Sudden death and hypertrophic cardiomyopathy: A review.

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Abstract

Hypertrophic cardiomyopathy is a genetic disease that affects the cardiac sarcomere, resulting in myocardial hypertrophy and disarray. Affected patients have a predisposition for malignant ventricular tachyarrhythmias and, consequently, sudden cardiac death. With the availability of therapeutic measures that prevent sudden death, the identification of high-risk patients is now of greater importance. The clinical electrophysiological study is of limited use for stratifying these patients. More recently, increased attention has been given to the degree of echocardiographically documented left ventricular hypertrophy and prognostically significant genetic mutations. Once a high-risk patient is identified, prophylactic treatment is warranted. Tools are now available to identify and treat high-risk patients with hypertrophic cardiomyopathy.

Keywords: Suddendeath, Hypertrophic cardiomyopathy, Risk stratification.

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Introduction

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac myopathic disorder. First described in the medical literature more than 50 years ago [1], HCM is now known to result from mutations within one of at least 10 genes coding for the various cardiac sarcomeric proteins and is inherited in an autosomal dominant manner. HCM results in small vessel coronary artery disease, myocardial disarray and fibrosis accompanied by varying degrees of left ventricular hypertrophy (LVH). The complexity of this disease stems from heterogeneous genotypical origins and the variable degree of penetrance of the clinical phenotype. As a result, patients may have diverse morphological, functional and clinical manifestations, including a higher risk of sudden cardiac death (SCD).

The clinical diagnosis is most often made by two-dimensional echocardiography. The most widely accepted echocardiographic definition of HCM is a maximal left ventricular (LV) wall thickness of 15 mm or greater or the presence of asymmetrical septal hypertrophy (i.e., a septum that is at least 1.3 to 1.5 times the thickness of the posterior wall when measured in diastole) in the absence of any condition that can explain such a degree of LVH [2-4]. However, contributions from genetic research may modify the way that we define this disease in the future because some patients are identified as carriers of a mutant gene without clinically manifesting the disease.

HCM has a clinical prevalence of one in 500. Patients suffering from this condition are often seen by cardiologists and internists [5,6]. The initial estimates of mortality rates from HCM were high but were subject to referral bias [7]. Most figures from nonreferral hospitals have indicated a better prognosis, with an annual mortality rate of approximately 1% [8, 9].

However, within the broad disease spectrum of HCM, a subset of patients exists who are at a higher risk of premature death.

These patients, who are more susceptible to a sudden death, represent approximately 10% to 20% of the HCM population [10,11]. When data from referral centres and community-based studies were analyzed, this subgroup's annual mortality was as high as 5% [12-14]. This devastating consequence can be the initial presentation of HCM and is the most common cause of mortality in patients with HCM who are younger than 30 years of age [8,13,15,16]. Is the most common cause of sudden cardiac death in trained athletes [17,18].

Therefore, the identification of individuals at risk of SCD remains a major challenge, especially because some of these deaths may be preventable by using prophylactic treatment strategies, including implantable cardioverter-defibrillators (ICDs).

Pathophysiological Mechanisms of SCD

Myocardial ischemia has long been known to complicate the clinical course of patients with HCM and may play a role in the occurrence of sudden death. In adults, the cumulative effects of ischemia (particularly subendocardial ischemia) damage the myocardium, leading to fibrosis and scarring, thus favouring re-entrant ventricular arrhythmias. In addition, the electrical instability from a disorganized myocardial architecture caused by myocardial disarray increases the susceptibility for re-entry [19,20]. In the pediatric population, the association between ischemia and SCD is well known, and it has been suggested that ischemia may act as a trigger for ventricular arrhythmias in children and adolescents [21,22]. Ischemia occurs from either an increased myocardial oxygen demand (from massive myocardial hypertrophy, myocyte disarray and abnormal architecture, diastolic dysfunction, arrhythmia or dynamic ventricular obstruction) or a reduced myocardial perfusion (from small vessel coronary artery disease, diminished myocardial coronary blood flow reserve from microvascular dysfunction, myocardial bridges with continued coronary underfilling due to impaired diastolic relaxation of the compressed vessel or abnormal vascular responses) [21,23-25].

Whatever the initial precipitant is in an individual patient (eg, ischemia or potential for re-entry), ventricular arrhythmias are ultimately responsible for sudden death in most cases. Ambulatory monitoring of patients with HCM with syncope has documented ventricular tachycardia degenerating into ventricular fibrillation [26,27]. As well, Cecchi et al. [28] showed that at the time of resuscitation from cardiac arrest, 31 of 32 patients with HCM were found to have documented ventricular fibrillation.

Furthermore, the ICD has provided us with a unique insight into the precise mechanism of SCD associated with this type of cardiomyopathy. Although initial observations seemed less convincing [29], subsequent observations from defibrillator recordings provided evidence that cardiac arrest is almost always due to ventricular tachycardia or ventricular fibrillation [30].

HCM, in majority of cases, is inherited as an autosomal dominant genetic trait with a 50% risk of transmission to offspring [31]. The likelihood of finding a causal mutation is highest in patients with familial disease and lowest in older patients and individuals with non-classical features.

Syncope

Syncope in HCM include as causes: hypovolemia, complete heart block [32], sinus node dysfunction, sustained ventricular tachycardia, LVOTO [32,33], and abnormal vascular reflexes [32,34,35]. Atrial arrhythmias with fast ventricular response can eventually precipitate syncope, particularly in individuals with preserved atrial function and high filling pressures [32,36]. There can be more than one reason why patients with HCM lose consciousness, including co-morbidities such as epilepsy and diabetes [37].

Syncope that occurs after prolonged standing in a hot environment, or during the postprandial absorptive state, is suggestive of neurally mediated (reflex) syncope, particularly when it is associated with nausea and vomiting. Syncope that occurs during exertion, or immediately following palpitation or chest pain, suggests a cardiac mechanism [37]. Provocable obstruction should be excluded when patients experience recurrent effort syncope in similar circumstances. Ventricular arrhythmias are an uncommon cause of syncope, but should be suspected after an unheralded episode, particularly when it occurs at rest or on minimal exertion.

As unexplained non-vasovagal syncope is a risk factor for sudden cardiac death [32,38,39], particularly when it occurs in young patients in close temporal proximity to their first evaluation [38], treatment with a prophylactic implantable cardioverter defibrillator (ICD) may be appropriate in individuals with other features indicative of high sudden death risk, even if the mechanism of syncope is undetermined. Knowing that syncope may be caused by mechanisms other than ventricular arrhythmia means that patients may remain at risk of recurrent syncope after ICD implantation.

Patients with syncope should undergo 12-lead ECG, standard upright exercise test and 48-hour ambulatory ECG monitoring and, if a bradyarrhythmia is identified, it should be treated in accordance with current Guidelines on cardiac pacing [39,40]. Exercise stress echocardiography should be considered, particularly in patients with exertional or postural syncope, to detect provocable LVOTO.

In patients with recurrent episodes of unexplained syncope, who are at low risk of SCD, an implantable loop recorder (ILR) should be considered [40,41]. There are few data on tilt testing in patients with HCM, but a high rate of positive tests in patients without a history of syncope suggests that it is not useful in routine assessment unless there are other features to suggest an autonomic mechanism [37,42,43].

Sudden Cardiac Death

The annual incidence for cardiovascular death in patients with HCM is of 1–2%, with SCD, heart failure and thromboembolism being the main causes of death. The most commonly reported fatal arrhythmic event is spontaneous ventricular fibrillation (VF), but asystole, AV block and pulseless electrical activity are described [32].

Clinical Risk Assessment

Estimation of SCD risk is an integral part of clinical management. A large body of evidence suggests that, in adolescents and adults, the risk assessment should comprise of clinical and family history, 48 hour ambulatory ECG, TTE (or CMR in the case of poor echo windows) and a symptom-limited exercise test.

Models for Estimating Sudden Cardiac Death Risk

Many Trials have shown that implantation of an ICD for primary and secondary prophylaxis can reduce mortality in other cardiovascular diseases [44,45]. However, the threshold of risk that justifies device implantation is usually defined by the clinical characteristics of the populations enrolled in such studies, rather than an a priori definition of acceptable risk. This gives rise to a number of inconsistencies as the characteristics of trial populations vary. It is also likely that societal, economic and cultural factors influence the recommendations made by guideline committees.

There are no randomized trials or statistically validated prospective prediction models that can be used to guide ICD implantation in patients with HCM. Recommendations are instead based on observational, retrospective cohort studies that have determined the relationship between clinical characteristics and prognosis.

In the previous version of these Guidelines [46] and a more recent guideline from the American College of Cardiology Foundation/American Heart Assocation [47] a small number of clinical characteristics (NSVT, maximal LV wall thickness ≥ 30 mm, family history of SCD, unexplained syncope, and abnormal blood pressure response to exercise) were used to estimate risk and to guide ICD therapy.

This approach has a number of limitations: specifically, it estimates relative and not absolute risk; it does not account for the different effect size of individual risk factors [48]; and some risk factors such as LV wall thickness are treated as binary variables when they are associated with a continuous increase in risk [49]. Consequently, current risk algorithms discriminate modestly between high- and low-risk patients [48].

Other clinical features, such as myocardial fibrosis (determined by contrast enhanced CMR), LV apical aneurysms and the inheritance of multiple sarcomere protein gene mutations, have been suggested as arbiters that can be used to guide ICD therapy in individuals who are at an intermediate risk, but there are few data to support this approach [49-51].

Recently, a multicentre, retrospective, longitudinal cohort study of 3675 patients-known as HCMRisk-SCD-developed and validated a new SCD risk prediction model [52]. HCM Risk-SCD uses predictor variables that have been associated with an increased risk of sudden death in at least one published multivariable analysis [52]. This excludes abnormal blood pressure response as a risk marker. The model provides individualized 5-year risk estimate and, in a head to head comparison with a model using four major risk factors, the performance of the prediction model improved substantially (C-index from 0.54 to 0.7) and compared favourably with other similar prediction algorithms such as CHA2DS2-VASc.

Prevention of Sudden Cardiac Death

Exercise

Although sustained ventricular arrhythmias induced by exercises are rare and most ICD therapies for ventricular arrhythmias occur in the absence of tachycardia or physical exertion [53,54], patients with HCM should be advised against participation in competitive sports and discouraged from intense physical activity, especially when they have risk factors for SCD and/ or LVOTO.

Anti-arrhythmic drugs

There are no randomized, controlled data to support the use of antiarrhythmics for the prevention of SCD in HCM. Amiodarone was associated with a lower incidence of SCD in one small observational study of patients with NSVT on Holter monitoring and in others, increased the threshold for VF, but observational data suggest that amiodarone often fails to prevent SCD [55,56]. Disopyramide does not appear to have a significant impact on the risk of SCD.

Implantable Cardioverter Defibrillators

Secondary prophylaxis

HCM patients who survive VF or sustained ventricular tachycardia are at very high risk of subsequent lethal cardiac arrhythmias and should receive an ICD [57-60].

Primary prophylaxis

Identification of individuals who are at high risk of SCD for primary prevention remains a challenge and only a small subgroup of individuals currently treated with an ICD receives potentially lifesaving shocks [61]. The HCM Risk-SCD dataset has been used to construct three categories of risk (high, intermediate and low) that were determined by consensus. The recommendations for primary prevention ICD therapy in each risk category take into account not only the absolute statistical risk, but also the age and general health of the patient, socio-economic factors and the psychological impact of therapy. The recommendations are meant to be sufficiently flexible to account for scenarios that are not covered by the HCM Risk-SCD model.

Practical aspects of ICD therapy

Prior to ICD implantation, patients should be counselled on the risk of inappropriate shocks, implant complications, and the social and occupational implications (including driving restrictions) of an ICD. Studies examining the role of defibrillation testing at the time of implantation are continuing, but high defibrillation thresholds are reported in patients with severe LVH and in those on amiodarone treatment [62-65]. Until data specific to HCM are available, defibrillation testing may be considered at the physician's discretion. For patients who have a high defibrillation threshold or who fail to cardiovert on defibrillation testing, options include sub-pectoral implantation and standard manoeuvres such as reversal of shocking vector polarity, changing the shock tilt, including/excluding a superior vena cava coil followed by re-testing and, if necessary, implantation of a subcutaneous array.

The VF zone of the device should be programmed at.220/ min to minimize shocks from rapidly conducted AF. An SVT discrimination zone, tailored to individual patient characteristics, may also be considered.

Observational data show that anti-tachycardia pacing is effective in terminating ventricular arrhythmias in HCM but does not reduce the incidence of appropriate shocks [53,62]. As atrial leads do not reduce the incidence of inappropriate shocks [59,60] most patients require only a single ventricular lead. Exceptions include patients with LVOTO, in whom an atrial lead provides the option for a short AV delay pacing, and patients in sinus rhythm with impaired LV systolic function, in whom CRT might be preferable. In the light of results from the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT), shock-only programming can be considered in primary prevention, although this trial was conducted in patients with low EF [66,67]. ß-Blockers and/or amiodarone are recommended in patients with an ICD, who continue to have symptomatic ventricular arrhythmias or recurrent shocks despite optimal treatment and device reprogramming.

Electrophysical study is recommended in patients with ICDs and inappropriate shocks due to regular supraventricular tachycardias, in order to identify and treat any ablatable arrhythmia substrate [68].

The newly developed subcutaneous ICD lead system has FDA approval and may be considered in HCM patients who have no indication for pacing [69]. Particular attention should be paid to ensuring optimal R-wave sensing at rest and on exercise, in order to avoid inappropriate shocks from T-wave oversensing. Each patient should have more than one ECG vector that passes screening, to allow alternative programming if oversensing does occur [70,71]. Data from a multicenter registry that included 58 HCM patients provided preliminary efficacy and safety data[72].

Risk of Sudden Death in Children

ICD implantation as secondary prophylaxis is indicated after a life-threatening ventricular arrhythmia in children. There is a lack of data for clinical risk stratification to determine the need

for primary prophylaxis with an ICD in very young children. The risk of death or heart transplantation is greatest in infants or in patients with inherited metabolic disorders and malformation syndromes [73]. There is general agreement that, as in adults, severe LVH, unexplained syncope, NSVT and a family history of sudden death represent major risk factors for sudden cardiac death [74]. The definition of severe hypertrophy in infants, children and pre-adolescents has been assessed using different approaches and measurements [75,76].

Conclusion

Implantation of an ICD should be considered in children who have two or more major risk factors. Single-chamber defibrillators suffice in the majority of cases and reduce the likelihood of complications.

In individual patients with a single risk factor, ICD implantation maybe considered after careful consideration of the risks and benefits to the child and family.

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