including young age, obstruction of the left ventricular outflow tract with no plan for intervention, late gadolinium enhancement, remote family history, and wall thickness, is uncertain (Class IIb).

ICD=implantable cardioverter-defibrillator.

Table 2: Comparison of two models that evaluate risk of sudden cardiac death and indication for implantable cardioverter-defibrillator implantation

Sudden cardiac death, risk stratification, and prevention

Hypertrophic obstructive cardiomyopathy has been associated with an increased risk of sudden cardiac death and heart failure. However, results of several studies have shown that patients with hypertrophic obstructive cardiomyopathy, aggressively treated in tertiary referral centres, have an acceptable long-term prognosis that is similar to the age-matched and sex-matched general population.[114,115,120–122] However, hypertrophic cardiomyopathy was shown to be one of the most common causes of sudden cardiac death in children and young adults,[147,148] and the most common cause of sudden cardiac death in young athletes.[149] Furthermore, left ventricular obstruction is an independent predictor of adverse outcomes in patients with hypertrophic cardiomyopathy.[123,129,130,150] Patients with hypertrophic obstructive cardiomyopathy at a young age (<35 years) are at higher risk of sudden cardiac death,[148] and a younger age at diagnosis is an independent predictor of adverse outcomes, even in patients up to 60 years of age.[151,152] Sudden mortality events (sudden cardiac death, resuscitation, and appropriate ICD discharge for ventricular tachycardia or fibrillation) occur at an incidence of 0·5–1·5% per year in adults,[150,151,153,154] and 2% per year in children, adolescents, or young adults.[155] This incidence is, however, largely dependent on the risk profiles of patients selected for analysis. Since some patients are prophylactically treated with ICD, the real sudden cardiac mortality rate is lower (about 0·5% per year).[151,153,155] Thus, despite treatment (especially ICD implantation and septal reduction), patients treated in specialised hypertrophic cardiomyopathy centres still have a low rate of mortality that is potentially attributable to hypertrophic cardiomyopathy (about 1% per year).[123,151,153–155] Most hypertrophic cardiomyopathy-related deaths occur suddenly until age 60, whereas older patients die more often of stroke or heart failure.[153,154,156]

In hypertrophic cardiomyopathy, the challenge remains to find the optimum path to identify the relatively small group of patients with the highest risk of sudden cardiac death. These patients should be treated with ICD implantation since it is the only therapy with sound evidence of life-saving potential.[112,155]

Currently, two different models for prediction of sudden death are available (table 2). Both models recommend implanting an ICD in all patients who have experienced sustained ventricular tachycardia or successful resuscitation for ventricular fibrillation.[1,2] However, there are differences in the evaluation of a patient's risk of sudden cardiac death in primary prevention. The North American model is based on the evaluation of five binary risk factors, and the presence of any one can be used as a consideration for ICD implantation.[2] Unfortunately, strict compliance with this model could lead to ICD implantation in up to 40–60% of patients with hypertrophic cardiomyopathy[151,157] with a low annual rate of appropriate ICD discharge of about 2% in large hypertrophic cardiomyopathy cohorts with implanted ICDs.[151,158] Thus, unsurprisingly, there remains a need for a more specific model that would better stratify the individual risk of each patient. The European model predicts the risk of sudden cardiac death over 5 years on the basis of a complex calculation of the individual values of several risk factors.[152] Patients with a risk of sudden cardiac death of at least 6% at 5 years are recommended for ICD implantation.[1,152] This model was shown to be sufficiently specific and associated with a lower rate of ICD implantations (20–26%),[157,159] but some patients with a predicted low risk of sudden mortality events were shown to be high-risk in clinical practice in one study.[159] Thus, the European model probably has acceptable specificity, but limited sensitivity for prediction of future malignant arrhythmias.[159] Although the European model clearly represents substantial progress in the risk stratification of sudden cardiac death in hypertrophic cardiomyopathy, a balance must be struck between the specificity of any diagnostic tool versus the management goals that vary on the basis of clinical context, patient preference, and

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physicians' opinions. Fully informed care, taking into account the potential advantages and disadvantages of either strategy of risk stratification, is recommended. An equally important adjunct to the conversation for ICD implantation is the discussion about related complications, including inappropriate discharges, infections, and lead or device dysfunctions, because the incidence of these complications is higher than the incidence of appropriate discharges.[158,160]

Future directions

Despite studies that suggest progress in the understanding of the genetic basis of hypertrophic cardiomyopathy, improvement in imaging methods with subsequent therapeutic consequences, and acceptable long-term outcome of patients treated with septal reduction techniques in dedicated centres, researchers working in this field should substantiate the evidence regarding the clinical effects of genetic examination, more individualised risk stratification of sudden cardiac death, the risk stratification of atrial fibrillation and consequent risk of cardiac embolisation, the effectiveness of medical therapy, the long-term safety of therapy with ICD, and the development of new therapies based on gene editing or modulation of responsible pathways. Septal reduction therapies should be restricted to the specialised hypertrophic cardiomyopathy centres of excellence with high volumes of experience and with acceptable historical outcomes (≤1% procedure-related mortality).

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