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REVIEW

Hypertrophic cardiomyopathy and sudden cardiac death

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Abstract

Hypertrophic cardiomyopathy (HCM) is a common genetic cardiovascular disease that affects the left ventricle. HCM can appear at any age, with the majority of the patients remaining clinically stable. When patients complain of symptoms, these include: dyspnea, dizziness, syncope and angina. HCM can lead to sudden cardiac death (SCD), mainly due to ventricular tachyarrhythmia or ventricular tachycardia. High-risk patients benefit from implantable cardioverter-defibrillators. Left ventricular outflow tract obstruction is not a rare feature in HCM, especially in symptomatic patients, and procedures that abolish that obstruction provide positive and consistent results that can improve long-term survival. HCM is the most common cause of sudden death in young competitive athletes and preparticipation screening programs have to be implemented to avoid these tragic fatalities. The structure of these programs is a matter of large debate. Worldwide registries are necessary to identify the full extent of HCM-related SCD.

GENETICS

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiovascular disease[1] and is associated with sudden death, especially in young adults[1-3]. For that reason, HCM constitutes a vast domain of clinical and experimental research and thousands of reports have been published in the international literature. HCM is defined as the presence of a hypertrophied, non-dilated left ventricle that occurs in the absence of another cardiac or systemic disease that could produce a similar degree of hypertrophy[2,4-6]. HCM is a relatively common, primary heart disease that affects one individual in every 500 in the general population[3,7]. It is inherited predominantly as a an autosomal dominant trait[1,8]. At least 24 genes have been associated with HCM and over 400 mutations have been discovered to date[9-14]. Although the majority of these genes encode sarcomeric proteins[1,6,15], recent research has indicated that some disease patterns might involve different pathways[9,16].

Genome studies that have identified new loci or pathways have indicated that there is long way ahead to un-

derstand completely the etiology of HCM[16-18]. These studies have basically followed two research approaches: (1) beginning from a mutation phenotype and advancing towards the identification of the mutated gene (forward genetics); and (2) beginning from a cloned DNA segment or a peptide sequence, they have introduced programmed mutations that aim to assess gene and protein function (reverse genetics)[19-23]. The mutations of any particular gene might lead to different phenotypic expressions as well as different disease time courses[1,6]. Furthermore, specific genes have been associated with favorable or unfavorable prognosis[6,8,9]. Some studies have managed to correlate septal morphology in HCM with a specific genotype[24,25], thus providing echocardiographic guidance to genetic screening. However, the phenotypic expression of HCM is further complicated by the existence of possible modifier genes or environmental factors[3,26]. Therefore, although promising, this discovery has a long way to go before its full implementation in screening protocols[27,28]. In addition, there is a possibility that genes implicated in ion channel abnormalities play a significant role in cardiomyopathy *via* a common pathway, or the possibility that genes that encode the same family of proteins might be implicated in different pathologies (such as HCM and arrhythmogenic right ventricular cardiomyopathy)[8]. For the moment, genetic screening can identify a mutation in 50%-60% of patients [29]. Additional factors or genetic loci remain to be discovered.

PATHOPHYSIOLOGY

Cellular changes

In the healthy myocardium, myocytes have a typical parallel alignment, however, in HCM they become hypertrophied, enlarged and distorted, which leads to disorientation of adjacent cells and arrangement in a random pattern (myocyte disarray). This disarray might be localized and surrounded by normal myocardium or it can occupy the majority of the ventricular surface. Pathological myocyte morphology leads to premature cellular death and continuous myocardial tissue remodeling, with the participation of cardiac fibroblasts. Furthermore, increased depositions of collagen are observed between the smooth muscle cells of the intramural coronary arteries[2,3,30].

Structural changes

Changes in myocyte architecture lead to ventricular hypertrophy, and the development of fibroblasts between myocytes results in fibrosis and extensive myocardial scarring. Collagen accumulation leads to thickened and narrowed intramural coronary artery walls[3,6,31].

Clinical pathophysiology

The aforementioned cellular and structural changes have major functional consequences, such as ventricular stiffness and reduced ventricular compliance, which in turn can lead to prolonged relaxation times that result in diastolic filling impairment and reduced cardiac output with increased filling pressure. Myocardial ischemia also develops, and combined with the increased muscle mass, has a potent ischemic effect[6,31].

Hypertrophy, fibrosis, myocardial ischemia and abnormal intramural coronary arteries can exist separately or simultaneously in HCM. Therefore, the resultant scarred myocardial tissue is an unfavorable substrate for both conduction and propagation of electrical impulses. Myocardium in HCM comprises zones of normal myocytes adjacent to or embedded in scar tissue, which decelerates or interrupts conduction. In addition, dispersion of repolarization occurs because of abnormalities in gap junction function and distribution. Furthermore, both left ventricular (LV) relaxation and contraction might not be uniform, because of the varied distribution of LV hypertrophy (LVH)[32]. These malfunctions lead to multiple asynchronized electrical impulses traversing the myocardium, and through reentry mechanisms, to ventricular tachyarrhythmia[10,32-35]. Of course, supraventricular arrhythmias are also frequent in this setting (10%-40% in HCM)[31,36,37]. In fact, atrial fibrillation (AF) is the most common sustained arrhythmia in HCM[1].

The increased ventricular wall stress, as in cases of LV outflow tract obstruction (LVOTO), can lead to increased oxygen demand, cell death and replacement fibrosis[3]. The elevated filling pressure might also result in subendocardial ischemia, and systolic compression of arteries can also occur. In addition, the disturbed reflex control of the vasculature is an important cause of myocardial ischemia, especially during exercise, where inappropriate hypotension occurs and results in myocardial hypoperfusion[6,31].

It is estimated that approximately 25% of the patients with HCM have LVOTO under resting conditions[38,39]. This mechanical impedance[39,40] creates outflow gradients of > 30 mmHg[41]. In HCM, outflow gradients are characteristically dynamic. This means that any given patient might present a large outflow gradient in some circumstances, but a reduced gradient in others (e.g. exercise, valsalva maneuver, or sudden standing from a squatting position)[1,6].

Until recently, clinical assessment and identification of LVOTO were undertaken in resting conditions to determine the obstructive form of HCM and commence further treatment. In 2003, the American College of Cardiology and the European Society of Cardiology, in their consensus document on HCM, proposed a division of the overall HCM disease spectrum into hemodynamic subgroups, (based on the representative peak instantaneous gradient as assessed with continuous wave Doppler) to facilitate decision making in treatment and to detect latent forms of LVOTO[3]. There are now indications that LVOTO is a more common feature in most patients with HCM (up to 70%) under exercise conditions. These observations could have clinical implications for both the evaluation and management of patients with HCM, especially whether subaortic gradients should be assessed in all patients[31,42].

NATURAL HISTORY

HCM is a disease that can appear at any age, from infancy to very old age, with a varied clinical course. Most patients remain clinically stable or asymptomatic, and in some cases, their symptoms might even improve over the course of time[1]. HCM has an annual mortality rate of 1%. Clinical deterioration is usually slow and elderly patients (> 75 years) can constitute up to 25% of the total patients[1,3]. The disease course might follow a specific subgroup pattern or interchange between patterns. It is estimated that about 5% of the patients among the vast HCM spectrum evolve towards the end-stage phase of the disease, which is LV wall thinning (extensive fibrosis), cavity dilatation and systolic impairment[1,29,43]. However, the most common mode of demise in HCM and its most serious complication is sudden death[1,6].

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Symptoms

Many patients with HCM can be completely asymptomatic. Symptomatic patients present commonly with symptoms associated with LVOTO. Dyspnea can be encountered in 90% of symptomatic patients[1,6]. Fatigue, dyspnea, exercise intolerance, dizziness, presyncope and syncope are also common. An important etiological factor for syncope or palpitations is cardiac arrhythmia. Patients with HCM might present with AF, premature ventricular depolarization, ventricular couplets, non-sustained ventricular tachycardia (VT), or sustained VT, which can deteriorate to ventricular fibrillation (VF). However, it should be noted that there is no particular course of progress (or deterioration) of arrhythmic events in HCM, and that patients with minor previous arrhythmic events might suffer VF cardiac arrest[10]. Congestive heart failure can be manifested with palpitations and/or paroxysmal nocturnal dyspnea. Chest pain (angina pectoris) can be experienced in 75% of symptomatic patients. It is attributed to the imbalance between oxygen supply and demand, pathological intramural coronary arteries, and increased LV wall pressure. Another contributing factor for myocardial ischemia could be pre-existent atheromatous disease in older patients. The severity of these symptoms, which are affected by many factors such as exertion or even dietary factors such as alcohol consumption, or a heavy meal, can change throughout the day[1,26]. Unfortunately, sudden death might be the first and only manifestation of HCM.

Physical examination

Physical examination can be normal in asymptomatic patients. In the presence of LVOTO, precordial examination might reveal a hyperdynamic apical precordial impulse, or a double apical impulse as a result of LV forceful contraction. A less common feature is a triple apical beat that occurs secondary to the addition of a palpable atrial gallop[37]. Carotid artery palpation can reveal a brisk rise in the pulse, with subsequent decline in mid-systole, followed by a secondary rise in late systole in cases of LVOTO[6,37]. In auscultation, S_1 is normal, but an S_4 can be heard during atrial systole. In patients with severe LVOTO, paradoxical S_2 splitting might be noted[37]. Auscultation can also reveal a harsh crescendo-decrescendo characteristic systolic murmur in patients with outflow obstruction. It usually starts after S_1 and can be heard from the apex until the sternal notch. Although characteristic of HCM, this murmur is not found in the majority of patients[37].

Physical examination should not be oriented only towards the cardiovascular system. For example, a hypertrophied left ventricle might also be encountered in genetic syndromes such as Fabry disease, or LEOPARD Syndrome. Sensorineuronal deafness, and eye and skin disorders should be carefully assessed with explicit attention, to make the diagnosis of HCM from other pathological entities[44,45].

Electrocardiographic manifestations

The majority of patients with HCM have abnormal electrocardiographic (ECG) patterns[37], which can be present even in cases in which hypertrophy is not yet echocardiographically detectable[26,46] as in adults with cardiac myosin-binding protein C mutations[30,47], which means that it is a helpful diagnostic tool in these cases. The most common abnormalities are ST segment and T-wave changes and large QRS complexes, which are evidence of LVH[3,48]. Deep, narrow Q-waves are present in 20-50% of cases, and involve inferior (Ⅱ, Ⅲ, aVF) and lateral leads (Ⅰ, aVL, V_5, V_6)[26]. High-voltage R-waves might also be present in the precordial leads[26,49]. Although QRS, ST and T-wave changes are the most common in HCM, Q-wave changes are more characteristic and should be given proper attention when encountered[37]. However, all these different ECG patterns can neither be accurately related to the degree of LVH nor predict HCM-related death[1,50].

Diagnosis

Marked ECG abnormalities, exertion fatigue, presyncopal events, dyspnea or palpitations of recent onset or discovery of a murmur in a routine evaluation should raise suspicion of HCM. Diagnosis is customarily made with 2D echocardiography or magnetic resonance imaging (MRI) when ultrasound studies are technically inadequate or segmental LV wall thickening is difficult to visualize with ultrasound[1,51-54]. Furthermore, MRI might play a significant role in the future in the evaluation of patients with HCM, because it can reliably estimate the degree of LVH[52] and the existence of intramural coronary arteriole dysplasia[53]. Furthermore, MRI with late gadolinium enhancement can detect early structural changes at the microvascular level, thus providing not only a helpful tool of significant diagnostic and prognostic importance, but also a means that could promote early intervention in the disease course[55,56].

HCM diagnosis is established by the identification of a hypertrophied and non-dilated left ventricle in the absence of other cardiovascular diseases that are capable of producing a similar magnitude of hypertrophy[1,3,4,54]. With normal wall thickness estimated at no more than 12 mm, echocardiography might reveal cases that range from mild hypertrophy (13-15 mm) to massive (> 30 mm) or even more extensive hypertrophy[48,57,58]. Usually echocardiography will also reveal some of the following features: small LV cavity, reduced septal motion, mitral valve prolapse or a hypokinetic septum.

SUDDEN CARDIAC DEATH IN HCM

Mechanisms of sudden cardiac death

LVOTO, myocardial ischemia and changes in vascular architecture play a significant role in sudden cardiac death (SCD), with a varied impact. A bimodal pattern in the circadian variability of SCD has been observed, with a distinctive peak in the early morning hours and a second, less prominent peak in the early evening. Recent studies, however, after the implementation of implantable cardioverter-defibrillators (ICDs), have reported a modest but significant increase in appropriate ICD interventions between noon to midnight, which indicates that there is a disparity in circadian variability of SCD in HCM patients[59,60]. These studies also suggest that ventricular tachyarrhythmia and/or VT is the most probable mechanism of SCD in HCM. SCD in HCM is rarely due to bradyarrhythmia (when the conduction system is infiltrated)[1,29,61].

Sudden death is the major and frequently the only complication of HCM. In fact, HCM is the most common cause of SCD in young people including competitive athletes[3,62]. Although adolescents and adults younger than 35 years of age show a high incidence of SCD, this does not mean that the other age groups are risk-free. SCD can occur during any kind of activity, from sleep to very severe exercise[2]. SCD has been reported to affect as much as 6% of the patients in selected cohorts from tertiary centers[3,40,63].

Risk stratification

Identification of HCM patients at high-risk for SCD is an important as well as difficult task, given the fact that SCD is a devastating complication, and many of these patients might have no symptoms at all before the fatal outcome. The heterogeneity of clinical expression of the disease has made the identification of a single prognostic index difficult. However, several observational studies[3,40,48,57,64-66] have managed to distinguish features of the disease that are indicative of a higher SCD risk. These risk factors have been categorized as "major" and "possible in individual patients" by successive consensus documents from the American College of Cardiologists, the American Heart Association and the European Society of Cardiology (Table 1)[3,67].

Table 1 Risk factors for sudden cardiac death in hypertrophic cardiomyopathy

Major risk factors	Possible in individual patients
Cardiac arrest (VF)	AF
Spontaneous sustained VT	Myocardial ischemia
Family history of premature sudden death	LVOTO
Unexplained syncope	High-risk mutation
LV thickness ⩾ 30 mm	Intense (competitive)
Abnormal exercise BP	physical exertion
Non-sustained spontaneous VT	

VF: Ventricular fibrillation; VT: Ventricular tachycardia; BP: Blood pressure; LV: Left ventricular; AF: Atrial fibrillation; LVOTO: Left ventricular outflow tract obstruction.

Genetic testing might play a role in HCM risk stratification in the future, but for the time being, it is bound by many limitations, such as the vast phenotypic variations of specific gene mutations, and the fact that it is a method restricted to research laboratories and not available to every day evaluation. In addition, the prevalence of identifiable mutations in HCM has reached only 60% of studied cohorts, which leaves more than a third of the patients with genetically unexplained disease[4,8,68,69]. Nevertheless, there are indications that genotype-phenotype associations can be established in HCM (mutations in cardiac myosin-binding protein C have a rather benign course, and prognosis in patients with β-myosin chain mutations is allele dependent and varies considerably)[8,9,11,15]. Finally, genetic analysis could be helpful in families with HCM, by providing a presymptomatic diagnosis and genetic counseling.

Many of the aforementioned risk factors are interdependent and the positive predictive value of each one individually is limited. Thus, multiple risk-factor estimation could lead to a better prediction of risk of SCD. In contrast, their high negative predictive values can be safely used as an estimate for favorable prognosis[31,48,67,70].

Role of electrophysiological studies

Induction of ventricular tachyarrhythmia by programmed ventricular stimulation is of limited value and does not offer any advantage over noninvasive risk stratification in HCM[10,67,71]. Even if invasive testing has not been abandoned, other methods are being studied, such as paced electrogram fractionation analysis (which might be able to detect patients at risk of VF)[72], but are still far from having an established value in risk stratification for SCD.

MANAGEMENT OF HCM AND PREVENTION OF SCD

Patient assessment

In a patient with HCM, routine examination should comprise personal and family history, physical examination, 12-lead ECG, 24-h Holter ECG, 2D echocardiography,

and exercise testing. Risk analysis should not be forgotten and should be performed based on the clinical situation. These patients should not participate in competitive sports. Intense exertion and other strenuous physical activities should be avoided[1,10,29]. However, these patients should not refrain from all physical activities. Asymptomatic patients with no LVOTO, no risks for SCD, and mild LVH can participate in recreational sports of mild to moderate intensity [73,74]. When a patient is diagnosed with HCM, first-degree relatives should be examined by ECG and echocardiography and clinical screening should be undertaken every 2 years in young relatives and about every 5 years in adults[10,29].

The wide range of phenotypic expressions of HCM and its possible devastating complications, especially in young asymptomatic populations, have created great concern and debate about how to prevent SCD. In 2006, the American College of Cardiologists, the American Heart Association and the European Society of Cardiology released new guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[67]. In this document, the role of ICDs in the prevention of SCD is primary, in contrast to the role of pharmacological treatment and electrophysiological testing. ICD therapy is strongly warranted (class I indication, level of evidence: B), as secondary prevention for SCD, for patients with HCM who have sustained VT and/or VF (prior cardiac arrest). ICD implantation is recommended as a reasonable procedure (class Ⅱa) for primary prophylaxis in patients with HCM who have one or more major risk factors. Nevertheless, since the positive predictive value of each individual risk factor for SCD is limited, caution has to be taken in not implanting ICDs in patients who do not need them, and putting them in danger from complications from the procedure. Thus, multiple risk factors are considered to offer a greater possibility of SCD[3,29,54,67]. However, data from a large multicenter registry study from ICDs implanted over a 17-year period have indicated that there was no significant difference in the probability of appropriate ICD discharges between patients with 1, 2, 3 or more noninvasive risk factors[75]. The matter of ICD implantation for primary prophylaxis needs further clarification. A possible logical approach would be that management approaches should be based on assessment of each patient's overall clinical profile[31,75]. There is a debate whether all ventricular arrhythmias occurring in non-ischemic cardiomyopathies are truly potentially fatal, or the majority of them are self-limited, thus making ICD implantation potentially harmful[75,76]. Nevertheless, data are strongly in favor of ICD implantation in selected patients. ICDs provide highly effective discharges, even in primary prevention of SCD in HCM[10,75,77,78], significantly reduce mortality[78], improve long-term survival, and increase quality-adjusted life expectancy[79,80].

Pharmacological therapy has little place in prevention of SCD in HCM. Amiodarone is the agent indicated because of its antiarrhythmic properties. Amiodarone can be used in patients with a history of sustained VT and/or VF (class Ⅱa), and can be considered (class Ⅱb recommendation) for primary prophylaxis for SCD in patients with one or more major risk factors for SCD, if ICD implantation is not feasible[67]. Furthermore, there is strong evidence of ineffectiveness of Amiodarone in preventing SCD in HCM, as indicated by several studies and the high incidence of appropriate ICD discharges in patients receiving amiodarone[75,81,82].

HCM pharmacological management is symptom-based. Patients with obstructive symptoms or heart failure are treated with β-blockers or calcium channel antagonists (principally verapamil). Reduced heart rate and decreased contractility resulting from their action, might alleviate symptoms related to LVOTO, such as presyncope, dyspnea, and angina. Both agents improve diastolic filling (by reducing the heart rate and improving relaxation, respectively) and can decrease the outflow gradient[1,3,54]. Disopyramide has also been used, probably for its depressing action on ventricular systolic performance[83].

The group of patients (5%) that progress to the end-stage phase of HCM should be treated for heart failure with the progressive addition of diuretics, ACE inhibitors and possibly digitalis. The final therapy point might be heart transplantation[1,3,54,84]. In cases that are unresponsive to drugs, septal surgical myectomy or percutaneous alcohol septal ablation (ASA) should be performed. Through a transaortic approach, myectomy is performed by excising a portion of the hypertrophied muscle. ASA creates a transmural scar in the proximal hypertrophied ventricular septum, by delivering alcohol through an angioplasty catheter, which reduces the outflow gradient[85]. Both interventions have been proven to be equally effective at reducing outflow obstruction[86], which results in substantial and consistent symptomatic benefit, and restoration of quality of life throughout long-term follow-up[87-89]. Furthermore, both techniques appear to have a comparable risk for procedural death and complications[90]. ASA creates a sizeable transmural myocardial infarction that comprises about 10% of the left ventricle, which could serve as a substrate for potentially life-threatening ventricular tachyarrhythmias and sudden death[90]. Hence in 2003, an expert consensus panel from the American College of Cardiology and the European Society of Cardiology suggested surgical myectomy as the primary treatment for patients with obstructive HCM and unrelenting symptoms, with ASA reserved as an alternative option for those patients who are judged not to be appropriate surgical candidates[3]. However, there is emerging evidence that ASA might not affect the occurrence of arrhythmic episodes[91,92]. It should be noted in this context that large cohort studies[93-96] have demonstrated an association between LVOTO abolition and improvement of overall survival. Furthermore, there are indications that myectomy is beneficial before ICD implantation[97]. These observations along with more careful diagnostic processes will probably change our view of HCM as a progressive heart muscle disorder with continued LV remodeling, despite the best available treatment interventions[3].

AF, a common feature in HCM, is associated with embolism, heart failure and is independently associated with heart-failure-related death and stroke[36,98]. Anticoagulant therapy with warfarin is warranted in patients with AF[79]. Amiodarone can be effectively used in paroxysmal AF[1,3,54].

Future therapeutic strategies

Recent research has unraveled the role of protein kinases in the regulation of myocyte repair, growth, contractility and myogenic differentiation. Furthermore, histone deacetylases (HDACs) seem to play a regulatory role in hypertrophic cardiac growth, in association with protein kinases[99-103]. Even if there is no clinical impact for the present, HDAC inhibitors, specific kinase-inhibitors in association with targeted gene therapy are expected to play a central role in the future.

Prevention of SCD in athletes

Sports participation increases the risk of SCD in HCM patients[1,62]. HCM is the single most common cause of young athlete mortality in the United States[104]. Therefore, attention has focused on development of preparticipation screening strategies on both sides of the Atlantic[104,105]. However, a major determinant in all prevention strategies is cost-effectiveness and that is a major issue of debate in the current literature of sports-related SCD prevention in patients with HCM. Thus, based on the Italian experience[106,107] of preparticipation screening of young competitive athletes, the European Society of Cardiology recommends a preparticipation screening strategy that comprises family and personal history, physical examination, and 12-lead ECG[105]. In contrast, the American Heart Association focuses on medical history (family and personal) and physical examination[104]. Recent data from the United States suggest that, in demographically similar regions of the United States and Italy, athlete sudden death rates have not differed significantly in recent years, despite different preparticipation screening strategies[108]. Nevertheless, it is a fact that preparticipation screening followed in Italy has given surprising and most importantly, life-saving results[105-107,109]. Both programs seem to be effective. However, it is probably more important to establish a worldwide registry that is aimed at determining the precise incidence of sudden death in young athletes than to further pursue a debate founded at different starting points.

CONCLUSION

The diagnosis of HCM has to be founded on a concrete basis and should not be confused with other syndromes with LVH. In this context,genetic testing will probably play a more significant role in the future. HCM course and gravity seems to be closely related to LVOTO. Procedures that abolish this obstruction are beneficial and improve survival, and their role could become more central provided that a solid diagnostic procedure is followed. Although unpredictable, HCM is a disease with symptoms that are amenable to treatment, and newer diagnostic strategies and interventions will hopefully prove helpful in preventing more sudden deaths. As for the sports-related deaths, certainly the implementation of preparticipation screening programs is indispensable. The proper strategy has yet to be elucidated. Additional attention should probably be paid to equipping public places and stadia with automated external defibrillators and implementing wide lay training programs.

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