Hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy is a common inherited cardiovascular disease present in one in 500 of the general population. It is caused by more than 1400 mutations in 11 or more genes encoding proteins of the cardiac sarcomere. Although hypertrophic cardiomyopathy is the most frequent cause of sudden death in young people (including trained athletes), and can lead to functional disability from heart failure and stroke, the majority of affected individuals probably remain undiagnosed and many do not experience greatly reduced life expectancy or substantial symptoms. Clinical diagnosis is based on otherwise unexplained left-ventricular hypertrophy identified by echocardiography or cardiovascular MRI. While presenting with a heterogeneous clinical profile and complex pathophysiology, effective treatment strategies are available, including implantable defibrillators to prevent sudden death, drugs and surgical myectomy (or, alternatively, alcohol septal ablation) for relief of outflow obstruction and symptoms of heart failure, and pharmacological strategies (and possibly radiofrequency ablation) to control atrial fibrillation and prevent embolic stroke. A subgroup of patients with genetic mutations but without left-ventricular hypertrophy has emerged, with unresolved natural history. Now, after more than 50 years, hypertrophic cardiomyopathy has been transformed from a rare and largely untreatable disorder to a common genetic disease with management strategies that permit realistic aspirations for restored quality of life and advanced longevity.

Introduction

Hypertrophic cardiomyopathy is a heterogeneous monogenic heart disease studied for more than 50 years and recognised to be an important cause of arrhythmic sudden death, heart failure, and atrial fibrillation (with embolic stroke).[1–8] In view of the growing complexity of clinical practice, international differences in strategic approaches, and advances in genetic diseases[5,8–13] and cardiac imaging,[14–17] not surprisingly the diagnosis, natural history, and management of hypertrophic cardiomyopathy have become sources of uncertainty, misunderstanding,[18] and debate.[9,11,12,19–28] In this Seminar, we aim to put into current context the rapidly changing and diverse clinical landscape of hypertrophic cardiomyopathy to enhance our understanding of this complex genetic disease.

Epidemiology

Hypertrophic cardiomyopathy is a truly global disease, with cases reported in more than 50 countries on all continents[3] and affecting people of both sexes[29] and of various ethnic and racial origins, yet with similar causal mutations, clinical course, and phenotypic expression.[3,28–35] Hypertrophic cardiomyopathy is either underrecognised or clinical diagnosis is delayed, more frequently in women[29] and people of African-American origin.[30]

In diverse regions, including the USA,[7,32] Europe,[13,25] Japan,[31] China, and east Africa, hypertrophic cardiomyopathy is established as a common genetic heart disease, with a prevalence of at least one in 500 (0·2%) in the general population.[32] These data extrapolate to about 600 000 affected people in the USA (120 000 in the UK), although this number is possibly an underestimate since available data do not account for the multiple affected relatives in families. This relatively high occurrence of hypertrophic cardiomyopathy in the population contrasts sharply with its much less frequent recognition in clinical practice,[4,7] inferring that many (if not most) individuals remain undiagnosed throughout life.

Search strategy and selection criteria

We did a systematic search of Medline and identified 11 370 relevant articles published in the English language from 1960 to July, 2012, which we selected to create a comprehensive balanced appraisal of hypertrophic cardiomyopathy. Most studies were observational and retrospective, but we gave greater weight to publications from the past 10 years that included large cohorts and were evidence-based, statistically powered, and of a controlled investigational design.

Nomenclature

Historically, an obstacle to understanding the clinical diversity of hypertrophic cardiomyopathy has been the many names (n=75) given to this disease entity.[18] Idiopathic hypertrophic subaortic stenosis or hypertrophic obstructive cardiomyopathy (popular in the UK) misleadingly infer that obstruction to left-ventricular outflow is invariable. Dynamic subaortic gradients are a highly visible feature of hypertrophic cardiomyopathy. About 70% of a hospital-based cohort will have outflow obstruction at rest or with physiological exercise, but the remaining third will have the non-obstructive form without capacity to generate outflow gradients.[35]

Clinical diagnosis of hypertrophic cardiomyopathy requires a hypertrophied non-dilated left ventricle without evidence of any other cardiac or systemic disease (eg, systemic hypertension) that could produce the extent of hypertrophy evident.[4,7] Application of the term hypertrophic cardiomyopathy to left-ventricular hypertrophy associated with metabolic or multiorgan genetic syndromes has been a potential source of confusion.[18]

Genetics

Basic principles

Findings of genetic studies show that hypertrophic cardiomyopathy is caused by dominant mutations in 11 or more genes encoding thick and thin contractile myofilament protein components of the sarcomere or the adjacent Z-disc (figure 1).[5,9–13,36] Of patients who have been genotyped successfully, about 70% have mutations in two genes, β-myosin heavy chain (*MYH7*) and myosin-binding protein C (*MYBPC3*). Troponin T (*TNNT2*) and several other genes each account for 5% or less of cases.[5,9–13,36] To underscore the vast genetic heterogeneity of hypertrophic cardiomyopathy, over the past 20 years, more than 1400 mutations (largely missense) have been identified, most of which are unique to individual families.[12] Genes linked to hypertrophic cardiomyopathy, but with less evidence for pathogenicity, include α-myosin heavy chain (*MYH6*), titin (*TTN*), muscle LIM protein (*CSRP3*), telethonin (*TCAP*), vinculin (*VCL*), and junctophilin 2 (*JPH2*).

Pathogenic mutations that cause hypertrophic cardiomyopathy are transmitted in an autosomal dominant pattern; every offspring of an affected relative has a 50% chance of inheritance and risk of developing disease,[5,7,8,13] although sporadic cases do arise due to de-novo mutations. Much phenotypic heterogeneity is evident between and within families, suggesting that mutations of the sarcomere are not the sole determinant of the hypertrophic cardiomyopathy phenotype. For example, current disease-causing mutations do not account entirely for morphological features such as mitral-valve enlargement,[37,38] microvascular abnormalities,[39,40] and segmental left-ventricular hypertrophy,[14,41] indicating a possible role for modifier genes and environmental factors.

The phenotype of hypertrophic cardiomyopathy undergoes remodelling, with left-ventricular wall thicknesses increasing[42] or decreasing[43] during various phases of life. Most individuals who inherit a disease-causing mutation will demonstrate left-ventricular hypertrophy by early adulthood, typically arising during accelerated adolescent growth, and which is usually complete with physical maturity (age ≥17 years).[42] Phenotypic development is usually not associated with symptom onset or disease progression.

However, age-related penetrance can occasionally result in delayed appearance of left-ventricular hypertrophy in the third decade and beyond.[10,28,44] Nevertheless, left-ventricular wall thicknesses evident in mid-life and at older ages are generally more modest, extreme left-ventricular hypertrophy is rare at advanced ages, and substantial increases are rarely seen in adults.[44,45] Because mutations in genes encoding proteins of the cardiac sarcomere lead to such diverse clinical and phenotypic expression, hypertrophic cardiomyopathy can be considered as one heterogeneous disease entity rather than a conglomeration of similar but unrelated disorders.[4,7,18]

Genetic testing

Rapid, automated, DNA sequencing provides opportunities for comprehensive commercially available

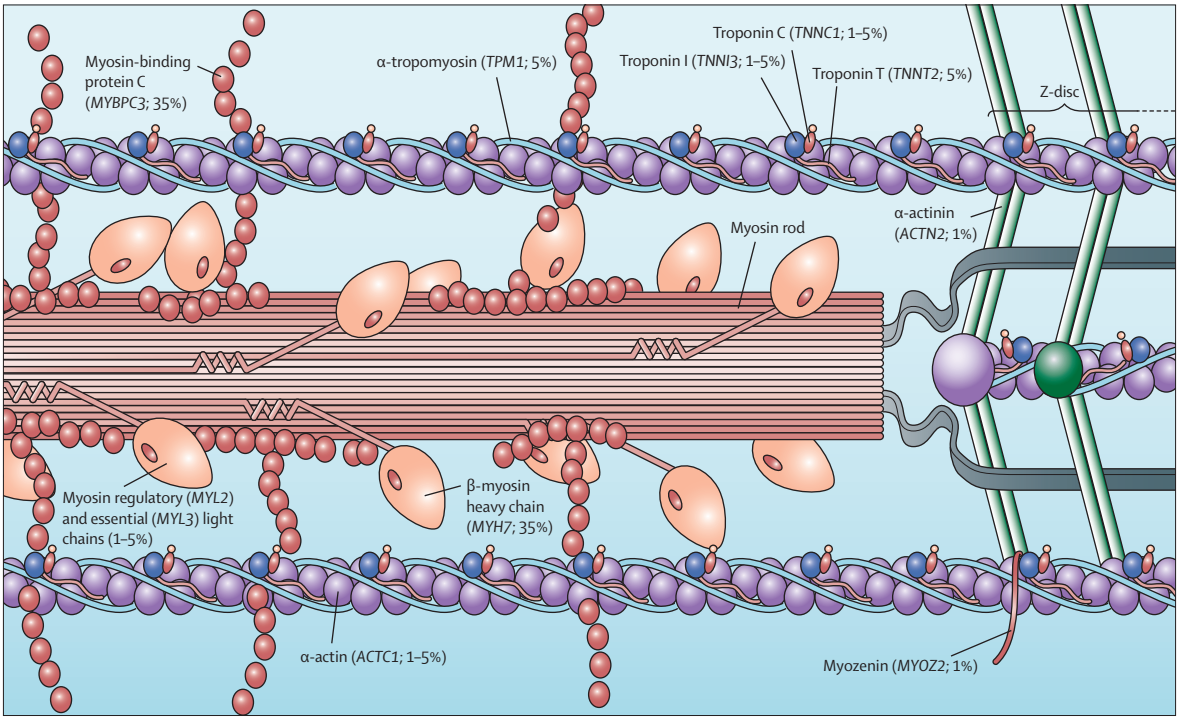

Figure 1: **Locations of genes within the cardiac sarcomere known to cause hypertrophic cardiomyopathy**
Prevalence of every gene (derived from data of unrelated hypertrophic cardiomyopathy probands with positive genotyping) is shown in parentheses.

genetic testing, identification of mutations causing hypertrophic cardiomyopathy, and molecular diagnosis in clinical practice.[5,8,12,36,46] However, pathogenic mutations can only be identified in fewer than 50% of clinically affected probands,[12,36,46] and therefore genetic defects that cause hypertrophic cardiomyopathy are presently unrecognised in a substantial proportion of patients. Furthermore, DNA-based testing not infrequently identifies novel DNA sequence variants for which pathogenicity is unresolved (variants of uncertain significance).[12,36,46] Such ambiguous variants have virtually no clinical use for family screening and promote confusion in interpretation of genetic testing results, and highlight the growing challenges entailed in translation of complex molecular science to patient care.

Prognosis

After two decades of molecular research, the relation between sarcomere mutations and clinical outcome in patients with hypertrophic cardiomyopathy has proved unreliable, attributable largely to genetic and phenotypic heterogeneity,[9,11,12,46,47] thus disputing the notion that specific single mutations can determine prognosis.[27,48,49] Therefore, despite much optimism and (perhaps unrealistic) expectations for a molecular paradigm to predict outcome and direct management of hypertrophic cardiomyopathy, this aspiration has been largely unrealised.[6,9,11,12,46,47] However, possible exceptions are emerging, including preliminary data suggesting that double, triple, or compound sarcomere mutations (evident in 5% of patients with hypertrophic cardiomyopathy) could be associated with greater disease severity,[50,51] including sudden death without conventional risk factors.[46,51]

Clinical application

Currently, the most compelling reason for genetic testing in clinical practice is to identify family members of patients with hypertrophic cardiomyopathy who do not have left-ventricular hypertrophy but may be at potential risk of developing disease. If a pathogenic mutation is identified in a relative expressing the phenotype, the genetic status of other family members can be resolved definitively, thereby eliminating anxiety associated with potential diagnosis and removing the need for future screening with cardiovascular testing.[8,12,36,46]

Genetic testing can also clarify diagnosis in patients with metabolic storage disorders for whom clinical presentation and pattern of left-ventricular hypertrophy is similar to hypertrophic cardiomyopathy but with different pathophysiology, natural history, and management—eg, Fabry's disease, PRKAG2, and LAMP2 (Danon's disease).[52,53] Genetic diagnosis is highly advantageous because LAMP2 cardiomyopathy is associated with a lethal natural history (with survival uncommon beyond 25 years) that requires early recognition to permit prophylactic heart transplant,[52] or enzyme replacement therapy in patients with Fabry's disease.[53] Occasionally, hypertrophic cardiomyopathy and restrictive non-hypertrophied cardiomyopathy arise in related individuals due to a troponin I mutation (*TNNI3*).[54]

Clinical diagnosis

Imaging

Suspicion of hypertrophic cardiomyopathy usually follows the onset of symptoms or a cardiac event but can also arise from recognition of a heart murmur or abnormal 12-lead electrocardiogram (ECG) during routine or preparticipation sports examinations, or in pedigree studies.[55,56] Clinical diagnosis is confirmed conventionally by imaging the hypertrophic cardiomyopathy phenotype with two-dimensional (2D) echocardiography,[7,32,33,41,47] cardiovascular MRI (figure 2),[14–16,57] or both. Imaging findings show an absolute increase in left-ventricular wall thickness (to 21–22 mm on average),[7,14,32,41,47] which can also be associated with mild right-ventricular hypertrophy.[58] Other common findings, such as mitral valve systolic anterior motion or hyperdynamic left ventricle, are not obligatory for a diagnosis of hypertrophic cardiomyopathy.[4,7,47]

Tomographic high resolution cardiovascular MRI has assumed an important role in the evaluation of hypertrophic cardiomyopathy patients and is often superior to echocardiography for characterisation of the phenotype—for example, presence and magnitude of left-ventricular hypertrophy in the anterolateral free wall,[14,15,59] apex,[14,16] or posterior septum (figure 2D),[14] and identification of high-risk apical aneurysms (figure 2F)[57] as well as determinants of subaortic obstruction—eg, elongated or enlarged mitral valves[38] or accessory and displaced hypertrophied papillary muscles (including anomalous insertion of papillary muscle into the mitral valve).[60]

In patients with hypertrophic cardiomyopathy, absolute left-ventricular wall thickness ranges widely from mild (13–15 mm) to massive (>50 mm).[4,7,14,41,61] In some cases, the magnitude of hypertrophy is the most substantial noted in any cardiac disease,[61] with thickness usually predominant at the confluence of the anterior septum and anterior free wall.[14] Many asymmetrical patterns of left-ventricular hypertrophy have been observed, including non-contiguous areas of hypertrophy (interrupted by regions of normal wall thickness; figure 2E).[14,41] Although diffuse left-ventricular wall thickening is evident in about 50% of patients (figure 2A), an important minority (10–20%) have segmental hypertrophy confined to small portions of the chamber (figure 2B),[14,41] and with normal left-ventricular mass by MRI.[62] Moreover, patients with hypertrophic cardiomyopathy may have unusual patterns of hypertrophy (eg, apical hypertrophy; figure 2C), which is associated with giant T-wave inversion on ECG and is typically caused by sarcomere mutations.[63,64] Truly symmetrical (concentric) left-ventricular hypertrophy is very rare.[14,41]

Occasionally, extreme expressions of physiological athlete's heart may result in left-ventricular wall thickness

measurements that overlap with hypertrophic cardiomyopathy and mild hypertrophy.[61,65] This differential diagnosis can be resolved by non-invasive testing, including regression of hypertrophy after deconditioning, or possibly by genetic testing (table).[46,65] Mass screening with ECGs has been suggested as a means to identify hypertrophic cardiomyopathy in populations of healthy young athletes.[66] Although ECGs are abnormal in 75–95% of patients with hypertrophic cardiomyopathy,[10,67,68] this strategy is limited by overlap with physiological ECG alterations (false positives) and by normal or near-normal ECGs in 10% of patients with hypertrophic cardiomyopathy (false negatives).[69]

Hypertrophic cardiomyopathy genotype without left-ventricular hypertrophy

Integration of commercial genetic testing into cardiovascular clinical practice has facilitated recognition of a subset of family members who have sarcomeric mutations but who do not have left-ventricular hypertrophy (although ECGs are abnormal in 50%).[70,71] These gene-positive phenotype-negative individuals expand the clinical spectrum of hypertrophic cardiomyopathy and show that any left-ventricular wall thickness can be consistent with this inherited cardiac disease.[70,71] Nevertheless, non-hypertrophied left-ventricular myocardium in such patients may show a variety of abnormalities—ie, myocardial fibrosis by contrast-enhanced MRI,[72] collagen biomarkers,[73] mitral leaflet elongation,[38] subclinical diastolic dysfunction,[70] blood-filled myocardial crypts,[74,75] and ECG abnormalities.[71]

At present, we do not know whether gene-positive phenotype-negative individuals are at risk of sudden death or disease progression[71] (although two such adults with cardiac arrest have been reported),[76] or even what proportion will eventually develop left-ventricular hypertrophy. Currently, decisions about disqualification from competitive sports participation[77] or prophylactic implantable defibrillators[71] are usually resolved on a case-by-case basis, although competitive sports are permitted by a US consensus panel.[77] This emerging subset of patients needs much longer follow-up before consistent management guidelines can be formulated.

Family screening

Clinical surveillance with 2D echocardiography and 12-lead ECG is recommended at intervals of 12–18 months for all relatives (age 12–18 years) of affected individuals, apart from those confirmed as genetically unaffected (panel 1).[78] Cardiovascular MRI should also be considered for routine family screening, particularly if echocardiography is equivocal, because of its superior recognition of left-ventricular hypertrophy.[14,59] Screening in pre-adolescence (or at more frequent intervals) is recommended when family history is characterised by severe disease, participation in intense competitive sports is anticipated, or early-onset disease is suspected.[47,78]

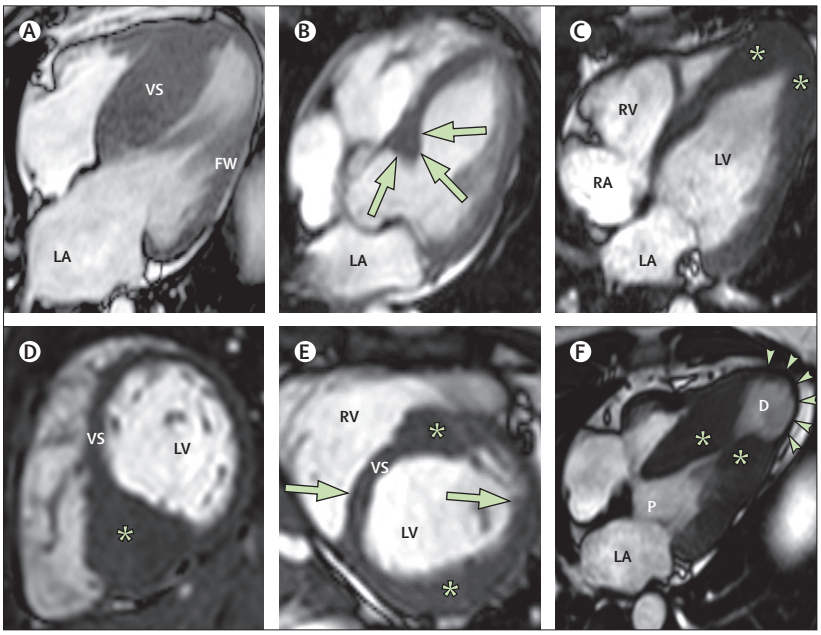

Figure 2: **Cardiovascular MRIs depicting the hypertrophic cardiomyopathy phenotype**
Diverse patterns of asymmetric left-ventricular hypertrophy. (A) Diffuse involvement of ventricular septum, but left-ventricular free wall is spared. (B) Focal area confined sharply to the basal anterior septum (arrows). (C) Localised to apex of the left ventricle (asterisks). (D) Extreme thickness of 33 mm restricted to posterior ventricular septum (asterisk). (E) Non-contiguous segmental areas of hypertrophy involving the basal anterior septum and posterior free wall (asterisks) separated by regions of normal left-ventricular thickness (arrows). (F) Mid-ventricular hypertrophy, with muscular apposition of hypertrophied septum and left-ventricular free wall (asterisks), produces distinct proximal (P) and distal (D) chambers associated with thin-walled apical aneurysm (arrowheads). FW=free wall. LA=left atrium. LV=left ventricle. RA=right atrium. RV=right ventricle. VS=ventricular septum. (A–E) Reproduced from reference 14, with permission of Elsevier. (F) Reproduced from reference 57, with permission of the American Heart Association.

Because delayed conversion to left-ventricular hypertrophy is possible at virtually any age,[10,28,44] continued imaging in some adults (at 5-year intervals) into mid-life could be prudent.[28,44,78]

Natural history and clinical course

Hypertrophic cardiomyopathy is perhaps unique among cardiovascular diseases, with presentation at any age from infancy to old age.[2,4,7,28–30,34,44,79–82] A growing number of children with sarcomeric hypertrophic cardiomyopathy are being identified with phenotypic expression at a young age (<10 years, including in infancy) and adults are surviving to advanced ages (>80 years).[80,81] Many patients with hypertrophic cardiomyopathy achieve normal life expectancy with little or no disability[4,7,28,80,81] and without the need for major therapeutic interventions.[24,80,81,83–86]

Historical misconceptions about the clinical course of hypertrophic cardiomyopathy derive from an era when skewed referral patterns to selected tertiary centres (eg, National Institutes of Health, Bethesda, MD, USA, and St George's Hospital, London, UK) resulted in overestimates of mortality, up to 6% annually.[7,47,87] Clinically stable low-risk patients (or those of advanced age) were under-represented in those cohorts, promoting the myth that hypertrophic cardiomyopathy is a generally

	Pathological left-ventricular hypertrophy (hypertrophic cardiomyopathy)	Physiological left-ventricular hypertrophy (athlete's heart)
Focal pattern of left-ventricular hypertrophy	+	0
Left-ventricular cavity <45 mm	+	0
Left-ventricular cavity >55 mm	0	+
Left atrium enlargement	+	0
Bizarre ECG patterns	+	+
Abnormal left-ventricular filling	+	0
Family history of hypertrophic cardiomyopathy	+	0
Decreased thickness with deconditioning	0	+
VO_2 increase >110%	0	+
Late gadolinium enhancement	+	0
Pathogenic sarcomere mutation	+	0

ECG=electrocardiogram. VO_2=peak oxygen consumption. +=present. 0=absent. Modified from reference 65, with permission of the American Heart Association.

Table: **Distinguishing hypertrophic cardiomyopathy from athlete's heart when left-ventricular hypertrophy is within the grey zone of overlap (thickness, 13–15 mm in males and 11–12 mm in females)**

Panel 1: **Proposed family screening clinical strategies with echocardiography or cardiovascular MRI (and 12-lead ECG) for detection of hypertrophic cardiomyopathy phenotype***

At age <12 years

Screening optional unless:

- Either a malignant family history of premature death from hypertrophic cardiomyopathy is known or other adverse complications are present
- Child is a competitive athlete in an intensive training programme
- Onset of symptoms
- Other clinical suspicion of early left-ventricular hypertrophy has been noted

At age 12–21 years†

Screening should be performed every 12–18 months

At older than 21 years

Imaging should be performed either at onset of symptoms or possibly at 5-year intervals (at least through mid-life); more frequent intervals are appropriate in families with a malignant clinical course or history of late-onset hypertrophic cardiomyopathy

*In family members who have not undergone genetic testing or in whom testing was unresolved or indeterminant. †Age range takes into consideration individual variability in reaching physical maturity; in some patients, screening might be justified at an earlier age, but initial assessment should take place no later than early pubescence. Modified from reference 78, with permission of Elsevier.

unfavourable disease[7,88] and creating unnecessary anxiety for many patients, even impairing their ability to secure health and life insurance benefits.

Over the past decade, a more balanced and comprehensive understanding of the natural history of hypertrophic cardiomyopathy has emerged, based on less selected cohorts. Mortality rates are more realistic than previously reported (about 1% per year) and do not differ significantly from those expected in the general US adult population.[7,29,34,80] This is a paradigm shift from the earlier unfavourable perceptions of hypertrophic cardiomyopathy,[7,88] a disease now amenable to contemporary treatment interventions that restore quality of life and opportunities for advanced longevity.[6,83,84,89]

Nevertheless, complications attributable to hypertrophic cardiomyopathy may progress in individual patients along one or more pathways (figure 3). First, sudden death usually occurs in asymptomatic or mildly symptomatic patients.[4,6,7,47,83,84,88] Second, progressive heart failure with preserved systolic function with or without outflow obstruction may develop,[4,7,86,88] and occasionally evolve to systolic dysfunction (end-stage hypertrophic cardiomyopathy).[43] Third, atrial fibrillation with risk for progressive heart failure symptoms and embolic stroke occurs in 20% of patients.[90,91]

Sudden death

Epidemiology and pathophysiology

Sudden death is the most visible, devastating, and unpredictable consequence of hypertrophic cardiomyopathy,[1,2,4,6,7,25,34,61,88,92–96] although it is relatively infrequent within the vast disease spectrum (about 5% in hospital-based populations).[24,34,92] Nevertheless, hypertrophic cardiomyopathy is the most common cause of sudden death in young people, with particular predilection for children and young adults (age <30 years),[6,7,34,79,83,84,92,93] although risk does not differ by sex.[29] Sudden death risk extends into mid-life but at a lower rate[33] and is significantly less common in patients 60 years or older (even in the presence of risk markers), suggesting that ageing mitigates the potential for lethal ventricular tachyarrhythmias in hypertrophic cardiomyopathy.[45] In older patients, morbidity and mortality is largely unrelated to hypertrophic cardiomyopathy, but more frequently due to other cardiac or non-cardiac comorbidities.

Sudden death is frequently the first clinical manifestation of hypertrophic cardiomyopathy, occurring without warning signs or symptoms.[4,6,7,47,94] Although most events are associated with mild exertion or sedentary activities (including sleep), sudden death with vigorous physical exertion is common, and hypertrophic cardiomyopathy is the most frequent cause of sudden death in US competitive athletes.[93]

Analysis of stored electrograms from implantable defibrillators shows the mechanism of sudden death in patients with hypertrophic cardiomyopathy is primary ventricular tachycardia and ventricular fibrillation.[6,83,84,94,95,97,98] The unstable electrophysiological substrate that leads to lethal ventricular tachyarrhythmias probably derives from

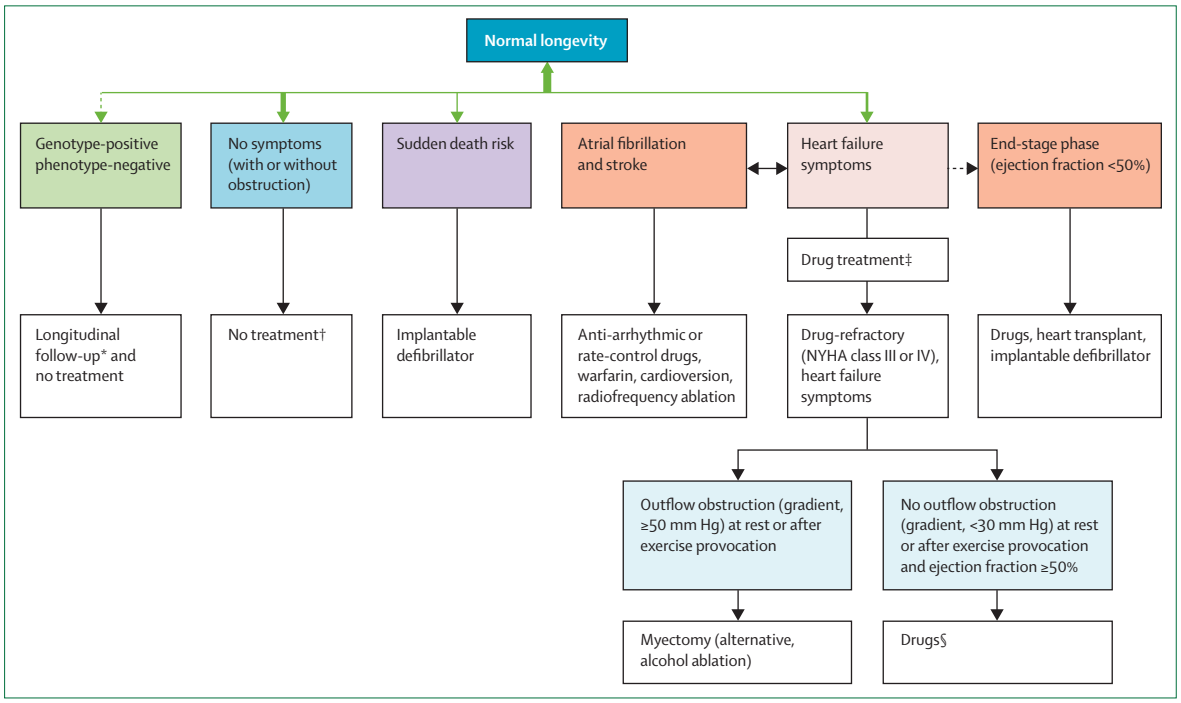

Figure 3: **Prognostic pathways and primary treatment strategies for various presentations of hypertrophic cardiomyopathy**
Adverse pathways are not necessarily mutually exclusive; patients might progress into more than one subset. Thickness of coloured arrows represents the proportion of patients affected for every pathway. NYHA=New York Heart Association. *Patients identified as genotype-positive phenotype-negative most typically develop morphological conversion to left-ventricular hypertrophy during adolescence. †No data on benefit of drug treatment in asymptomatic patients, although in clinical practice, β blockers or calcium-channel blockers are sometimes administered prophylactically. ‡Usually β blockers and calcium-channel blockers, occasionally disopyramide, and possibly diuretics (administered judiciously). §An occasional patient in this subgroup requires heart transplantation due to severe diastolic dysfunctions.[43]

characteristic histopathological features. For example, cellular architecture is disorganised, with sizeable areas of the left ventricle comprised of myocytes arranged at perpendicular and oblique angles.[99] Second, replacement myocardial fibrosis results from bursts of silent microvascular ischaemia, which lead to cell death.[100,101] Third, an increased extracellular volume of interstitial fibrosis is possibly arrythmogenic.[102]

Risk-stratification guidelines

The complex aim to identify patients with hypertrophic cardiomyopathy who are at highest risk of sudden death has spanned much of five decades. This initiative is now of particular importance in view of the availability and known efficacy of implantable defibrillators for sudden death prevention. A primary prevention risk-stratification model, based on non-invasive clinical markers (most applicable to patients younger than 50 years),[6,7,25,61,96,103] identifies most patients with hypertrophic cardiomyopathy who are likely to benefit from an implantable defibrillator (panel 2).[6,83,84] There is no dispute over use of defibrillators for secondary prevention—ie, implants after cardiac arrest or sustained ventricular tachycardia.[6,7,47]

For primary prevention, multiple risk factors intuitively convey the greatest sudden death risk.[6,83,92,98] However, data in high-risk patients present compelling evidence that a single strong risk marker within the clinical profile of an individual patient is often sufficient to raise the option of a primary prevention defibrillator.[6,83,84,98,104] Indeed, patients with an implantable defibrillator who had one risk factor for sudden death were as likely to receive an appropriate intervention for ventricular tachycardia and ventricular fibrillation as were those with two or three risk markers.[84] Moreover, 35% of all discharges from implantable defibrillators were in patients who had only one risk marker for sudden death (most commonly syncope).[84] Practice patterns and selection of patients for implantable defibrillators differs internationally, with European cardiologists being more conservative and often requiring more than one risk factor for implantation.

Not uncommonly, decisions about prophylactic implantable defibrillators can be ambiguous (a grey zone) for patients in whom risk level remains uncertain after assessment with conventional markers;[6,84] however, other features of hypertrophic cardiomyopathy can be used to arbitrate on a case-by-case basis (panel 2, figure 4). For example, left-ventricular apical aneurysm with regional scarring (figure 2F),[57] striking left-ventricular outflow obstruction at rest,[105,106] and co-existent atherosclerotic coronary artery disease[107] can help arbitrate difficult defibrillator decisions.

Late gadolinium enhancement on contrast-enhanced MRI (a marker for myocardial fibrosis; figure 4E), has been linked to the electrophysiological substrate in hypertrophic

Panel 2: **Risk factors for sudden death**

Secondary prevention
- Cardiac arrest or sustained ventricular tachycardia

Conventional primary prevention risk markers
- Family history of sudden death due to hypertrophic cardiomyopathy
- Unexplained recent syncope
- Multiple repetitive non-sustained ventricular tachycardia (on ambulatory ECG)
- Hypotensive or attenuated blood pressure response to exercise
- Massive left-ventricular hypertrophy (thickness, ≥30 mm*)
- Extensive and diffuse late gadolinium enhancement

Potential high-risk subsets for primary prevention
- End-stage phase (ejection fraction <50%)
- Left-ventricular apical aneurysm and scarring

Potential arbitrators for primary prevention†
- Substantial left-ventricular outflow gradient at rest
- Alcohol septal ablation
- Multiple sarcomere mutations
- Modifiable
  - Intense competitive sports
  - Coronary artery disease

*Or the equivalent in children according to body size. †To arbitrate decision-making about implantable defibrillators in patients for whom risk level remains ambiguous after assessment by the conventional risk factor algorithm. ECG=electrocardiogram. Modified from reference 6, with permission of the American Heart Association.

cardiomyopathy by association with ventricular tachyarrhythmias on ambulatory (Holter) ECG.[108] More recently, extensive distribution of late gadolinium enhancement (≥20% of left-ventricular myocardium) on contrast MRI identifies a subgroup of patients with hypertrophic cardiomyopathy in whom sudden death risk is increased (even in the absence of traditional risk markers) and in whom prophylactic defibrillators should be considered.[109] Furthermore, extensive gadolinium enhancement can also act as a potential arbitrator for decisions about prophylactic defibrillators in patients for whom risk level is otherwise uncertain.[109] Engagement in intense competitive sports is judged a modifiable risk factor for sudden death, even without other markers,[65,93] and disqualification can reduce this risk.[77,110]

The many ECG patterns recorded in hypertrophic cardiomyopathy fail to reliably predict prognosis. However, normal ECGs are generally associated with a less severe phenotype and favourable outcome.[68] T-wave alternans or coronary arterial bridging are not reliable risk predictors.[111] Electrophysiological testing (programmed ventricular stimulation) while directly probing myocardial electrical properties has been abandoned—as part of risk stratification in hypertrophic cardiomyopathy—as irrelevant to the clinical arrhythmia environment.

The risk-factor algorithm used in hypertrophic cardiomyopathy is incomplete, as shown by infrequent sudden deaths in patients judged clinically not to be at high risk (about 0·5% a year).[6,92,94] Recognition that low-risk individuals might, nevertheless, die suddenly underscores the aspiration to identify additional, or one dominant quantitative marker of risk (similar to ejection fraction in coronary artery disease). Primary prevention risk factors used successfully in adults with hypertrophic cardiomyopathy cannot always translate easily to children,[61,79] particularly non-sustained ventricular tachycardia.[103]

Prevention of sudden death

Risk of sudden death is not mitigated by pharmacological strategies,[112] including rhythm-modulating drugs such as amiodarone, an agent unlikely to be tolerated because of potential toxic effects over the long periods requiring protection in young patients. Prophylactic administration of β blockers to young asymptomatic patients (sometimes in high doses) to reduce risk of sudden death is an obsolete strategy unsupported by evidence and a remnant of the era before implantable defibrillators.

The implantable defibrillator has been used in patients with hypertrophic cardiomyopathy over the past 10 years[83] and is now established as the most effective treatment for high-risk patients. It is the only strategy capable of prolonging life and altering the natural history of hypertrophic cardiomyopathy due to its potential to reliably abort lethal ventricular tachyarrthymias.[83,84,113] An international multicentre registry included more than 500 patients with hypertrophic cardiomyopathy judged high risk for sudden death.[84] Defibrillators implanted at a mean age of 42 years, usually in patients with no or mildly limiting symptoms, terminated ventricular tachycardia and ventricular fibrillation and restored sinus rhythm in 20% (at an average of 44 years), including those with a substantial increase in left-ventricular mass or outflow-tract obstruction. The rate of appropriate device interventions was 11% per year for secondary prevention and 4% per year for primary prevention. Other independent reports from Spain, Poland, Canada, Portugal, the UK, Germany, Australia, Italy, and the USA show similar effectiveness for the implantable defibrillator in patients with hypertrophic cardiomyopathy. Furthermore, defibrillator intervention rates are similar in children and adolescents, with massive left-ventricular hypertrophy the predominant risk factor associated with sudden death events in this age-group. The significant rate of device complications make implantable defibrillator decision-making complicated in young hypertrophic cardiomyopathy patients.

One exception to the efficacy of implantable defibrillators is in patients with the LAMP2 phenotype and massive left-ventricular hypertrophy, which usually proves refractory to defibrillation.[52] Although successful radiofrequency ablation for monomorphic ventricular

tachycardia has been reported,[114] this method is used rarely in patients with hypertrophic cardiomyopathy.

Unpredictability of the electrophysiological substrate in patients with hypertrophic cardiomyopathy is underscored by the observation that appropriate interventions by defibrillators can be delayed for prolonged periods after implant (eg, 5–10 years).[83,84,97,98] Moreover, this largely random timing of implanted defibrillator shocks[95] suggests that a home use external defibrillator strategy will probably be ineffective. There is no evidence that therapy from an implantable defibrillator in patients with hypertrophic cardiomyopathy merely shifts the mode of demise from sudden death to refractory heart failure, as suggested in patients with coronary artery disease.[97]

Inevitably, clinical dilemmas arise concerning prophylactic use of implantable defibrillators when risk level cannot be assessed with precision by the risk-stratification model and when gaps in knowledge and definitive data exist.[6,47] Resolution depends on transparency, full disclosure, and informed consent associated with judgment of the individual cardiologist, and autonomous input from patients who are fully aware of the potential for preservation of life versus possible device complications (and have carefully weighed both possibilities). Industry-related problems with implantable defibrillators have disproportionally affected patients with hypertrophic cardiomyopathy, with recalls of defective generators and small-diameter high-voltage leads prone to fracture both resulting in substantial morbidity and even death.[115]

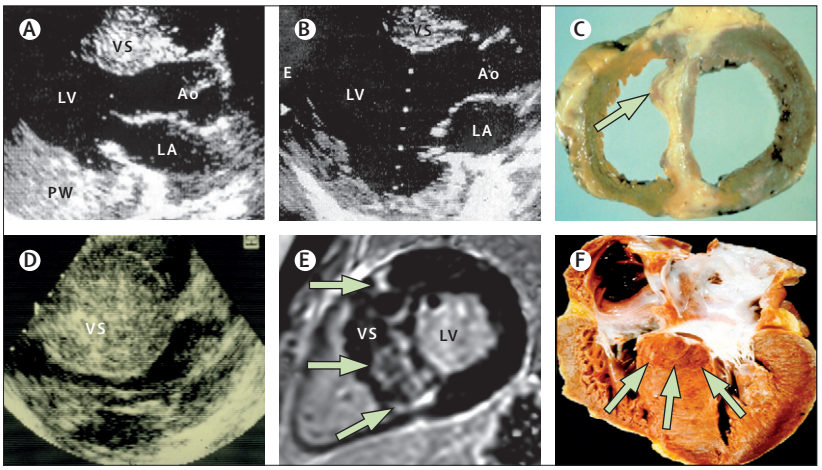

Figure 4: **Adverse outcomes in hypertrophic cardiomyopathy**
(A–C) End-stage hypertrophic cardiomyopathy. (A) Parasternal long-axis echocardiographic image in a man age 37 years at baseline, showing hypertrophied ventricular septum and left-ventricular posterior wall, reduced cavity size, and normal ejection fraction. (B) Same patient shown with subsequent conversion to end-stage disease and systolic dysfunction, septal and free-wall thinning, and left-ventricular cavity enlargement. (C) Explanted heart from a 52-year-old man in the end stage showing extensive transmural scarring throughout the ventricular septum and extending into the free wall; residual segmental area of septal hypertrophy (arrow). (D) Massive asymmetric left-ventricular hypertrophy (ventricular septal thickness of 55 mm) in a 23-year-old man. (E) Contrast-enhanced MRI in a high-risk 32-year-old man, showing transmural late gadolinium enhancement (a marker of myocardial fibrosis) in the ventricular septum (arrows) associated with multiple bursts of non-sustained ventricular tachycardia on ambulatory electrocardiogram monitoring. (F) Post-mortem heart from a 46-year-old woman who developed ventricular tachyarrythmias and died suddenly after percutaneous alcohol septal ablation, which produced a large transmural infarction of the basal septum (arrows). Ao=aorta. LA=left atrium. LV=left ventricle. PW=posterior wall. RV=right ventricle. VS=ventricular septum.

Heart failure

Presentation

Symptoms related to heart failure, which are associated with preserved left-ventricular systolic function (ie, exertional dyspnoea), can arise at virtually any age, but most frequently in middle-aged adults.[2,4,7,29,47,86,88,116] Evolution to severe progressive heart failure disability (ie, New York Heart Association [NYHA] functional classes III or IV) represents a relatively small but important subset of patients, comprising 10–20% of an unselected hospital-based cohort.[2,4,7,29,47,88] Previous characterisation of hypertrophic cardiomyopathy as a relentless progressive disease throughout life is no longer tenable.[89] Functional limitation can evolve at varying rates but is often gradual, punctuated by long periods of relative stability or substantial day-to-day variability. A difference by sex is recognised, with women having more severe symptoms of heart failure occurring later in life than men, and frequently associated with left-ventricular outflow-tract obstruction.[29] B-type natriuretic peptide assays have limited value in hypertrophic cardiomyopathy for prediction of heart-failure symptoms or outcome.[117]

Heart failure with outflow obstruction

Determinants of heart failure in patients with hypertrophic cardiomyopathy include left-ventricular outflow obstruction (figure 5),[106,118] atrial fibrillation,[90,91] and diastolic dysfunction,[119] although left-ventricular wall thickness is not predictive of progressive symptoms.[120]

Outflow-tract gradients of 30 mm Hg or more under resting conditions (measured by continuous-wave doppler) are independent determinants of symptoms of progressive heart failure and death.[106,118] This mechanical impedance to outflow is produced by systolic anterior motion of either the anterior[121] or posterior leaflet[122] but occasionally by mid-cavity muscular apposition from papillary muscle insertion directly into the anterior mitral leaflet.[60] Notably, outflow gradients in patients with hypertrophic cardiomyopathy are dynamic, characterised by spontaneous variability on a day-to-day (or even hourly) basis, and are affected by various factors that alter left-ventricular contractility and loading, including dehydration, ingestion of alcohol, or heavy meals.[1,23,123]

Exercise (stress) echocardiography is the preferred method for provoking outflow-tract gradients in patients with hypertrophic cardiomyopathy.[35] Historically, pharmacological agents (eg, amyl nitrite, dobutamine, or isoproterenol [rINN isoprenaline]) or the Valsalva manoeuvre were used to induce outflow-tract gradients in patients without obstruction at rest.[1] However, concern that such non-physiological approaches may not accurately reflect the degree of outflow obstruction generated during day-to-day physical activities (when symptoms are provoked)[35] has reduced their role to

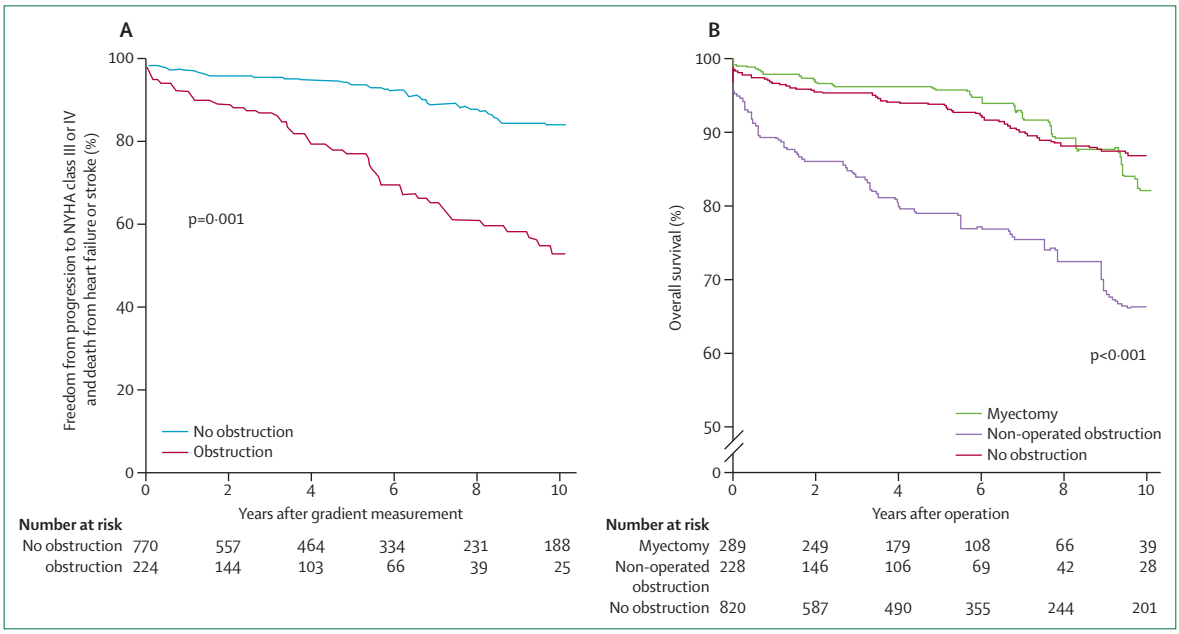

Figure 5: **Clinical importance of left-ventricular outflow-tract obstruction in hypertrophic cardiomyopathy**
(A) Kaplan-Meier estimates show greater probability of progression to severe heart failure (NYHA functional class III or IV) and death from heart failure or stroke in patients with outflow obstruction (gradient, ≥30 mm Hg at rest). Reproduced from reference 104, with permission of the Massachussets Medical Society. (B) Abolition of left-ventricular outflow gradient by surgical septal myectomy has a survival rate similar to that of non-obstructive patients (and that expected in the general US population) but greater compared to non-operated obstructive patients. Reproduced from reference 86, with permission of Elsevier.

selected circumstances in which uncertainty persists after exercise echocardiography.

When exertional heart failure symptoms intervene in patients with outflow obstruction, the first option is pharmacological treatment with β blockers or verapamil.[2,4,7,47] Verapamil should, however, be avoided in those with substantial resting obstruction and particularly advanced heart failure. Disopyramide is the only drug used in hypertrophic cardiomyopathy with the potential for reducing outflow gradients at rest and has been proposed as an alternative strategy to control symptoms.[124] Although there is no evidence that β blockers or verapamil reliably suppress outflow gradients at rest, β blockers can mitigate exercise-provoked gradients.[1,125]

Outflow obstruction and septal reduction intervention

For patients with symptoms of advanced limiting heart failure that are refractory to medical management, and associated with an outflow gradient of 50 mm Hg or more (at rest or with physiological provocation), surgical septal myectomy[126] has repeatedly been judged the preferred treatment option on the basis of expert consensus and guideline recommendations.[7,47] Indeed, findings of long-term studies from the past 40 years[19,26,47,86,126–130] show hypertrophic cardiomyopathy-related heart failure to be reversible with: permanent abolition of mechanical obstruction to left-ventricular outflow and normalisation of intraventricular pressures, reduction in mitral regurgitation, relief of symptoms with substantially improved quality of life (usually to NYHA class I), and extended longevity with postoperative survival similar to that in the general population (figure 5). Notably, operative mortality at surgical centres is now low, reduced to less than 1%.[19,86,128,129]

Percutaneous alcohol septal ablation is an alternative to surgical myectomy, which can reduce the left-ventricular outflow gradient and symptoms in many patients (but to a lesser degree than myectomy in some studies).[17,22,24,47,85,130–135] However, myectomy and alcohol ablation are very different treatment interventions, because alcohol ablation creates a large septal infarct (usually transmural, occupying about 10% of the left ventricle) by infusion of absolute alcohol into the first major septal perforator artery (figure 4F).[17] By contrast, myectomy entails resection of a small amount of muscle from the basal septum, without producing intramyocardial scarring.[17]

In addition to a procedural mortality of about 2%,[22,131,133,135] alcohol ablation is also associated with a 10–20% likelihood of permanent pacemaker implantation for heart block. A relatively small, but not inconsequential, risk of life-threatening ventricular tachyarrhythmias (and sudden death) is present, attributable to the septal scar,[6,22,24,47,84,85,131–133] although criteria for selection of patients for post-procedural defibrillator implant remains unresolved.[47]

Although myectomy is the primary treatment option for most patients with severe symptoms of obstructive hypertrophic cardiomyopathy, alcohol ablation has been recommended as a selective alternative for older patients, those with comorbidities, or patients with an absolute

reluctance toward surgery.[7,47] However, practice patterns have evolved in different directions internationally, with surgical myectomy the preferred treatment in the USA and Canada, but discarded in much of Europe in favour of alcohol ablation.[127] A randomised trial to assess myectomy versus ablation is impractical due largely to the infrequency of hypertrophic cardiomyopathy in cardiovascular practice.[20]

Dual-chamber pacing—initially promoted with enthusiasm—was abandoned as a primary treatment option when data emerged from randomised, double-blind, crossover trials that a patient's perceived benefit was probably accounted for as a spurious placebo effect.[136] Experts in hypertrophic cardiomyopathy continue to favour antimicrobial prophylaxis for bacterial endocarditis before dental procedures, particularly in patients with outflow obstruction.[137,138]

Heart failure without outflow obstruction

At least a third of patients with hypertrophic cardiomyopathy have the non-obstructive form of the disease, with no or very small outflow gradients (<30 mm Hg) both at rest and with exercise.[35] Some patients in this haemodynamic subset have exertional dyspnoea (with preserved systolic function), largely as a result of diastolic dysfunction,[119] and management strategies are largely restricted to drugs (eg, β blockers, verapamil, or diuretics).[2,7,47] However, diastolic function is difficult to assess clinically in hypertrophic cardiomyopathy since non-invasive measures do not reflect left-ventricular filling pressures reliably.[139] At present, it appears that most patients with non-obstructive hypertrophic cardiomyopathy probably do not develop severe progressive heart failure during their clinical course (figure 5B).

The most advanced form of heart failure is end-stage (or "burned out") hypertrophic cardiomyopathy, which arises in a small distinct subset of patients with non-obstructive disease (prevalence 3%).[43,116] Progression of heart failure is associated with conversion to systolic dysfunction (ejection fraction <50%) and a remodelling transformation from a typical hypertrophied non-dilated and hyperdynamic left ventricle to regression of hypertrophy or cavity enlargement, or both, which can mimic dilated cardiomyopathy (figure 4A–C). The end-stage disease phase is attributable to an irreversible process of extensive (transmural) replacement scarring, presumably due to microvascular ischaemia,[40,43] evident after explant or at autopsy[43,116] or detectable by contrast-enhanced MRI as late gadolinium enhancement. Patients with borderline or low-to-normal ejection fraction (50–60%) and substantial late gadolinium enhancement could be in transition to end-stage disease.[140] The only known predictor of end-stage hypertrophic cardiomyopathy is a family history of end-stage disease.[43]

The clinical course of end-stage hypertrophic cardiomyopathy is variable and unpredictable, with some patients remaining well compensated (even asymptomatic) for many years after systolic dysfunction arises.[43] Although treatment with β blockers, diuretics, afterload-reducing agents, and prophylactic implantable defibrillators (and possibly biventricular pacing) are prudent treatment options, heart transplantation is the only definitive therapeutic option as a last resort (undertaken at a mean age of 43 years).[141] Survival of patients with hypertrophic cardiomyopathy after heart transplantation (75% at 5 years, 60% at 10 years) is similar to or possibly more favourable than that for patients with other cardiovascular diseases.[141] Left-ventricular assist devices can be effective as a bridge to transplantation in end-stage patients.[142] Occasionally, patients with non-obstructive hypertrophic cardiomyopathy and preserved systolic function can develop severe refractory heart failure due to diastolic dysfunction and become candidates for heart transplantation.[43]

Chest pain

Patients with or without outflow obstruction may experience chest pain (in some cases similar to angina), usually associated with exertional dyspnoea but occasionally as the predominant symptom, which raise the possibility of obstructive atherosclerotic disease[107] or myocardial bridging.[111] Chest pain related to hypertrophic cardiomyopathy is possibly due to microvascular ischaemia,[39,40,100,143] and although challenging to manage, verapamil (or β blockers) can be effective.[40,47] No data are available in patients with hypertrophic cardiomyopathy with respect to novel drugs for angina (eg, ranolazine).

Atrial fibrillation

Atrial fibrillation is the most common sustained arrhythmia in hypertrophic cardiomyopathy, occurring in about 20% of patients, four times the proportion expected in the general population. Atrial fibrillation affects patients with hypertrophic cardiomyopathy by increasing the risk of heart-failure progression or embolic stroke (prevalence 6%, incidence 0·8% per year),[90,91] which is most substantial in patients with left-ventricular outflow obstruction.

Susceptibility to atrial fibrillation is linked to ageing and substantial left-atrial enlargement (usually ≥50 mm transverse dimension, greatly increased volume, or both).[90,91] Atrial fibrillation has not been associated consistently with (or explained by) other disease variables, eg, left-ventricular outflow obstruction or mitral regurgitation, or a particular genetic substrate.

Paroxysmal or chronic atrial fibrillation can account for frequent hospital visits and unscheduled work absence, with a substantial effect on quality of life.[90,91,144] However, no evidence is available to suggest that atrial fibrillation is an independent determinant of sudden death.[6,7,47,90] Infrequent episodes of atrial fibrillation, reversed by drugs and electrical or pharmacological cardioversion, are well tolerated by most patients and only occasionally trigger acute clinical decompensation.

Although there are no data specifically in hypertrophic cardiomyopathy defining the relative benefits of rate versus rhythm control, amiodarone is generally regarded as the most effective drug for controlling recurrences of atrial fibrillation,[47,90] although side-effects can limit use in this relatively young population. For paroxysmal or chronic atrial fibrillation, anticoagulation with the vitamin K antagonist warfarin is recommended, although newer oral agents are available (eg, dabigatran or rivaroxaban). Aspirin is only an alternative for patients in whom oral anticoagulation is contraindicated. The CHADS score[145] is not validated in hypertrophic cardiomyopathy, and the threshold number of atrial fibrillation episodes necessary to initiate anticoagulation remains unresolved. However, anticoagulation could be considered even in patients with only one episode, particularly in view of the high likelihood of recurrence of atrial fibrillation and risk of embolic stroke.[90,91]

Radiofrequency catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy is at a preliminary stage.[146] However, available data suggest that restoration of sinus rhythm and suppression of atrial fibrillation recurrence is achieved in about two-thirds of patients over 1–2 years and, therefore, is a therapeutic option in patients with drug-refractory symptomatic atrial fibrillation. Although data on the Maze procedure in hypertrophic cardiomyopathy are sparse, this approach is a reasonable consideration in patients with a history of atrial fibrillation undergoing surgical myectomy.

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BJM and MSM contributed equally to the writing of the text, construction of the figures and tables, and additional research for this Seminar.

Conflicts of interest

BJM has consulted for GeneDx and received grants from Medtronic and Genzyme. MSM has consulted for PGx Health and received grants from Genzyme.

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