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HYPERTROPHIC CARDIOMYOPATHY: MANAGEMENT, RISK STRATIFICATION, AND PREVENTION OF SUDDEN DEATH

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William J McKenna, Elijah R Behr

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Hypertrophic cardiomyopathy (HCM) is an inherited cardiac muscle disorder disease that affects sarcomeric proteins, resulting in small vessel disease, myocyte and myofibrillar disorganisation, and fibrosis with or without myocardial hypertrophy. These features may result in significant cardiac symptoms and are a potential substrate for arrhythmias. Before the identification of disease causing genes the World Health Organization defined HCM as the presence of left or biventricular hypertrophy in the absence of any cardiac or systemic cause.^{w1} When these criteria are applied to a western population the estimated prevalence of HCM is approximately 1 in 500.^{1 w2} Morphological evidence of left ventricular hypertrophy, however, may be absent in up to 20% of gene carriers.^{w3} Adults are often asymptomatic but their estimated mortality rate may nonetheless be as high as 1–2% per annum.^{2 w4} This article will present the natural history of HCM and relate it to the need for medical intervention to alleviate symptoms and prevent sudden death.

NATURAL HISTORY AND PROGNOSIS

The expression of disease is age related, occurring during or soon after periods of rapid somatic growth. Detectable cardiovascular abnormalities usually develop during adolescence.^{w5} For this reason the regular evaluation of the offspring of carriers during puberty and early adulthood is necessary for diagnosis and risk stratification. HCM has been described in infants and young children but data are limited. Children diagnosed before 14 years of age have a worse prognosis once they reach adolescence and early adulthood with a 2–4% annual incidence of sudden death.³ The development of clinical features of HCM in the elderly is associated with myosin binding protein C (MyBPC) mutations.^{w6} Although MyBPC disease appears benign in that presentation is in the later decades, once disease develops patients are at risk of all the recognised complications of HCM including arrhythmia, stroke, and sudden death.^{w7} A subanalysis of data from patients who had received an implantable cardioverter-defibrillator (ICD) indicated a higher proportion of individuals (40–50%) undergoing defibrillation in the age groups 11–20 years and > 55 years compared to the 21–55 years range.⁴ Aggressive management in these higher risk age groups may therefore be required.

In adults, left ventricular hypertrophy caused by mutations in genes other than MyBPC is not progressive and in the majority is usually benign in its clinical course. Most affected individuals go unrecognised and are asymptomatic or experience only paroxysmal manifestations.^{w8} Chronic exertional symptoms such as chest pain and dyspnoea can be secondary to myocardial ischaemia (table 1), diastolic dysfunction and/or congestive cardiac failure, and tend to deteriorate slowly with age. The classical pattern of asymmetric septal hypertrophy (ASH) may be accompanied by systolic anterior motion of the mitral valve (SAM) and dynamic left ventricular outflow tract (LVOT) obstruction that can also cause exertional symptoms of impaired consciousness, dyspnoea, and chest pain. A subset of patients, however, who represent < 5% of the total, exhibit progressive symptomatic deterioration in left ventricular systolic function with myocardial thinning and dilatation.⁵ This is usually accompanied by the development of systolic cardiac failure. The severity of symptoms and exercise limitation caused by obstruction and/or cardiac dysfunction will dictate symptomatic management while the presence of arrhythmias and abnormal vascular responses will influence the need for prevention of sudden death. The risk of stroke secondary to atrial fibrillation (AF) must also be considered.

MECHANISMS OF CARDIAC ARREST

Fortuitous observations have recorded several mechanisms for the generation of ventricular fibrillation (VF). These include paroxysmal AF, sinus tachycardia with abnormal vascular responses and/or myocardial ischaemia, sustained monomorphic ventricular tachycardia (VT), rapid atrioventricular (AV) conduction via an accessory pathway, and AV block. Recent data have reported that appropriate discharges by ICDs (that is, probable aborted sudden death) were related to the occurrence of monomorphic VT, VF preceded by VT, and VF alone.⁶ ICD Holter data, however,

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Table 1 Possible mechanisms for myocardial ischaemia in HCM

Increased myocardial oxygen demand	Reduced myocardial perfusion
Myocardial hypertrophy	Small vessel disease
Diastolic dysfunction	Abnormal vascular responses
Myocyte disarray	Myocardial bridges
Left ventricular outflow obstruction	Increased coronary vascular resistance
Arrhythmia	

may not establish the importance of a trigger—for example, an abnormal vascular response or preceding ischaemia, in precipitating cardiac arrest. In the young this may be related to the haemodynamic changes of paradoxical vasodilatation in the presence of sinus tachycardia or primary atrial and ventricular arrhythmias. The development of a sustained ventricular arrhythmia would then represent a terminal event.^{6–9}

SYMPTOMATIC TREATMENT

The diagnosis of HCM relies on the demonstration of otherwise unexplained electrocardiographic (ECG) and two dimensional echocardiographic (echo) abnormalities (see accompanying article in this series, by Wigle *Heart* 2001;**86**:709–14). Echo is also of use in the assessment of diastolic and systolic dysfunction. The measurement of peak oxygen consumption during maximal upright exercise with continuous ECG and blood pressure monitoring facilitates symptomatic assessment of the HCM patient and provides an objective measure of functional limitation, vascular responses, and ischaemia. This helps to identify those patients with sub-clinical involvement and provides a useful objective correlate for subjective symptoms that may be particularly difficult to evaluate in young patients. The detection of a significant LVOT gradient either at rest or during exercise will guide symptomatic treatment (fig 1). Angiography is usually necessary to exclude coronary artery disease in older patients with chest pain or ECG abnormalities.

Obstructive HCM: medical treatment

β Blockers are the first line treatment in patients with LVOT obstruction. The majority of patients show improvement upon treatment although high doses are often required. Side effects, however, can limit utility as well as induce pharmacological chronotropic incompetence, blunting the heart rate response to exercise and causing symptomatic deterioration. Verapamil is best avoided in individuals with obstruction because of possible peripheral vasodilatation and haemodynamic collapse. Unfortunately much of the data on verapamil or β blockers is observational and uncontrolled.^{w10}

Disopyramide has been evaluated more systematically and is also effective in gradient and symptom reduction, probably because of negative inotropism.^{w11} It may have a superior effect on exercise tolerance compared to β blockers.⁷ They are, however, best used in combination as disopyramide alone tends to accelerate AV node conduction and increase the potential risk from supraventricular arrhythmias. Disopyramide should be administered in the maximum tolerated dose; the limiting factor is usually the anticholinergic side effects.

Obstructive HCM: non-medical treatment

Surgical septal myectomy remains the gold standard for those individuals with drug refractory symptoms and a resting gradient of ≥ 50 mm Hg. The aim is to widen the outflow

Abbreviations

AF, atrial fibrillation
ASH, asymmetric septal hypertrophy
AV, atrioventricular
HCM, hypertrophic cardiomyopathy
ICD, implantable cardioverter-defibrillator
LVOT, left ventricular outflow tract
MyBPC, myosin binding protein C
NSVT, non-sustained ventricular tachycardia
SAM, systolic anterior motion of the mitral valve
SVT, supraventricular tachycardia
VF, ventricular fibrillation
VT, ventricular tachycardia
WPW, Wolff-Parkinson-White

tract, eliminating systolic mitral leaflet septal contact. There is a success rate of $> 80\%$ that can be achieved with a perioperative mortality rate of 2% or less. Long term symptom relief is maintained in up to 70% of patients.^{8 w12} The operation should be tailored to the patient's anatomy including the severity of hypertrophy, the location and size of papillary muscles, and mitral valve anatomy. Mitral regurgitation can develop secondary to SAM and obstruction, and cause significant dyspnoea because of pulmonary oedema. The requirement for mitral valve surgery and/or myectomy needs to be individualised and can be guided by careful preoperative as well as intraoperative echocardiography.

Two other modalities have been developed for the treatment of LVOT obstruction: dual chamber pacing and alcohol septal ablation. The efficacy of pacing is controversial. Adult HCM patients were evaluated in randomised double blind trials of DDD or AAI pacing.^{9 w13} Gradient reduction during active DDD pacing was approximately 50%. No other differences in objective measures were detected between the two pacing modalities. While 60% felt better with DDD pacing, 40% experienced symptomatic improvement with the pacemaker effectively turned off.⁹ This suggested a substantial placebo effect.^{9 w14 w15}

Alcohol ablation in experienced hands is effective and safe.¹⁰ The technique involves injection of alcohol into the perforators of the left anterior descending coronary artery to cause a limited septal myocardial infarction.^{w16} This reduces septal hypertrophy and the associated obstruction.^{w16} Experienced centres are vital for good results as these are dependent on appropriate patient selection as well as good technique in order to ensure the delivery of alcohol is to the correct areas.^{w16} The extent of myocardial perfusion by septal vessels is variable and may include papillary muscles and wide areas of both ventricles. Accurate definition by contrast echo of the area perfused is vital to avoid diffuse myocardial damage, particularly to papillary muscles.

Non-obstructive HCM: medical treatment

Agents such as β blockers, verapamil, and diltiazem are used to treat chest pain and dyspnoea and improve exercise tolerance. The mechanism probably involves improvement of left ventricular diastolic function and myocardial ischaemia. The response can be suboptimal although those patients with severe chest pain often benefit from high doses of verapamil or diltiazem. Pulmonary congestion has been treated with diuretics but there is a risk of decompensation in individuals with severe diastolic dysfunction. Diuretics should only be used judiciously and if possible only in the short term, as

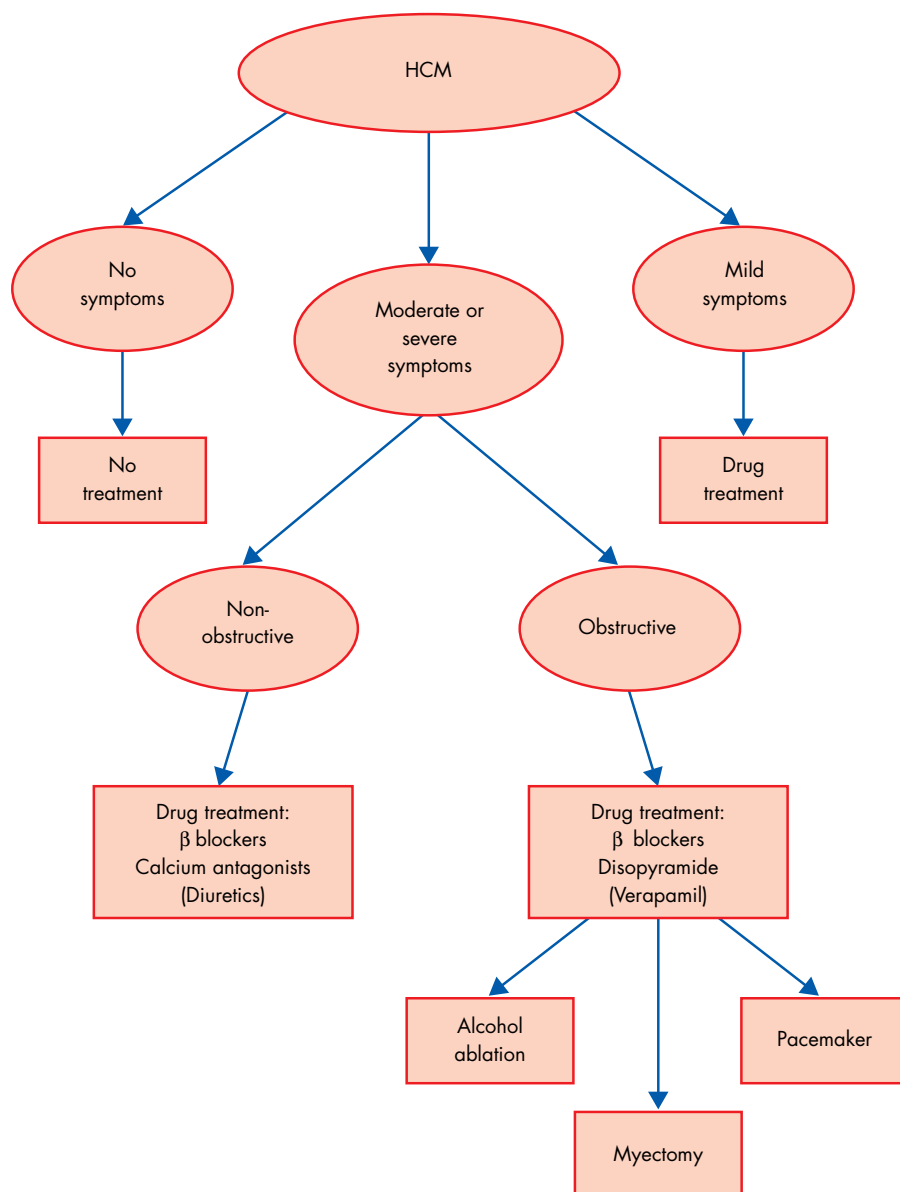


Figure 1 Algorithm for symptomatic treatment

chronic prescription tends to result in a reduction in stroke volume and cardiac output that ultimately lowers exercise capacity.^{w8}

The subset that develops systolic impairment should receive treatment for conventional cardiac failure, including angiotensin converting enzyme (ACE) inhibitors, β blockers, digoxin, spironolactone, and if necessary cardiac transplantation.

SUPRAVENTRICULAR ARRHYTHMIAS

Supraventricular arrhythmias are common in HCM. They are related to left atrial enlargement and fibrosis developing in the context of chronically elevated filling pressures as a consequence of obstruction, diastolic dysfunction, and/or mitral valve dysfunction.^{w8} Paroxysms of supraventricular tachycardia (SVT) and AF can be detected on Holter monitoring in up to 30% of adults, although the incidence in the young is closer to 5–10%. Sustained or symptomatic episodes are much less common and warrant treatment with amiodarone, which is

usually effective in reducing recurrences and attenuating the development of permanent AF.¹¹ The threshold for starting anticoagulation should be low to minimise embolic complications.^{w17}

Established AF is uncommon in the young, while in adults the prevalence can be up to 30%.¹¹ It is more common in elderly HCM patients and has been associated with a poorer overall prognosis, an enlarged atrial size, and increased risk of thromboembolism including stroke.^{6 11 w17 w18} Its onset is associated with an acute deterioration in symptoms that usually reverses with control of the ventricular response.¹¹ The long term outlook, with appropriate treatment to control heart rate and prevent emboli, is usually good.^{12 w17 w19} Repeated cardioversions to restore sinus rhythm are not warranted. In most HCM patients the contribution of atrial systoles to stroke volume is negligible by the time AF develops—that is, patients have a palpable atrial beat but no fourth heart sound.

A slurred upstroke to a broad QRS complex is a common surface ECG finding in HCM patients. In less than 5% of these

Table 2 The recognised markers of risk in HCM and their sensitivity, specificity, positive and negative predictive accuracy (PPA and NPA)

Risk factor	Sensitivity (%)	Specificity (%)	PPA (%)	NPA (%)
Abnormal blood pressure response: <40 years old ¹⁹	75	66	15	97
NSVT: adult <45 years old ¹⁸	69	80	22	97
NSVT: ≤21 years old ²³	<10	89	<10	85
Inducible VT/VF: High risk population ^{w30}	82	68	17	98
*Syncope: <45 years old ³	35	82	25	86
*Family history: at least one unexplained sudden death ± HCM ³	42	79	28	88
†LVH ≥3 cm ¹⁷	26	88	13	95
‡Two or more risk factors ²	45	90	23	96

*Figures provided are for the risk of death from all causes rather than sudden death only.

†Figures provided are for risk of sudden death and/or appropriate ICD discharge.

‡In this data set from Elliott and colleagues, family history and syncope were combined in order to achieve statistical significance of relative risk.

LVH, left ventricular hypertrophy; NSVT, non-sustained ventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 3 Five year survival rates free of death, cardiac arrest or appropriate ICD discharge in studies of HCM patients treated for secondary prevention of cardiac arrest or haemodynamically compromising ventricular arrhythmias

Study	5 year survival rates (95% CI)
Cecchi 1989 ¹⁴	65% (18%)
Elliott 1999 ¹⁵	59% (25%)
Maron 2000 ⁴	45% (CI unavailable)

CI, confidence interval.

patients, however, is an accessory pathway found at electrophysiological testing.¹³ This may then be amenable to radiofrequency ablation. Enhanced AV nodal conduction may be more frequent in HCM and may facilitate the rapid conduction of pre-excited arrhythmias and so precipitate VF.^{w20}

SUDDEN DEATH: RISK ASSESSMENT

All patients should undergo non-invasive risk factor stratification with a clinical history, Holter monitoring, and maximal exercise testing regardless of symptomatic status or the apparent severity of morphological disease.

History

Syncope and symptoms

Unexplained, exertion related syncope is a predictor of risk in all age groups, but especially in children and adolescents with severe symptoms.³ This is an insensitive measure, however, as most patients who die suddenly have no prior history of syncope. In adults the severity of symptoms of chest pain and dyspnoea does not add to the predictive value (table 2).³

Prior cardiac arrest

Early evidence suggested that the short and medium term prognosis after a cardiac arrest was not as ominous as expected. The data indicated that roughly one third of survivors died within seven years while receiving non-systematic medical or surgical treatment.¹⁴ The most recent ICD data, however, suggests a poorer prognosis with appropriate discharge rates of approximately 10% in survivors of cardiac arrest (table 3).^{4, 15}

Family history

Unpublished tertiary referral centre data indicates that 25% of HCM patients have a family history of premature sudden

death (< 45 years old) while less than 5% had two or more HCM related sudden deaths in the family. Family history of premature sudden death is also an insensitive but relatively specific marker of risk (table 2). The combination of a history of syncope with a family history of sudden death, however, does increase significantly the overall positive predictive accuracy for sudden death (Cox model multivariate relative risk 5.3, 95% confidence interval (CI) 1.9 to 14.9).^{2, 3}

Echocardiogram

Early echocardiographic and Doppler data has not suggested any predictive value from the degree of hypertrophy or severity of outflow tract obstruction.^{w21} More recent studies have, however, identified severe (≥ 3 cm) hypertrophy as a risk factor for sudden death.^{16, 17} Spirito and colleagues had concluded that severe hypertrophy alone justified ICD insertion, particularly in the young.¹⁶ This has been criticised, however, for failing to consider the distribution of left ventricular hypertrophy (LVH) and the fact that the majority of patients with maximal wall thicknesses ≥ 3 cm survived without prophylactic treatment. The data from Elliott and colleagues support a significantly increased risk of sudden death or ICD discharge associated with a maximal hypertrophy ≥ 3 cm (Cox model relative risk 2.1, 95% CI 1.0 to 4.2) but argues against prophylactic treatment solely on the basis of left ventricular wall thickness.¹⁷ All the individuals with a mean left ventricular wall thickness ≥ 3 cm who died suddenly had additional risk factors, while those without other risk factors all survived.¹⁷ In addition, 74% of Elliott's and 82% of Spirito's subgroups who died suddenly had hypertrophy of less than 3 cm.^{16, 17} The severity of wall thickness in isolation has insufficient predictive accuracy to guide decisions regarding prophylactic treatment.

Holter monitor

Twenty per cent of adult HCM patients exhibit non-sustained ventricular tachycardia (NSVT) during Holter monitoring. In adults it is the most sensitive marker for increased risk of sudden death, conferring a doubled relative risk in a selected low risk population and an eightfold increase in relative risk in a consecutive referral centre population.^{18, w22} The absence of NSVT in adults is particularly reassuring because of its high negative predictive accuracy (table 2).

NSVT, however, is seen infrequently in adolescents and rarely in children, but when detected is more ominous and specific with an up to eightfold increase in relative risk for sudden death.^{18, 19} The relative rarity of ventricular arrhythmias

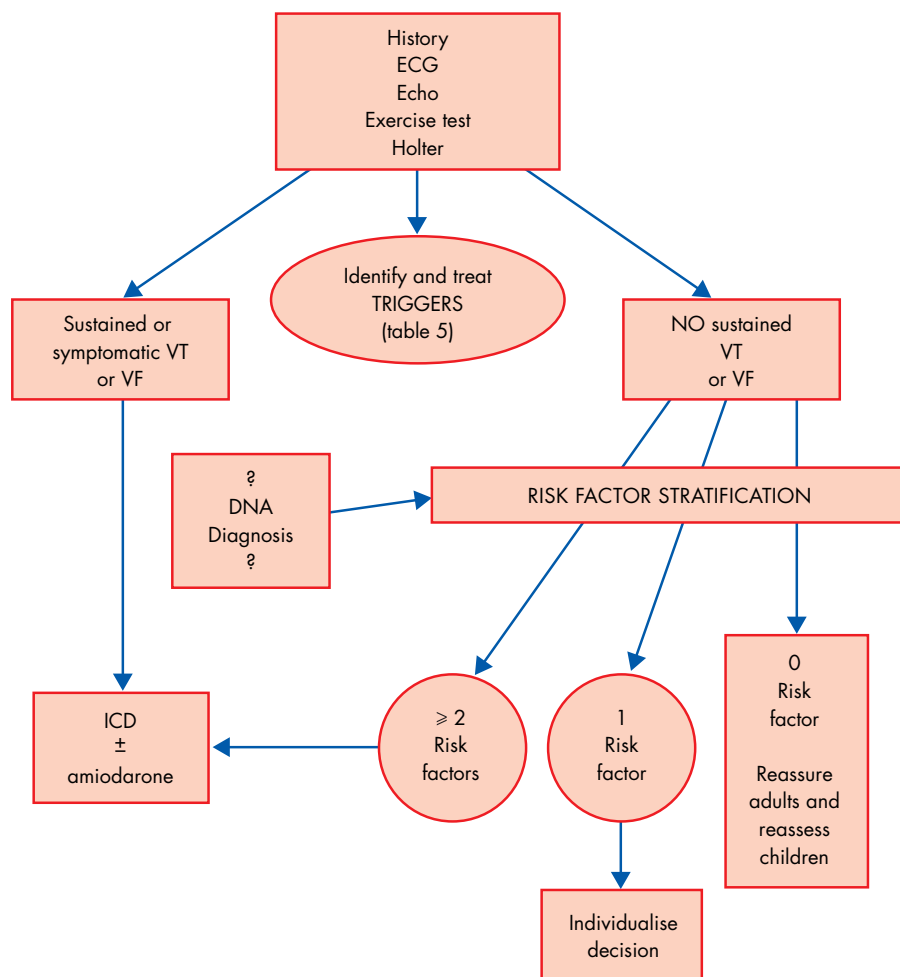


Figure 2 Algorithm for risk stratification and prevention of sudden death.

in children limits its utility in this population. In the young little reassurance is provided by the absence of NSVT while its presence even in isolation warrants prophylactic treatment.

SVT and AF have been observed as antecedent events in the development of VF and sudden death. Prophylaxis may therefore have an additional benefit in the reduction of the risk of sudden death.

Blood pressure response to exercise testing

During upright exercise HCM patients commonly demonstrate an abnormal blood pressure response, with either a fall or failure of blood pressure to rise.^{w23 w24} Inappropriate arterial vasodilatation in non-exercising muscles has been documented and it is postulated that this is related to activation of left ventricular baroreceptors by wall stress or ischaemia.^{w23 w25}

An abnormal blood pressure response during exercise is defined as a failure to either augment and/or sustain a systolic blood pressure of > 25 mm Hg above the resting systolic blood pressure during exercise. It can be detected in 25% of HCM patients and thus its positive predictive accuracy for sudden death is low at 15% (table 2).^{20 w24} It is a more sensitive indicator of risk in younger patients (< 40 years old) and is associated with sudden death, although the relative risk is low (1.8).^{2 20} Therefore a positive result should be used in conjunction with other risk factors. The absence of an abnormal blood pressure response is reassuring, however, as its negative predictive value for sudden death is 97% (table 2) and in the

young, in the absence of other risk factors, permits accurate reassurance.

Other investigations

Thallium cardiac perfusion scanning reveals reversible thallium defects in young HCM patients with histories of prior cardiac arrest or syncope.^{w26} These findings have not been borne out in larger mixed groups of prospectively studied patients although in a small subset of patients ischaemia is important.^{w27}

An angiographic study of children with HCM suggested that myocardial bridging was a significant risk factor for sudden death.^{w28} These children were a highly selected group by virtue of having to undergo angiography and were examined retrospectively, making these findings difficult to extrapolate to the general paediatric HCM population. The significance of myocardial bridging and ischaemia in triggering secondary arrhythmias remains unknown but the available data do not provide sufficient justification for routine angiography.

Other non-invasive electrophysiological investigations have been assessed in risk stratification with little success.^{w8} Signal averaged ECGs and heart rate variability studies are commonly abnormal in HCM patients, but there is no association with increased risk. QT interval analysis, including QT dispersion, has provided contradictory results. Beat to beat QT variability has been studied in β myosin mutations and was found to be increased in patients with Arg403Gln mutations of the β

Table 4 Recognised markers of increased risk of sudden death in HCM

Risk factor
1. Previous cardiac arrest
2. Non-sustained VT on Holter or exercise
3. Abnormal exertional blood pressure response
4. Unexplained syncope
5. Family history of premature sudden death
6. Severe left ventricular hypertrophy ≥ 3 cm

myosin heavy chain gene, but there are no data as yet on follow up and outcomes.^{w29}

Invasive electrophysiological investigations have been used as research and potential clinical tools. Programmed stimulation studies using aggressive protocols have suggested that inducible VT is associated with a higher risk of future sudden death (table 2).^{w30} These protocols, however, result in a low positive predictive accuracy similar to non-invasive methods. Therefore the hazard and inconvenience of electrophysiological studies cannot be justified.

Genetic testing

Recent studies have suggested that some mutations in HCM may carry prognostic significance. Troponin T mutations can be exceptionally lethal and appear to be more homogenous in their high level of risk than the prognostic allelic heterogeneity which characterises the other sarcomeric gene abnormalities.²¹ Troponin T patients tend to exhibit subtle or absent hypertrophy but with significant myocyte disarray, and thus may be at risk without conspicuous evidence of disease.^{w31} β Myosin mutations are heterogeneous in their associated levels of risk. Arg403Glu and Arg453Cys mutations appear to predispose to sudden death while the Val606Met mutation appears to carry a better prognosis.²¹

Nevertheless the genotype-phenotype relation has to be clarified further to allow proband risk prediction as the existing data have been elicited from selected groups of patients and their families. In addition there may be pronounced heterogeneity of disease within a family with the same mutation. For example, a MyBPC mutation has demonstrated a wide variation in expression in a large German family.^{w7} Only a minority of the family exhibited full expression, which was partly age related, and once disease developed placed them at high risk of syncope, arrhythmias, and sudden death. In addition, DNA diagnosis is limited by the lack of clinical testing outside of research institutions.

Recently mutations in the gene PRKAG2 encoding the gamma-2 subunit of an AMP activated protein kinase have been identified in families with Wolff-Parkinson-White (WPW) syndrome with premature conduction disease and HCM.^{w32 w33} Genetic testing may prove useful as this phenotype has a high incidence of pre-excitation, paroxysmal AF, and flutter and the development of premature conduction disease.

SUDDEN DEATH: PROPHYLAXIS

It is accepted practice to treat aggressively those patients who have experienced cardiac arrest and/or sustained or symptomatic ventricular arrhythmias (secondary prevention) using ICDs because of their high risk (table 3).^{4 15} Most cardiac arrest victims with HCM do not survive the initial event, making it imperative to evaluate all HCM patients for risk and institute primary prevention accordingly (fig 2).

Table 5 Triggers for sudden death and their associated treatment

Factor/trigger	Treatment
Paroxysmal atrial fibrillation	Amiodarone \pm anticoagulation
Sustained monomorphic VT	ICD \pm amiodarone
Conduction system disease	Permanent pacemaker
Accessory pathway	Radiofrequency ablation
Myocardial ischaemia	High dose verapamil

There are several recognised markers for risk of sudden death (table 4). Individually they all have low positive predictive accuracy (table 2). The proposed risk management algorithm (fig 2) advocates reassurance of individuals with no risk factors and no evidence of ischaemia. This is justifiable given the high negative predictive accuracy seen in patients without risk factors (table 2).² Individuals with two or more risk factors have annual sudden death rates of 3% (95% CI 2% to 7%) and should be offered prophylaxis with ICD and/or amiodarone.² Individuals with only one risk factor have annual sudden death rates of approximately 1% but with wide confidence limits (95% CI 0.3% to 1.5%); their management should therefore be tailored according to age, genotype, intensity of the risk factor, and the acceptability of risk for each individual.² For example, a patient's only risk factor may be a family history of premature sudden death, but if the proportion of affected individuals in a pedigree who suffer premature sudden death is high the justification for prophylaxis is greater than if the proportion was low.

Triggers

In approximately 30% of patients risk factor stratification identifies potential triggers for sudden death which are usually amenable to specific treatments (table 5).

Lifestyle

Over 60% of cases of sudden death in HCM die during or immediately after mild to moderate exertion.^{w21} In addition, necropsy studies of sudden death in young athletes have shown that the majority had HCM and that two thirds of them died during or immediately after exertion.²² It is therefore reasonable to advise those at risk of sudden death not to undertake strenuous exercise or competitive sports which require extreme physical exertion.²²

Drug and device treatment

In the absence of a recognised trigger, treatment of high risk patients is limited to ICD and/or amiodarone.^{4 23} There are limited data to define who should receive which treatment. In those at the highest risk an ICD is appropriate while amiodarone may be prescribed in lower risk patients. Amiodarone is also recommended if there is evidence of additional features that require prophylaxis such as paroxysmal supraventricular arrhythmia.

The use of amiodarone in children and adolescents may be complicated by anxiety about the potential dose/duration side effects. It can be used temporarily, however, as bridging therapy to delay ICD insertion in high risk young individuals in whom a device is thought to be the long term treatment of choice. In addition it can provide prophylaxis during a period of high risk until adulthood is reached and a lower risk profile is achieved.^{4 w34} A recent retrospective and non-randomised paediatric study suggested a 5–10 fold reduction in risk with

Management of HCM: key points

- ▶ Symptomatic relief:
 - in non-obstructive HCM treatment relies on calcium channel antagonists and β blockers
 - in obstructive HCM pharmacological treatment relies on β blockers and disopyramide initially
 - myectomy, alcohol ablation, and dual chamber pacing are alternative interventions in obstructive HCM in the drug refractory patient
- ▶ Atrial fibrillation should be treated aggressively to minimise the risks of thromboembolism
- ▶ Sudden death prophylaxis:
 - all HCM patients should undergo risk stratification for sudden death
 - patients suffering prior cardiac arrest or sustained ventricular arrhythmia warrant prophylactic treatment
 - patients with two or more recognised risk factors warrant prophylaxis (table 4)
 - patients with one risk factor require individualised decision making in relation to the strength of the risk factor (table 4)
 - effective prophylactic treatment includes the use of ICD and/or amiodarone
- ▶ Clarification of the genotype–phenotype relation in HCM may ultimately assist decision making

high dose β blockade.^{w35} Interpretation of these data is limited by the small sample size derived from a heterogeneous population of young patients (all diagnosed < 19 years old), which included a high proportion of patients with “HCM” unrelated to sarcomeric contractile protein gene mutations (38% Noonan’s syndrome). The sudden death risk of “HCM” caused by mitochondrial disease, Noonan’s, Friedreich’s ataxia, and Fabry’s disease is likely to be different to the risk of HCM caused by mutations in contractile protein genes.

More recently retrospective registry data on ICD therapy have become available from US and Italian investigators.⁴ The risk profile of the patients is incomplete but the primary prevention data suggest that individuals not at excessively high risk were treated. Extrapolation to a 10 year period suggested an annual appropriate discharge rate of 2.5%. This correlates with the experience of the European ICD registry (M Borggrefe MD, personal communication).

The complications of ICD therapy, however, appear to be greater in patients with HCM compared to high risk dilated cardiomyopathy or coronary artery disease patients. For example, 25% of the whole Italo-American group and 22% of European registry patients suffered inappropriate discharges and 15% had significant complications caused by lead failure or local effects of insertion (for example, infection, haemorrhage, and subclavian thrombosis). Amiodarone may reduce the frequency and rate of ventricular and supraventricular tachycardias and hence reduce the number of inappropriate and appropriate discharges. In the Italo-American population, however, it was used less frequently than one might have expected (25%). In addition the young are also more at risk of complications. Children are more likely to require insertion in an abdominal position with redundant intratrial loops of lead required to allow for further growth.^{w34} Adolescents often have psychological problems adapting to the device, while young people in general will require multiple box and lead placements resulting in difficult vascular access and an increase in complications.^{w34}

It is still necessary to determine which prophylactic treatment is appropriate for which patient. Thus a continued registry of ICD and amiodarone treatment in HCM, incorporating genetic testing and risk stratification, may be the only definitive way to guide therapy in relation to genotype and phenotype.

CONCLUSION

The management of HCM remains an important clinical challenge necessitating regular longitudinal follow up of young individuals. Treatment of obstruction offers several effective options but symptom relief can be difficult, particularly in non-obstructive patients. Stratification of the risk of sudden death is feasible using available non-invasive techniques. Ultimately, genotyping may further refine our predictive abilities. The potential benefit of risk assessment also includes the reassurance of low risk individuals, while for high risk individuals there are prophylactic treatments available. The weight of evidence supports the judicious use of amiodarone and ICD therapy in primary prevention. Secondary prevention data support ICD therapy as mandatory. Data on treatment in the younger age groups are limited despite their relatively high risk of sudden death.

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