Hypertrophic cardiomyopathy (HCM) is an inherited disease (or perhaps more correctly, in view of its genetic heterogeneity it should be considered as a group of diseases). It exhibits pronounced phenotypic variability, including extent of hypertrophy, presence and severity of symptoms, and natural history. The early literature, derived from a small group of tertiary referral centres, suggested that it was a relatively uncommon but extremely malignant disorder, with annual mortality rates of 2–4% in adults and 6% in adolescents and children, the majority of these deaths being sudden.\(^1\) More recently it has become apparent that HCM is in fact a common disorder, with a prevalence estimated from echocardiographic population screening of 0.2%.\(^2\) However, it is also now clear that HCM is overall much more benign than these earlier studies had suggested, with an annual mortality rate in large unselected series of approximately 1%, at least half of these deaths being sudden, and the remainder principally caused by heart failure and stroke.\(^1\)

Nevertheless, HCM is an important cause of sudden cardiac death (SCD); in most (but not all) series it is the most important cause of SCD in young adults and in athletes.\(^2\) Many of these deaths occur in patients with minimal or no symptoms (indeed the diagnosis of HCM is sadly often made first at the postmortem examination, following the sudden cardiac death of a previously healthy individual). With the development of automatic implantable cardioverter-defibrillators (AICDs), effective preventive therapy is now available. The challenge is to distinguish high risk from low risk patients with HCM in order to target prophylactic therapies (AICD\(^\pm\) amiodarone) to those at risk. The need for such risk stratification is more than simply one of health economics. Compared with patients with coronary artery disease who undergo AICD implantation, HCM patients who are implanted are much younger, and have a much lower annual event (or AICD discharge) rate. It is likely that their lifetime risk of serious AICD related complications will be high.\(^3\)

SUDDEN CARDIAC DEATH IN HCM: TRIGGER VERSUS SUBSTRATE

The terminal event in patients who die suddenly from HCM is probably most commonly ventricular fibrillation (VF) (fig 1). Data from HCM patients who have received appropriate AICD discharges have shown that these discharges have occurred in response to sustained monomorphic ventricular tachycardia (VT), VT leading to VF or unheralded VF.\(^3\) However, even in those patients in whom an AICD has been implanted because of a documented resuscitated episode of VT or VF, the annual rate of appropriate AICD discharge is only 11%.\(^3\) This leads to the conclusion that the development of a malignant arrhythmia requires the coalescence of triggers at a critical moment in time as well as a pro-arrhythmic substrate.

The substrate is most likely the presence of extensive myocyte disarray and/or fibrosis. These changes probably predispose to re-entrant ventricular arrhythmias. Myocyte disarray is more extensive at postmortem examination in patients with HCM who die suddenly.\(^3\)\(^3\) Similarly, troponin T mutations, generally associated with a high risk of sudden cardiac death, are associated with minor left ventricular hypertrophy, but extensive myocyte disarray.\(^3\)\(^3\)

Various triggers are postulated to be involved in the development of malignant ventricular tachyarrhythmia in HCM. These include myocardial ischaemia, hypotension caused by inappropriate vasodilation or by exacerbation of outflow tract obstruction, altered autonomic tone, rapid atrioventricular conduction along an accessory pathway, conduction system disease, and paroxysmal atrial fibrillation.

AICD interrogations and/or Holter recordings have demonstrated that the development of VT or VF may be preceded by sinus tachycardia or bradycardia, by AV block, or by pronounced ST segment changes.\(^3\)\(^3\) Observations such as these support the concept that ventricular arrhythmia may not be a primary event in many cases.
Several risk factors have been shown to be associated with increased risk of sudden cardiac death in HCM. The predictive accuracy of each of these risk factors is generally low during medium term follow up. Consequently the use of single risk factors to advise patients of their risk and to guide risk factor stratification is generally inappropriate. McKenna and colleagues have persuasively argued that the risk factor profile of patients with HCM is much more accurately assessed in terms of their total burden of risk factors. In this review the evidence for each of the proposed risk factors will be briefly discussed. This will be followed by an algorithm for risk factor stratification based on the proposals of McKenna and colleagues.

Figure 1  Mechanism(s) of sudden cardiac death in hypertrophic cardiomyopathy: current concepts. LV, left ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.
Prior cardiac arrest
HCM patients who have survived a cardiac arrest and who were treated with conventional medical therapy and/or with surgery had a seven year mortality rate of approximately 33%. As noted above, the appropriate AICD discharge rate in HCM patients in whom the device was implanted because of cardiac arrest caused by documented VT or VF was approximately 11% per year. Prior documented cardiac arrest is therefore a sufficient indication in its own right that serious consideration should be given to implantation of an AICD.

History of recurrent syncope and family history of SCD
Unexplained syncope (one or more episodes within the previous 12 months), particularly when it occurred on exertion, was associated with an increased risk of SCD, especially in children and adolescents in a tertiary referral population reported in 1981. However, the majority of patients who die suddenly do not have a history of syncope. In younger patients than 45 years the sensitivity was rather low (35%), but the specificity was high (82%), with positive and negative predictive accuracies of 25% and 86%, respectively.

A family history of one or more SCDs was also associated with an increased risk of SCD in this study: sensitivity (42%), specificity (79%), positive predictive accuracy (28%), negative predictive accuracy (88%).

In a recent community based population of 225 consecutive patients with HCM, the annual SCD rate was 0.5%; a history of syncope was the only independent predictor of SCD in a multivariate model which also included family history of HCM and SCD, presence of non-sustained VT on Holter monitoring, atrial fibrillation, resting left ventricular outflow tract obstruction > 50 mm Hg, and maximum wall thickness > 25 mm.

In a larger (368 patients) recent tertiary referral population followed for a mean of 3.6 years, the annual rate of SCD was approximately 1.5%. On univariate analysis, the relative risks of syncope and family history of SCD for SCD during follow up were 2.0 and 1.9, respectively. In a multivariate model the combination was a significant additive predictor of risk of SCD (relative risk (RR) 5.3, 95% confidence interval (CI) 1.9 to 14.9).

An important practical point is that the prognostic impact of a family history of SCD should be interpreted in the context of the number of family members affected by HCM. A single SCD in a large family with multiple affected members is likely to carry less weight than it would in a small family with only two or three affected members.

Severe left ventricular hypertrophy
While early studies did not report any association between magnitude of left ventricular hypertrophy (LVH) and risk of SCD, the observation that extreme hypertrophy is uncommon in older patients with HCM caused this to be re-evaluated. Two groups recently reported that extreme LVH (maximum wall thickness > 30 mm) was associated with an increased risk of SCD during follow up. The authors of one of these papers suggested that the presence of extreme LVH alone should be an indication to consider AICD implantation and conversely that patients with mild LVH could be reassured. However, this argument is flawed. It ignores the fact that some patients with HCM who die suddenly have minimal hypertrophy, and this is particularly true of those with troponin mutations. The presence of only mild LVH does not necessarily provide reassurance therefore.

The other group (McKenna and colleagues) confirmed that patients with maximum wall thickness > 30 mm had a higher probability of SCD or AICD discharge than those with maximum wall thickness < 30 mm (RR 2.07, 95% CI 1.00 to 4.25). However, they noted that approximately 75% of those who died suddenly had a maximum wall thickness < 30 mm and also that the five year risk of sudden death or AICD discharge was only 5% in patients with severe LVH as their only risk factor. In contrast to the above studies, two recent smaller studies have not confirmed the association between severe LVH and increased SCD risk.

In summary, severe LVH is a risk factor for SCD but its predictive accuracy is low—sensitivity 26%, specificity 88%, positive predictive accuracy 13%, and negative predictive accuracy 95%. Further practical points to note are that the magnitude of LVH appears to be a continuous rather than a dichotomous risk factor and the “maximum wall thickness” used in these studies was derived from careful measurements in multiple segments. Standard clinical echocardiographic studies which do not conform to these protocols will frequently significantly underestimate the maximum wall thickness, which is often localised.

Left ventricular outflow tract obstruction
A recent large study reported that patients with a resting peak instantaneous outflow tract gradient > 30 mm Hg were at increased risk of total mortality (RR 2.0, 95% CI 1.3 to 3.0), of death from heart failure or stroke (RR 4.4, 95% CI 3.3 to 5.9), and of SCD (RR 2.1, 95% CI 1.1 to 3.7). There was no evidence of increasing risk with progressively increasing gradients above this threshold. The negative predictive accuracy for SCD was very high (95%) but the positive predictive accuracy was very low (7%). The impact of treatments aimed at reducing outflow tract obstruction (medical, surgical, and alcohol septal ablation) on the risk of SCD has not been formally assessed.

Abnormal blood pressure response during exercise
Approximately half of SCDs occur during or soon after mild or moderate exercise. This may in part relate to abnormal haemodynamic and autonomic responses during exercise in these patients. About a third of patients with HCM have abnormal blood pressure responses (ABPRs) during maximal treadmill exercise—with a flat blood pressure response, or uncommonly a fall in blood pressure. ABPRs are more frequent in younger than older patients. ABPR appears to be most commonly caused by an exaggerated fall in systemic vascular resistance, probably via activation of mechanosensitive receptors in the left ventricle. In some patients an impaired cardiac output (caused by obstruction and/or diastolic dysfunction) may be the predominant mechanism.

In a tertiary population of 161 HCM patients (< 40 years), ABPR was associated with an increased risk of SCD. The positive predictive accuracy of ABPR was low (15%), but the negative predictive accuracy was high (97%). Another study confirmed similar findings in an older (mean age 42 years) population where ABPR was observed in 22%. A larger study (368 patients followed for mean 3.6 years) reported that in patients < 40 years, an increase in systolic blood pressure < 25 mm Hg (from baseline to end of exercise) or a > 15 mm Hg drop in systolic blood pressure
(from peak recorded to end of exercise) were the most predictive values for a flat or hypotensive blood pressure response, respectively. The multivariate risk ratio for SCD for ABPR in patients < 40 years was 1.8. In patients > 40 years ABPR was not predictive of SCD.

A Japanese study of 309 consecutive patients also reported a flat blood pressure response to be associated with an independent effect on SCD risk on multivariate analysis during (mean) 10 year follow up.

The abnormal vascular behaviour responsible for most cases of ABPR may cause hypotension in other settings—for example, during postural stress or in response to arrhythmia such as paroxysmal atrial fibrillation. The accurate measurement of blood pressure during exercise can be problematic. Only systolic blood pressure can be measured with any reliability (either by palpation or auscultation of the brachial artery). Blood pressure must be measured each minute during exercise and at peak exercise, because blood pressure falls can occur abruptly.

Presence of non-sustained ventricular tachycardia during ambulatory ECG monitoring

Approximately 15–20% of adult patients with HCM demonstrate non-sustained ventricular tachycardia (NSVT) (defined as a run of three or more ventricular beats at a rate of at least 120 bpm) during 48 hour ambulatory ECG recording. Two groups independently reported the association between NSVT and increased risk of SCD in 1981. Both were from tertiary referral populations. In adult patients NSVT was an insensitive but relatively specific marker of risk (sensitivity 35%, specificity 82%, positive predictive accuracy 25%, negative predictive accuracy 85%). In a community based population of 167 patients with HCM, Cecchi and colleagues reported that isolated non-repetitive bursts of NSVT were not associated with an adverse prognosis; however, there were only nine HCM related deaths in this study of which only one was sudden. In a more recent study of 368 patients age 14–65 years, the multivariate risk ratio of NSVT for SCD was 1.9.

In contrast to the adult HCM population, NSVT is very uncommon in children and adolescents with HCM. When present it carries a high risk. Whereas in adults the absence of NSVT is reassuring, this is not so in children and adolescents.

MARKERS OF UNPROVEN VALUE OR OF LIMITED CLINICAL UTILITY

Non-invasive and invasive electrophysiological tests

Programmed electrical stimulation studies have limited clinical utility in the assessment of risk in hypertrophic cardiomyopathy. Fananapazir and colleagues provoked sustained ventricular arrhythmias (>30 beats or requiring termination because of haemodynamic compromise) in 36% of a selected (high risk) population of 228 patients, but in the majority this was polymorphic rather than monomorphic. These were associated with an increased risk of cardiac events during follow up. However, the predictive value of this highly invasive strategy performed in a high risk subset was no better than that of the simple non-invasive markers in unselected cohorts (positive predictive accuracy 17%, negative predictive accuracy 98%).

A potentially interesting approach which may assess the “substrate” for ventricular arrhythmia genesis involves assessing the changes in intracardiac electrogram duration following premature right ventricular extrastimuli. Patients with prior VF had evidence of notably slowed or delayed myocardial activation versus those without prior VF. The prognostic utility of this approach remains to be evaluated.

Signal average ECG, heart rate variability, and QT dispersion are of no proven value for risk factor stratification of HCM patients.

Angiographic abnormalities

In a highly selected retrospective study of 36 children with HCM who had undergone coronary angiography, myocardial bridging of epicardial coronary arteries was associated with an increased risk of death or successful resuscitation from cardiac arrest during follow up.

Thallium perfusion scanning

A small highly selected study reported that reversible thallium abnormalities were seen in all 15 patients with prior cardiac arrest (n = 8) or history of syncope (n = 7) versus only three of eight patients without either history. However, a subsequent study of 216 patients reported no association between either fixed or reversible (dipyridamole) thallium defects and subsequent disease related death.

Gadolinium cardiovascular magnetic resonance imaging

Focally increased interstitial myocardial space appears as hyperenhancement with gadolinium enhanced cardiovascular magnetic resonance imaging. It may therefore potentially identify a “substrate” for increased risk of SCD. A recent paper studied 53 HCM patients selected for the absence (n = 30) or presence (n = 23) of “conventional” risk factors (family history of premature SCD, unexplained syncope, non-sustained VT, ABPR, and maximum wall thickness >30 mm). There was a greater extent of hyperenhancement in patients with two or more risk factors for SCD and in those who demonstrated “progressive disease” during follow up (wall thinning, cavity enlargement, and/or deterioration in systolic function). A large prospective study in a consecutive population may be warranted to evaluate the predictive accuracy of this technique for both SCD and the development of systolic dysfunction.

Genotype and risk

Until recently, adult HCM was believed to be a “disease of the sarcomere”. Mutations in eight genes coding for different sarcomere proteins have been shown to cause HCM. However, mutations of genes coding for mitochondrial enzymes (either nuclear or mitochondrial genes), can be associated with the HCM phenotype, especially when presentation is in childhood. Recently mutations in the gene PRKAG2 which encodes the γ-2 subunit of an AMP activated protein kinase have been identified. These families display a phenotype comprising “HCM” together with Wolff-Parkinson-White syndrome and/or conduction system disease. On the basis of the above and on studies in mouse models, it has been suggested that disturbed myocardial energy production and/or utilisation may play a key role in the development of hypertrophy. Interestingly, myocardial disarray, the hallmark of HCM caused by sarcomere gene mutations, is conspicuously absent in patients with mutations of the PRKAG2 gene, suggesting that it may be a fundamentally different disease. It is clear, therefore, that HCM is a highly genetically heterogeneous disease.
Since HCM is a “monogenic” disorder, it is tempting to believe that the phenotype and the natural history may be in large part determined by the genotype, and that the very wide phenotypic variability in HCM would be explicable on the basis of genotypic variability. Early studies lent strong support to this concept. The Arg403Glu and Arg453Cys mutations of the β myosin heavy chain gene were reported to be associated with a high risk of SCD, whereas the Val606Met mutation was associated with a relatively benign prognosis.25 Patients with mutations of the gene encoding the protein troponin T were reported to have modest (or even no) hypertrophy, but extensive histological myocyte disarray and a high risk of SCD.25, w3

However, it has become clear more recently that the link between genotype and risk is not simple. First, Ackerman and colleagues examined the prevalence of several mutations in a population of 293 HCM patients at a tertiary referral centre (Mayo Clinic). Mutations previously reported to be “malignant” (MYH7 and TNNT2) were found in only three (1%) of the 293 patients.26 Second, there may be wide phenotypic variation (including natural history) between affected individuals within the same family, let alone between different families sharing the same genotype. For example, in a large Scottish family with HCM caused by a TNNT2 mutation, eight affected members died suddenly age <30 years, whereas eight other affected members survived into old age.25 Explanations proposed to explain this phenotypic variability include: compound heterozygosity, modifier genes, epigenetic factors (DNA methylation and imprinting), epistasis (interaction between genes), post-transcriptional and post-translational modifications of gene products, presence of coexisting diseases, and environmental influences.27

From a practical perspective, given the above limitations and the absence of widespread availability of genetic testing for HCM, genotype assessment does not form part of the current risk factor stratification of patients with HCM.

THE CONCEPT OF GLOBAL RISK BURDEN

It will be apparent from the above that several factors are predictive of the risk of SCD during follow up, the predictive value of each is rather low. This makes the use of single risk factors to advise patients of their risk and to guide prophylactic therapy rather inaccurate. McKenna and colleagues have shown convincingly that consideration of the overall burden of risk factors considerably improves the predictive accuracy. They considered four variables (ABPR, maximum wall thickness > 30 mm, NSVT, and the “combined variable” of family history of SCD in at least one relative < 45 years and history of syncope) in a group of 368 consecutive patients. The estimated six year SCD-free survival rates according to the number of risk factors present were as follows: 0 (n = 203), 95% (CI 91% to 99%); 1 (n = 122), 93% (CI 87% to 99%); 2 (n = 36), 82% (CI 67% to 96%); 3 (n = 7), 36% (CI 0% to 75%).

Patients with two or more risk factors had a significantly lower six year SCD-free survival rate versus those with one or no risk factors. The presence of two or more risk factors had a positive predictive accuracy of 23% and a negative predictive accuracy of 90% for SCD during (medium term) follow up.4

Complete acceptance of the validity of this concept requires its application to a separate validation sample of patients from whom this model was not derived. This has not yet been done.

PRACTICAL IMPLICATIONS FOR THE RISK FACTOR STRATIFICATION OF PATIENTS WITH HCM

- Patients with previous cardiac arrest or spontaneous sustained VT are at high risk and should be considered for prophylactic therapy (AICD).
- In the absence of such a history, risk is probably best assessed on the basis of the total number of the following risk factors:
  - maximum wall thickness > 30 mm (multiple segments at multiple levels)
  - systolic blood pressure response measured each minute during maximal upright exercise in patients < 40 years (ABPR = failure to increase by > 25 mm Hg or fall from peak during continued exercise > 15 mm Hg)
  - NSVT during 48 hour ambulatory ECG monitoring
  - history of at least one SCD in a relative < 45 years together with a history of syncope
  - resting peak instantaneous left ventricular outflow tract gradient > 30 mm Hg

Patients with no risk factors can be strongly reassured. Those with two or more risk factors are at high risk and should be considered for prophylactic therapy (AICD) and/or

| Documented previous cardiac arrest | No risk factors | ≥2 risk factors | 1 risk factor |
|-----------------------------------|----------------|----------------|--------------|
| Consider AICD                     | Reassure       | Consider AICD  | Individual decision |
| (or 7 amiodarone)                 |                | (or 7 amiodarone) |              |

Figure 2 Targeting preventive treatment for sudden cardiac death in hypertrophic cardiomyopathy. AICD, automatic implantable cardioverter-defibrillator.
amiodarone). Those with a single risk factor are at intermediate risk (fig 2).

Important questions remain. In particular what is the impact of removal of risk factors by treatment on the subsequent risk of SCD? Outflow tract obstruction may be effectively relieved by septal myectomy and by alcohol septal ablation. Furthermore, these treatments may abolish syncope and may correct the abnormal blood pressure response." A patient undergoing such treatment might therefore be converted from three to zero risk factors. Does this mean they are now at a low risk? How often should risk factor stratification be repeated in patients with HCM? At present it seems reasonable to repeat every 3–5 years.

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