Risk factors and stratification for sudden cardiac death in patients with hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is a primary cardiac disease characterised by a diverse clinical expression¹⁻⁶ in which premature sudden unexpected death has been regarded as a critical feature of its natural history.¹⁻²³ However, it is also apparent that not all patients within the disease spectrum are at equal risk of premature death, and indeed in some individuals the disease seems to convey little or no risk.^{17-19 24 25}

Consequently, intense investigative interest and substantial energy have been directed toward the identification of "risk factors"—that is, those features of the disease that are perceived to predispose specific patients with HCM to sudden death or cardiac arrest.^{7 8 12 14 16-19 26-31} Nevertheless, despite these exploratory studies in risk stratification, there are few comprehensive and prospectively obtained long-term data analysed in a multivariate fashion. Though knowledge is rapidly evolving and workable approaches are beginning to emerge, the definition of precise approaches for most patients and clinical situations remains incomplete. Indeed, because such controversy persists regarding the definition of risk it seems justified and timely to review the available data to summarise what is known about the risk of sudden death in HCM. We hope to show that prospective trials are needed and to evolve a practical approach and workable guidelines to aid the development of diagnostic and therapeutic strategies.

Factors influencing prevalence of sudden death

Published reports indicate that premature death in patients with HCM is most often sudden and unexpected.^{1-5 7-22 30-33} (Sudden death is defined as unexpected, non-traumatic death occurring instantaneously or within one hour after the onset of acute symptoms or signs of cardiac dysfunction.) Reported annual mortality ranges from about 1% to 6%.^{2-4 7 8 11 13 16 18 21 33-37} Several factors seem to be responsible for this wide range, which is found even among comparable referral centres. First, the demographic characteristics of various study groups with HCM may differ substantially. For example, annual mortality reported in studies from the 1970s is still frequently cited. These studies, however, predated echocardiography and more widespread identification of the disease (particularly the non-obstructive form). Subsequent widespread application of echocardiography

dramatically altered the composition of the population of patients with HCM. Furthermore, the diagnostic criteria for HCM have evolved and have been clarified and now there is greater appreciation of the true frequency of the non-obstructive form of HCM.

Another contributing variable is the intrinsic heterogeneity and diversity of the disease's genetic and phenotypic expression, haemodynamic state, and clinical course.^{2 3 5 6 8 24 25 38-41} Furthermore, various subgroups of patients may show different relative risks. For example, mortality was reported to be highest in children^{8 11 13 16 22 33 38} and may also differ in symptom free untreated patients and those treated in various ways.

Limitations in ascertaining risk

Several factors have limited the ability of investigators to stratify the risk of sudden cardiac death in individual patients with HCM. These include the heterogeneity of phenotypic expression^{2 3 5 6 8 24 25 38-41} which made it exceedingly difficult to establish principles of risk stratification that apply to all or most subgroups. Also, HCM is uncommon, occurring in about 0.2% of the general population,⁴² so few centres can easily assemble a patient population large enough to define risk factors for a subgroup or minority of these patients.

Consequently, certain inherent biases in patient selection and referral patterns for HCM have become important determinants of the apparent risk for sudden death. Distribution of patients among medical centres has been particularly skewed⁴³ and most previous studies on clinical course, natural history, or risk stratification have been conducted retrospectively in a few selected tertiary referral institutions in North America and Western Europe.^{6 43 44} Patients are generally referred to such tertiary centres because they are already perceived to be at high risk owing to progressive symptoms; or because of a propensity to sudden premature death; or they are referred for investigational drug treatment, electrophysiological study, surgical intervention, or specialised instrumentation and device implantation. Such referral institutions may also become immersed in the detailed analysis of selected high risk pedigrees from which additional patients with unfavorable prognosis are introduced in disproportionate numbers into the overall cohort. In addition, because HCM is a complex disease, a multitude of disease variables

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Figure 1 Clinical profile of patients with HCM and sudden cardiac death. (A) Age distribution of 78 patients who died suddenly or experienced cardiac arrest. (B) Functional state before sudden death or cardiac arrest (SVT, supraventricular tachycardia). (C) Activity at time of sudden death or cardiac arrest. *Includes 4 patients who died during sleep. (From Maron, et al⁶; reproduced with permission of the American Heart Association).

and potential risk factors have been identified (and continue to be described), further confounding risk stratification assessment. Previous efforts at establishing relative risk in patients with HCM should be viewed in the context of these limitations, particularly the utilisation of patients at tertiary centres who were already largely preselected because they were perceived to be at increased risk even before they were referred.^{6 43}

Clinical profile

Sudden cardiac death in hypertrophic cardiomyopathy seems to be most common in children and young adults, aged 12–35 years^{1–3 7–16 19 21 23 31–33} (fig 1), though it may also occur in older adults, even in those who have previously been symptom free.^{4 8} Sudden death seems to be uncommon in the first decade of life: currently, however, there are few data on this subgroup of patients. Most patients with HCM who die suddenly have been symptom free (or have had only mild symptoms) and often their disease has not been identified clinically^{2 3 7 9 12 14} (fig 1). Patients with functional limitation can also die suddenly and unexpectedly; however, we regard deaths that occur suddenly in patients with profound congestive heart failure

(whether or not this is associated with the end stage of HCM) to be outside the context of this discussion. Most patients (about 60%) experience sudden death while they are inactive or only mildly active. But about 40% die during or just after vigorous physical activities, including competitive sports⁹ (fig 1); indeed, HCM seems to be the most common cause of sudden death in young competitive athletes.^{10 45 46} Also, although operation (usually septal myotomy/myectomy) relieves symptoms in most patients, such individuals can die suddenly many years after successful surgical relief of outflow obstruction.⁴⁷

Mechanisms of sudden death

Because so few sudden deaths have been fortuitously monitored, earlier descriptions of mechanisms for sudden death unavoidably have been based largely on anecdotal observations or inference.^{15 48 49}

Therefore, various potential mechanisms that singly or in combination can lead to sudden death in patients with HCM have been studied in those who have experienced recurrent syncope,⁴⁹ have survived cardiac arrest,⁵⁰ or have been considered to be at increased risk of such events.^{28 29 51–54} These mechanisms are undoubtedly not identical in all at risk patients and may differ in youthful and older patients. Furthermore, the origins of some mechanisms appear to be primarily haemodynamic whereas others are arrhythmic.

Proposed mechanisms of sudden death (based on such observations) include spontaneous primary ventricular tachycardia/fibrillation, paroxysmal atrial fibrillation and other supraventricular tachyarrhythmias (with or without accessory atrioventricular pathways) leading to accelerated atrioventricular conduction and ventricular fibrillation or hypotension, and conduction abnormalities involving dysfunction of the sinoatrial or atrioventricular nodes or the distal His-Purkinje system (including complete heart block).^{2 3 7 19 48 51 54}

The haemodynamic consequences of such electrophysiological abnormalities may be exaggerated by the presence of dynamic obstruction to left ventricular outflow, by severe impairment of diastolic filling, or by the induction of myocardial ischaemia (possibly owing to reduced coronary reserve secondary to abnormalities of the intramural small vessels) and fibrosis,^{2 3 19 54–56} which can reduce the threshold for ventricular arrhythmias. Alternatively, the finding of ischaemia or outflow obstruction in patients with syncope or aborted cardiac arrest, or of severe exercise hypotension despite an appropriate increase in cardiac output^{26 27 49} suggests that in some patients these pathophysiological mechanisms can have a primary role in provoking sudden cardiac death.^{2 3 7 15 19 54–59}

What determines the clinical outcome after an arrhythmic, ischaemic, or vascular triggering event? Though unproven, the working hypothesis of many investigators is that the arrhythmogenic substrate is the extent and

Table 1 Probable risk factors associated with sudden cardiac death in hypertrophic cardiomyopathy

- Youth
- “Malignant” family history of sudden death
- Gene abnormalities associated with increased prevalence of sudden death
- Aborted sudden cardiac death
- Sustained ventricular or supraventricular tachyarrhythmias
- Recurrent syncope in the young
- Non-sustained ventricular tachycardia (Holter monitoring)
- Bradyarrhythmias (occult conduction disease)

severity of myocardial disarray^{2 19 52 59 60} and that this is an important determinant of electrical stability and survival. Identification of the arrhythmogenic substrate (or measurements that reflect it) remains a major goal in the characterisation of patients with HCM.

Finally, as in ischaemic heart disease, sudden death in HCM is common in the mid-morning hours (7am-1pm). The significance of this circadian pattern is uncertain, although it does suggest a possible role for the temporally related physiological changes (possibly involving arrhythmias and the electrical vulnerability of the myocardium).²⁰

Risk factors for sudden death

Tables 1 and 2 summarise the large number of disease variables that have at one time or another been regarded as risk factors for patients with HCM. They underline the inherent complexities of risk factor stratification strategies in this disease.

CLINICAL FEATURES

Some patients with HCM die young,^{2 3 7 9 11-14 19} but the risk declines with increasing age. In addition, there is evidence from unusually frequent occurrence (or “clusters”) of sudden death in some pedigrees that such a “malignant” family history may itself be a risk factor for those surviving and for affected relatives in the same pedigree.¹² Indeed, this view is consistent with the recent observation that particular genetic defects involving contractile proteins, troponin T, α tropomyosin,⁶¹ and various missense mutations in the β myosin heavy chain gene²⁵ may be associated with favourable or unfavourable clinical course in certain families. Among the particular cardiac symptoms incurred by patients with HCM, only syncope in children and adolescents has been shown to be associated with subsequent sudden death^{8 11}; however, a likely mechanism for syncope can be identified in only <20% of patients.

ARRHYTHMIAS

Various arrhythmias are common in patients with HCM.^{2 3 7 17 18 31 59} In many instances of sudden death the circumstances suggest a primary ventricular arrhythmia as the cause, and a close relation between ventricular arrhythmias and sudden death has been inferred.^{2 7 15 17-20 28 29 31 33 36 52 59} Therefore, understandably, considerable effort has focused on the potential significance of ventricular arrhythmias identified on the ambulatory (Holter) electrocardiogram in stratifying risk in this disease. Two tertiary referral centres independently studied a total of 169 largely medically treated and predominantly adult patients with HCM and linked short runs of asymptomatic ventricular tachycardia on ambulatory electrocardiogram (usually 3 to 10 consecutive beats) with an enhanced risk of sudden cardiac death.^{17 18} In these studies ventricular tachycardia conferred an 8% per year risk of sudden death (over the subsequent 3 years) as compared with less than 1% per year in the absence of ventricular tachycardia (fig 2), with a high negative and low positive predictive accuracy (96% and 26%, respectively). The low positive predictive accuracy indicates significant heterogeneity of risk within the subset of patients with non-sustained ventricular tachycardia. It has also been suggested that non-sustained ventricular tachycardia may not have identical significance as a marker of sudden cardiac death in “stable low-risk” and unselected groups of patients with HCM compared with those into which higher risk patients have been preferentially referred.⁶²

Despite this limitation, the finding of ventricular tachycardia on Holter monitoring remains a useful and practical non-invasive screening test for risk of sudden cardiac death in adult patients with HCM. The presence of ventricular tachycardia places the patient in a high risk group for which further risk evaluation or empirical treatment to prevent sudden death should be considered. In those patients in whom non-sustained tachycardia is a risk factor, it may primarily reflect the arrhythmogenic substrate or more specifically act as a trigger mechanism for sudden cardiac death.^{2 7 19 38 52 54 57} The absence of ventricular tachycardia on 24 or 48 hour Holter monitoring in an adult patient with an otherwise low risk clinical profile (that is, no history of syncope or familial sudden death) permits reassurance and limits the necessity for further risk factor evaluation. Similarly, non-sustained ventricular tachycardia on treadmill exercise test (although less common than on Holter) also has important prognostic implications for patients with HCM.

Initially, investigators advocated treating such non-sustained runs of ventricular tachycardia with various antiarrhythmic agents.^{17 18} McKenna *et al* reported that long-term treatment with low doses of amiodarone (maintenance dose, 150 mg/day) protected against sudden death and prolonged survival in patients with HCM (fig 3); others have used antiarrhythmic agents such as quinidine and

Figure 2 Comparisons of prevalence of sudden death (or cardiac arrest) in 169 HCM patients with or without ventricular tachycardia (VT) on ambulatory (Holter) electrocardiography. Shown separately for 83 patients studied in the United States (Bethesda, MD) with 24 h Holter recording and for 86 patients studied in the United Kingdom (London) with 72 h Holter.^{17 18}

Table 2 Potential risk factors for sudden cardiac death in hypertrophic cardiomyopathy

- Pronounced increase in left ventricular thickness and mass
- Tachycardia-induced myocardial ischaemia
- Pronounced dynamic left ventricular outflow tract obstruction
- Dispersion and inhomogeneity of intraventricular conduction
- Exercise-induced hypotension
- Pronounced physical exertion
- Morning hours of the day

Figure 3 Proposed benefit of amiodarone in patients with HCM. Cumulative survival rate was greater in 21 mildly symptomatic patients with HCM and non-sustained ventricular tachycardia (VT) (on ambulatory ECG monitoring) treated with amiodarone than in a similar group of 24 patients with HCM and non-sustained ventricular tachycardia treated with conventional antiarrhythmic medications. 123 patients with HCM without ventricular tachycardia are shown for comparison (adapted from McKenna *et al*³⁶; reproduced with permission of the British Heart Journal).

procainamide, though there is some concern about the proarrhythmic potential of these agents when they are used to treat asymptomatic arrhythmias in patients with HCM. Current recommendations are to perform further risk evaluation to determine the need for treatment and to identify potential mechanisms of sudden death for which targeted therapy is available.

HAEMODYNAMICS

Many patients with HCM show evidence of haemodynamic instability during exercise with systemic hypotension owing to a fall in systemic vascular resistance (and in the presence of increasing cardiac index).²⁶ The ultimate clinical significance of this finding is unresolved, although the findings of haemodynamic instability, youth, and a family history of sudden death have been regarded as a constellation that may predispose the patient to sudden death.²⁶

In contrast, several other haemodynamic variables do not seem to be predictable determinants of the risk of sudden death in HCM. For example, patients with outflow obstruction and those without may both experience sudden death and no relation between the magnitude of outflow gradient and likelihood of sudden death has ever been established.² Nevertheless, it is still possible that in many patients considerable left ventricular outflow tract gradients and raised intraventricular systolic (and diastolic) pressures, through several pathophysiological mechanisms, predispose patients to potentially lethal arrhythmia and sudden cardiac death. Furthermore, indices of systolic or diastolic dysfunction (assessed by radionuclide or contrast angiography or echocardiography) have not been linked convincingly with sudden cardiac death and have not contributed measurably to risk stratification.⁶³

MORPHOLOGY

Initial necropsy descriptions of patients who died suddenly of HCM consistently showed a striking expression of the disease with a substantial increase in left ventricular wall thickness and mass.^{64,65} Though the pattern and extent of left ventricular wall thickening in HCM is diverse,⁴⁰ echocardiographic analyses of selected patients have shown some statistical

association between considerable and diffuse hypertrophy and subsequent sudden cardiac death and also with non-sustained ventricular tachycardia on the ambulatory electrocardiogram.^{30,31} In one such study, considerably increased left ventricular wall thickness and diffuse distribution of hypertrophy was eight times more common in patients with HCM and sudden cardiac death than in surviving controls with this disease.³⁰ On the other hand, relatively mild degrees of hypertrophy are not without risk of sudden death^{30,31} and even occasional patients, apparently within the disease spectrum of HCM but without left ventricular wall thickening have died.^{66,67}

Though these relations between the extent of hypertrophy and the predisposition to sudden death may be statistically significant they also show substantial overlap. Also, it is often difficult to relate the magnitude of left ventricular hypertrophy to the clinical course because wall thickness measurements can change with time and with age.^{68,69} Consequently, at present we cannot use echocardiography to predict reliably which patients with HCM are at the greatest risk of sudden death.⁷⁰

ELECTROPHYSIOLOGICAL STUDIES

Electrophysiological investigation and programmed electrical stimulation are often performed in patients with HCM who are judged to be at increased risk for sudden death (for example, history of syncope or aborted sudden death). This is because of the perception that sudden death in this disease is most often related to an arrhythmia and also because of an awareness that non-invasive evaluation may not always reliably identify those patients at high risk.^{28,29,52,71-78} Therefore, such electrophysiological studies have two aims: to target those patients at increased risk of sudden death who should be considered for antiarrhythmic intervention and to identify the substrate and trigger mechanisms for sudden death in HCM in those patients recognised to be at high risk.^{28,29,52,71-74,77,78}

Intensive ventricular stimulation protocols (triple extrastimuli administered at rapid drive rates) in patients with HCM usually induce ventricular arrhythmias that require resuscitation. Most (>80%) of the ventricular arrhythmias provoked by triple ventricular premature depolarisations in patients with HCM are either polymorphic ventricular tachycardia or primary ventricular fibrillation—both of which are non-specific or irrelevant consequences of intensive programmed electrical stimulation, and which often do not resemble the clinically relevant ventricular arrhythmias that are evident in the same patients. Conversely, sustained monomorphic ventricular tachycardia is uncommon in HCM. Less intensive stimulation protocols^{71,73,78} are less likely to induce these ventricular arrhythmias, even in those patients with prior ventricular fibrillation. Also, because most patients with HCM selected for programmed electrical stimulation have already shown that they are at higher risk, inducible ventricular arrhyth-

mias can have little remaining discriminating power to stratify further the level of risk.

Consequently, most experienced electrophysiologists believe that programmed ventricular stimulation has a limited role in identifying patients with HCM who are at higher risk and require treatment for the prevention of sudden death.⁷¹⁻⁷⁹ This contrasts with patients with coronary artery disease and myocardial infarction in whom the reproducible induction of sustained monomorphic ventricular tachycardia often identifies a potential trigger, which usually reflects documented clinical arrhythmias as well as the electrophysiological substrate for arrhythmogenic risk.⁸² Certainly, in symptom free patients with HCM and non-sustained ventricular tachycardia on Holter monitoring the yield of programmed electrical stimulation is too low to warrant routine electrophysiological testing.

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