# Sudden Death Risk Stratification in Hypertrophic Cardiomyopathy: Genetic and Clinical Bases

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Following the initial reports of Teare[1] and Brock[2], a growing number of publications on hypertrophic cardiomyopathy (HCM) have been generated each year reflecting the exponential progress in the understanding of this extremely complex clinical entity.

HCM presents as left ventricular hypertrophy associated with myofibril disarray and interstitial fibrosis, factors that cause diastolic dysfunction, myocardial ischemia and arrhythmias. The preliminary diagnosis, based on the clinical detection of forms with left ventricular outflow tract obstruction, evolved, with the advent of M-mode and two-dimensional echocardiography, to the identification of marked hypertrophy in the interventricular septum[3], a trait that was initially highlighted by Teare[1]. Subsequent studies have demonstrated the heterogeneity of the disease for both the extent of hypertrophy[4] and the clinical presentation, evolution and prognosis[5-7]. The introduction of molecular genetics during the past decade provided a new paradigm for the diagnosis of HCM, offering a better understanding of the pathogenetic mechanisms involved as well as the individualization of distinct anatomic and functional risk patterns.

HCM is the most common form of genetic cardiovascular disease and is responsible for one case in every 500 individuals[8]. It is characterized by the great variation of phenotypes. The echocardiogram demonstrates various degrees of the severity of left ventricle hypertrophy[8]. The absence of hypertrophy in 20% of the adults who have inherited the disease demonstrates that it can manifest with an incomplete phenotypic expression[9]. These individuals are also susceptible to develop complications such as arrhythmias and sudden death that confirms the importance of a diagnosis in the pre-clinical stage.

HCM is the main cause of sudden death in young people and athletes. This dramatic and unpredictable complication, affects individuals in any age group but is more prevalent in adolescents and young adults who often were never diagnosed with the disease and are asymptomatic[5,10]. The annual incidence of sudden death varies according to the selection criteria for the patients used in the studies and the clinical management methods. Data collected during the phase before the introduction of automatic implantable cardioverter defibrillators reveal numbers between 3% and 6% for children and adolescents[5], and between 2% and 4% for adults[5,6]. The majority of the epidemiological information available was collected at the few referral centers whose patients had a higher incidence of sudden death in relation to populations with a lower degree of selection criteria in whom the disease could have a benign evolution and lower annual mortality rates of approximately 1%[7,11,12].

Sudden death affects those that present left ventricle hypertrophy or myofibril disarray with normal wall thicknesses[8,13]. It usually occurs without prodromes either during or immediately after physical exercise that is not necessarily strenuous. It is estimated that these conditions account for approximately 50% of the deaths[8]. Sudden death can occur at rest, in the morning when awakening or with minimal exertion. Since the risk is higher while practicing competitive sports, the benefit of an early diagnosis is of utmost importance so that this type of activity, even during adolescence, can be avoided[14].

Sudden death in HCM has an arrhythmogenic basis. Records obtained in patients with automatic implantable cardioverter defibrillators reveal that appropriate discharges are related to ventricular fibrillation that may or may not be associated with previous monomorphic ventricular tachycardia[15,16]. Other rhythm disorders can intervene in the development of fatal ventricular arrhythmias such as atrial fibrillation with rapid ventricular rates, supraventricular tachycardia with rapid atrioventricular conduction over an accessory pathway, sinus tachycardia and atrioventricular blocks[17]. In the presence of these conditions, sustained ventricular arrhythmia is a fatal event.

Arrhythmias express the electrical instability of the myocardium and the presence of distorted electrophysiological transmission which is caused by myofibril disarray associated with interstitial fibrosis[18]. The characteristic histopathological substrate leaves the myocardium susceptible to factors that induce arrhythmogenesis. These factors may be intrinsic such as myocardial hypertrophy and outflow tract obstructions or extrinsic such as physical exercise. Left ventricular hypertrophy, in interfering with diastolic filling and constricting coronary circulation by increasing filling pressures, would facilitate the onset of ischemia. Outflow tract obstructions, abnormal peripheral vascular response to exercise and compromised microcirculation have a similar

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effect, since they alter coronary perfusion[18,19]. Although primary ventricular arrhythmias may exist, one of the main causal mechanisms is myocardial ischemia[14,18]. The consequent development of myocardial necrosis or reparative fibrosis can also cause reentrant arrhythmias[18,20].

Risk stratification for sudden death in HCM is a fundamental issue of clinical importance considering that it accounts for 50% to 70% of the deaths associated with this disease[10,21]. The acknowledgment that automatic implantable cardioverter defibrillators are effective in primary and secondary sudden death prevention has motivated the investigation for criteria to identify high risk patients. The low mortality rates, even in referral centers, and the evaluation of a limited number of case studies has jeopardized the individualization of risk factors and their respective interaction.

## Genetic Bases

Risk stratification criteria in HCM are difficult to define due to the clinical and genetic heterogeneity. The confirmation that sudden death often affects individuals without any known risk factors indicates that clinical evaluation may be insufficient to identify high risk situations. Patients with the same clinical profile from a genetic perspective could comprise a heterogenous population. The analysis of phenotype/genotype relations have enabled the discovery that genetic factors directly influence the development of sudden death and have a decisive role in risk stratification.

HCM is essentially a genetic process. More than 250 mutations involving eleven distinct genes have been identified so far[22-24]. Through the detection of mutations in sarcomere proteins it was possible to determine that the disease is caused by disorders that directly affect the generation or regulation of contractile energy. Recently, other proteins not related to sarcomeres such as the AMP-activated protein kinase, have been reported in the development of similar phenotypes[25]. Histopathological analysis of forms not related to sarcomeres with pseudohypertrophy invariably reveal the absence of myofibril disarray and the presence of vacuoles containing glycogen[26]. These situations must be differentiated from true HCM in which there is no indication of infiltration or storage processes. The clinical management and risk stratification analyzed in this paper relates to HCM caused by sarcomere disease and does not include genetic processes from other origins.

The phenotype is determined by the mutant gene, but there is great clinical variation between and within families[22]. Phenotypic expression is influenced by environmental factors, the action of modifier genes and by the fact that it incides on a surprising number of heterozygote individuals composed of multiple mutations within the same gene or in distinct genes[24,27-29]. Even though the modifier genes are not the cause of the disease, they determine the degree of hypertrophy and the propensity for sudden death[30]. The most important one is the insertion/deletion polymorphism of the angiotensin converting enzyme, which is related to severe hypertrophy and the tendency for sudden death. The DD genotype is more often found in high risk families[30].

The allelic heterogeneity in addition to the small number of families evaluated, that often have distinct mutations, complicate the analysis of phenotype/genotype relationships.[29,31] Clinical correlation studies have revealed differences between the genes that cause the disease in regard to penetration, age of onset, morphology and prognosis. As a result, it can be stated that HCM has eleven subforms, each with a distinct pathogenic and clinical picture. The identification of malignant mutations and others with favorable evolution is the basis of genetic molecular diagnosis in sudden death risk stratification. Nevertheless, the clinical profile of the various mutations has been determined in analyses conducted in referral centers with large concentrations of high risk patients. Even though the individualization of benign and malignant mutations offers a certain amount of homogeneity among the patients, consideration must be given to the fact that the clinical symptoms vary from individual to individual.

## Genes and Mutations

Among the various genes involved, those that codify the cardiac beta-myosin heavy chain, myosinbinding protein-C and troponin T are predominant and account for 60% to 70% of the cases[28]. The actual incidence of each gene needs to be verified in large scale epidemiological analyses. The others account for a minority of patients, corresponding to no more than 5% of the cases[28,29]. It is believed that most of the genes have been identified.

Mutations of the cardiac beta-myosin heavy chain affect 15% to 35% of the people with HCM[29,32-34]. Most are distinct and designated as missense in which the substitution of a single DNA basis results in the replacement of the coded aminoacid[32]. Among the more than 100 mutations identified the individual incidence is reduced[32,35]. The majority are characterized by a high penetrance rate, severe hypertrophy and onset at a young age[32,33,35]. The susceptibility to sudden death is variable according to the mutation and is generally proportional to the degree of hypertrophy[27]. Those that are malignant correspond to roughly one third of the cases, present with accentuated hypertrophy, left ventricle outflow tract obstructions and premature sudden death before 35-40 years[29,32]. There is a great phenotypic variation between individuals and even among family members with the same mutation. Theclinical presentation form can be insufficient for risk stratification since early onset and a family history of sudden death have been observed in patients with either benign or malignant mutations[33].

Among the more than forty myosinbinding protein C mutations that have been mapped, the majority are “de novo” and exhibit low individual prevalence.[28] They are characterized by a low penetrance rate and late

onset, usually after fifty years of age[36,37]. They usually present a benign evolution but sudden death has been reported in some families[38]. The increased mortality rate is related to age and the development of the left ventricular hypertrophy[36,37]. Many of the affected individuals demonstrate normal wall thicknesses on the echocardiogram and no electrocardiograph alterations. The usually favorable evolution can be justified by the fact that this protein does not participate directly in the contractile process[28]. Its clinical characteristics are incompatible with the principle that patients who genetically inherit the disease will invariably present the phenotype during adolescence. As a result, evaluations of affected families should include all individuals regardless of age. It is not known why the mutations present at birth manifest later.

The troponin-T gene is involved in the development of the disease in 20% of the cases[39]. Left ventricle hypertrophy, which is usually minimal, could be absent in 25% of the patients evaluated with an echocardiogram[39]. The mutations of this gene are responsible for 15% to 30% of the cases of sudden death which is often associated with minimal left ventricular hypertrophy or normal wall thicknesses[13,39]. Although many patients may be asymptomatic the prognosis is similar to that of malignant cardiac beta-myosin heavy chain mutations. There is a relationship between sudden death and the presence of extensive myofibril disarray, with no myocardial thickening and a lower percentage of fibrosis[20]. This confirmation raises the hypothesis that myofibril disarray is an important arrhythmogenic substrate. One possibility that has been considered is that this process requires a greater energy requirement for the interaction between thick and thin filaments that induces myocardial ischemia[20]. Patients with mutations in other genes, victims of sudden death, usually paradoxically present a greater degree of fibrosis which favors the development of ectopic foci and consequently ventricular tachycardia[20].

Alpha-tropomyosin mutations have a low prevalence. These mutations are usually benign forms but there are reports of malignant mutations affecting young people with various degrees of left ventricular hypertrophy[39,40]. Gene impairments in the essential and regulatory myosin light chains are related to midventricular obstructions that may or may not be associated with skeletal myopathy[22]. Cardiac troponin-I mutations have no specific pattern and produce extremely heterogeneous phenotypes even among members of the same family. Sudden death is observed in the descendents of asymptomatic individuals with mutations[41]. The mutations of alpha-actin, troponin C and titanin have been described in a limited number of cases with variable phenotypic expressions.

HCM results from distinct genetic disorders that directly or indirectly affect the sarcomeric structure and function. The mechanisms used by the mutations to generate the phenotypic expressions requires further investigation in order to introduce effective therapeutic measures during the early stages of the disease.

## Genetic Diagnosis

Laboratory DNA analysis is the most definite method for establishing the diagnosis of HCM. The major benefit of this analysis is the possible identification of patients before the pre-clinical stage of the disease. Even though the distinction between mutations with a favorable and unfavorable prognosis is not always sustainable, genotyping is the basis for risk stratification and the respective clinical management enabling the prevention of sudden death even among patients without heart disease symptoms. It is decisive in the evaluation of individuals from affected families, especially those in which sudden death was associated with borderline left ventricle wall thickness.

Large scale laboratory genetic diagnosis application requires efficient techniques with an expressive cost/effectiveness ratio for a disease with great molecular diversity. However, due to the great complexity, time required and high cost it is restricted to a few centers and the assessment of a highly selected group of patients. The fact that there is no predominant mutation as well as the low individual frequency, especially for malignant forms, creates practical difficulties[28]. In the recent evaluations of case studies, 60% of the mutations had not yet been described[29]. This complicates genetic molecular diagnosis application as mapping of the entire gene sequence is required as opposed to that of only the known mutations. The possibility that two mutations could affect the same gene or distinct genes cannot be ignored and therefore the analysis should not be interrupted when the first genetic defect is mapped particularly in the case of severe phenotypes[28,29]. The mapping of just the four most prevalent genes involves the analysis of 15kb of DNA sequences, making routine evaluations difficult[31]. Mutations involving the known genes are detected in 50% to 80% of the cases[31]. The reason that mutant genes have not been individualized is due to the limitations of the methods used for indirect genetic diagnosis, the presence of mutations in sequences that have not been evaluated or the involvement of unknown genes[29].

The cost of genotyping is usually higher than the proportionate savings of liberating family members who are not affected by the disease. The development of automated tests with direct DNA sequencing would facilitate large scale mutation mapping and enable risk stratification strategies to be based on the molecular profile of each patient[24].

In order for laboratory genetic analysis to define its role in sudden death risk stratification, detailed evaluations of the phenotype/genotype relationships must be conducted, particularly for individuals with the same genetic defect who are not related[31,42]. Another essential consideration is a better definition of the natural history of the known mutations based on the great variations between and within families. Likewise new phenotypes need to be identified. Molecular diagnosis is relevant in the pre-clinical stage of the disease, particularly if it discloses means to intervene in the presence of myocardial hypertrophy and the evolution to sudden death. The plurality of structural and functional disorders that affect the contractile proteins makes it difficult to introduce effective therapeutic

measures. This is the objective of genotyping and even though the implementation is a challenging task, its contribution is unquestionable in the identification of high risk patients.

## Clinical Bases

Risk stratification based on clinical variables has not yet been completely systemized in HCM. Doubts remain regarding the individual predictive value of the risk markers and the natural history of the disease which are partially based on verifications from highly selected samples. Follow-up of patients with this disease revealed that only a small subset represent high risk. Approximately 55% of the patients do not present sudden death predictors even though 5% of them could develop this complication[10,43]. The presence of a single risk factor is observed in 20% of the cases[43].

The task of identifying susceptible situations is difficult and complex due to the clinical heterogeneity. Sudden death can affect anyone with the disease although there is a higher correlation with younger age groups. Roughly 70% of the victims are younger than 35 and 40% are asymptomatic[14]. Since there are late onset forms, reaching adulthood does not guarantee immunity. The susceptibility with controlled phenotypes is also not eliminated since there is an association of certain genetic defects with sudden death even when the presence of hypertrophy is minimal or absent. Risk stratification should include all people with the disease and their first degree family members since the transmission by autosomal dominant inheritance makes 50% of the family members susceptible. The value of this for persons over sixty is questionable[8,14].

Prognostic evaluation using recognized clinical indicators is limited since no variables or diagnostic tests have demonstrated a sufficient level of accuracy to identify all susceptible patients[44]. The risk factors have low positive predictive values that range from 10% to 28%[17] based on the fact that even in referral centers, annual death rates do not exceed 3%[29]. These figures, obtained from select populations, could be a confirmation of the low prevalence of malignant mutations that was noted earlier[35]. Although restricted, therapeutic interventions in relation to sudden death predictors have demonstrated a favorable effect on clinical evolution and on the prognosis[21].

Risk stratification is sustained in the recognition of clinical elements that are able to express left ventricle morphology and the degree of electrical and hemodynamic instability. It can be implemented at the outpatient level and include a medical history, physical examination, electrocardiogram at rest, annual exercise stress test, 24 or 48-hour Holter monitoring and a Doppler echocardiogram[14].

## Risk Factors

Risk stratification is multifactorial. The following clinical indicators are associated with higher rates of sudden death (chart 1):

**Chart 1 – Clinical risk factors for sudden death in hypertrophic cardiomyopathy**

| |
|---|
| 1. Prior cardiopulmonary arrest (ventricular fibrillation) |
| 2. Spontaneous sustained ventricular tachycardia |
| 3. Family history of sudden death |
| 4. Syncope |
| 5. Nonsustained ventricular tachycardia |
| 6. Abnormal blood pressure response to exercise |
| 7. Massive left ventricular hypertrophy ≥ 30 mm |

### Prior cardiopulmonary arrest or spontaneous sustained ventricular tachycardia

Resuscitation rates for patients who suffer a cardiopulmonary arrest are extremely low out of reference centers. A previous history of ventricular fibrillation or sustained ventricular tachycardia defines the clinical group with the highest risk for sudden death since the possibility to develop a new episode if adequate preventive measures are not taken are as high as 10% per year[15,16]. Clinical detection of sustained ventricular tachycardia is rare. When recorded, it can reveal an association with ischemic heart diseases or apical aneurisms, which could later develop into forms with of midventricular obstructions[43].

### Family history of sudden death

Only 10% to 25% of HCM patients have a family history of sudden death and only 5% have a family history of two or more cases.[17] Although the positive predictive value is low, young people with a compatible history should be considered as high risk individuals[5]. The identification of two or more cases of sudden death in the family indicates the possible presence of malignant genetic mutations which requires genotyping. A history of sudden death in first degree family members under the ages of 40 to 45 years is considered a risk factor for any age group[43].

### Syncope

Syncope is a risk factor mainly for children and young people especially if it is associated with other predictors; it is a result of exertion or has been recurrent with multiple episodes during the past year[15]. There is a strong interaction between syncope and a family history of sudden death[10]. Analysis based on an outpatient population identified syncope as the only independent risk factor[11]. The origin of syncope is complex. It can be a consequence of ventricular and supraventricular tachyarrhythmias or brady arrhythmias that are primary or secondary to myocardial ischemia, left ventricle diastolic dysfunction, autonomic disorders or outflow tract obstructions[44]. The contribution of each one of these factors varies from case to case. The presence of symptoms is the criterium used to perform Holter monitoring and an exercise stress test in order to evaluate the presence of abnormal blood pressure response to exercise or any incidental arrthymias[44]. Syncope associated

with massive left ventricular hypertrophy requires prophylactic treatment, especially in young people[43,44]. In adults, it would not necessarily be indicated[43]. In repetitive syncope the therapy should be individual in accordance with the triggering mechanism.

## Nonsustained ventricular tachycardia

Although the relationship between nonsustained ventricular tachycardia and sudden death has been noted, its value as a risk predictor is considered questionable. The association between the two was established on a preliminary basis in contemporary studies conducted in referral centers[45,46]. The combined analysis of the respective data revealed a reduced positive predictive value and elevated negative predictive value. A subsequent retrospective investigation identified that patients with few or no symptoms who presented brief and infrequent episodes of nonsustained ventricular tachycardia during Holter monitoring presented a favorable evolution and mortality rates lower than 1.5% per year[47]. Neither of these studies[10] were able to prove the association with sudden death. A subsequent evaluation that was also comprised of outpatients revealed similar sudden death rates between individuals with and without records of nonsustained ventricular tachycardia[11]. The disagreement between the studies is attributed to factors such as the patient selection criteria and average age of the patients evaluated. The patients that presented this arrhythmia form a group with heterogeneous electrophysiological characteristics that in some cases are close to normal and in others are similar to those with a previous history of cardiopulmonary arrest[48].

In a recent study it was demonstrated that the association of nonsustained ventricular tachycardia and sudden death is particularly prominent before age thirty regardless of the respective duration or frequency[49]. In this age group, a high propensity for arrhythmias was noted in relation to factors such as myofibril disarray or myocardial ischemia. Children, adolescents and young adults rarely have ventricular arrhythmias but when they are present they reveal an elevated positive predictive value[17]. Or in other words, if they are detected they could be malignant and require effective preventative measures. In the majority of sudden death cases among young people there is no previous record of ventricular arrhythmias[43]. In this age group, Holter monitoring is insufficient for prognostic evaluation which should include comparisons with other predictors. Among adults, the record of nonsustained ventricular tachycardia is more frequent but has a lower positive predictive value[17]. In these cases, when it is an isolated risk factor it slightly increases the incidence of sudden death[43].

It is estimated that 20% to 30% of the adults with HCM present nonsustained ventricular tachycardia and that it would be recorded in 30% of those considered high risk[50]. When sporadic and transient, it is benign and does not usually produce symptoms. The risk is higher in cases with frequent, repetitive and prolonged episodes although objective data on the subject are limited. The presence of five or more intervals of at least 10 beats during the 24 or 48-hour Holter monitoring was randomly suggested as an indication of a higher propensity for sudden death[44].

## Abnormal blood pressure response to exercise while standing upright

Abnormal blood pressure in response to exercise while standing upright is defined as the inability to elevate systolic blood pressure by 20-25 mmHg or more, or by hypotension with a reduction ≥ 15 mmHg during the exertion or recuperation phases of the exercise stress test.[51,52] It is associated with sudden death especially in individuals under fifty years of age.[52] Evidence of this abnormality is present in roughly 30% of the patients.[43] Among young people it presents a reduced positive predictive value and an elevated negative predictive value.[51,52] It develops by inappropriate vasodilation of the unexercised skeletal muscle vessels and is associated with the stimulation of baroreceptors due to wall stress or ischemia.[51,52] The lack of pathological vasoconstriction or dilation of the capacitance vessels contributes to the generation of blood pressure abnormalities during or immediately following upright physical exercise. The mechanism would be similar to that of vasovagal syncope, which in healthy people does not contribute to the development of sudden death as there is no anomalous electrophysiological substrate. This disorder produces hemodynamic collapse in HCM followed by myocardial ischemia which leads to the development of fatal ventricular arrhythmias. This occurs more frequently in patients with a family history of sudden death and in patients with small ventricles[53]. When it is an isolated abnormality and not associated with other risk markers it does not require prophylactic treatment[14].

## Massive left ventricular hypertrophy

Maximum LV wall thickness ≥ 30 mm is characteristic of young people and is not usually applicable after age fifty[8]. The progressive remodeling of the heart chamber related to age or early sudden death could justify these findings. The association between the extent of left ventricular hypertrophy determined by the echocardiogram and mortality was identified on a preliminary basis in a study conducted on a select population but with a low positive predictive value[53]. The results were confirmed in a subsequent investigation in which the degree of hypertrophy was demonstrated as a reliable and independent prognosis marker[54]. In this analysis, the annual risk of sudden death varied from 0/1,000 in patients with left ventricle wall thicknesses between 10 and 15 mm to 18.2/1,000 in those with measurements ≥ 30 mm. Concurrent results were seen in contemporary studies conducted in a distinct institution[10,55]. However, a later study that grouped the patients according to degree of hypertrophy did not find any relation between maximum LV wall thickness and cardiovascular mortality during an average follow-up timeframe of twelve years[56].

The association between sudden death and massive left ventricular hypertrophy is based on genetics, since it is a predominant characteristic of the cardiac beta-myosin heavy chain mutations. The cases that are related to the troponin-T gene contradict this concept. The risk of sudden death or activation of the automatic implantable cardioverter defibrillator proved that the number of risk factors was much more influential than the extent of hypertrophy on its own. Among patients with maximum LV wall thickness ≥ 30 mm, sudden death affects only 5% of those without other risk factors in comparison to 34% of the individuals with three or more additional risk predictors during a five year timeframe[55].

It has not been confirmed whether or not the presence of massive LV hypertrophy is indicative of prophylactic treatment for sudden death. In very young patients, the risk would be higher and justify the implantation of an automatic cardioverter defibrillator[54,56]. In the others, the predictive accuracy would be lower, since most of the patients who die suddenly have measurements less than 30 mm[54,55].

Considering the elevated negative predictive value of the risk factors, the subset of patients regarded as less susceptible to sudden death is made up of adults who are asymptomatic or have minor symptoms in the NYHA functional classes I/II, do not have a compatible family history, syncope, nonsustained ventricular tachycardia during Holter monitoring or abnormal blood pressure response during exercise and exhibit a pressure gradient ≤ 30 mmHg, maximum LV wall thicknesses ≤ 20 mm and left atrium diameters ≤ 45 mm[14]. This subset represents the majority of patients attended to out of reference centers ,who have sudden death risk of less than 1% per year[14].

The higher the number of factors, the higher the risk. Considering only family history of sudden death, abnormal blood pressure response during exercise, nonsustained ventricular tachycardia and massive left ventricle hypertrophy, the presence of two or more indicators relates to a higher annual risk with mortality rates in excess of 3%[10]. In individuals with just one marker, the positive predictive value is only 20% and the annual incidence of sudden death ranges from 1% to 1.5%[10].

Other elements can contribute to the development of sudden death in HCM. They do not individually represent independent prognosis markers. They act as contributing factors. Some examples are myocardial ischemia, obstruction of the LV outflow tract, paroxysmal atrial fibrillation, nonvisible conduction system disease, accessory pathway and sympathetic stimulation[17]. It is of utmost importance to identify these conditions in patients with a high risk profile even though they will be absent in most patients[48]. The degree of individual tolerance also varies. The clinical evaluation of these factors is complex and current therapeutic methods can only be applied in 30% of the patients (chart 2)[17].

Detection of myocardial ischemia is difficult as the electrocardiograph and scintigraphy alterations only show the presence of hypertrophy. In a study using a positron emission tomography, the evaluation of the coronary flow at rest and after the administration of dipyridamole lower values with pharmacological stress in HCM patients when compared to the control individuals[19]. The response to dipyridamole could be useful for sudden death risk stratification although the positive predictive value would also be low.

**Chart 2 – Clinical Factors that contribute to the development of sudden death in hypertrophic cardiomyopathy and the respective therapy**

| Contributing Factor | Therapy |
|---|---|
| 1. Myocardial ischemia | Verapamil |
| 2. Left ventricular outflow obstruction | Myectomy, dual-chamber pacemaker, septal ablation |
| 3. Paroxysmal atrial fibrillation | Amiodarone + anticoagulants<br>Radio frequency ablation |
| 4. Conduction system disease | Pacemaker |
| 5. Accessory pathway | Radio frequency ablation |
| 6. Sympathetic stimulation | Beta-blockers |

Supraventricular arrhythmias induce an increased oxygen intake by the myocardium which can cause ventricular fibrillation[14,17] . They are associated with the presence of fibrosis and left atrial dilation, both consequences of LV diastolic dysfunction.

An obstruction of the LV outflow tract is the only clinical factor that can be eliminated. It may contribute to the development of ischemia and the genesis of fatal arrhythmias. Because of its dynamic traits, this condition tends to decrease as the patient ages. It could be a potential risk factor, since mortality rates are higher when combined with pressure gradients ≥ 30 mmHg[57]. Among individuals who are asymptomatic or have minor symptoms it would be a significant mortality predictor, a fact that would not be true for patients with severe functional limitations[58]. Procedures such as a myectomy, implantation of a dual-chamber pacemaker and septal ablation would not alter the mortality rates.

Electrophysiological studies with programmed ventricular stimulation have proved to be of little use in sudden death risk stratification in HCM. Although a relationship between cause and prognosis has been seen, the predictive accuracy is questionable[8,14] . Processes that use three extra premature stimuli, induce monomorphic ventricular tachycardia in isolated cases, but cause polymorphic ventricular tachycardia in roughly 40% of the cases and 50% of these degenerate to ventricular fibrillation[44] . The necessity to revert this quickly makes it difficult to evaluate whether or not the arrhythmia is sustained. Even though the specificity of this type of response in other forms of heart disease would be classified as low, in the case of HCM it is difficult to determine whether it is a result of hemodynamic and electrical instability or is merely due to excessive electrostimulation in hypertrophic ventricles that do not tolerate elevated frequencies. The positive predictive value

is reduced, since arrhythmias can be induced even in low risk patients. The high resolution electrocardiogram including the analysis of the QT interval dispersion and heart rate variations identify abnormalities which have a low predictive accuracy[17] .

## Prevention

The administration of beta-blockers and verapamil to control symptoms has not proven to have any preventive effect in relation to sudden death. Amiodarone in low dosages, less than or equal to 300 mg/day, is associated with improved life expectancy [14]. Careful monitoring is required, particularly in young people who require a prolonged administration period.

For those considered high risk, the implantation of an automatic cardioverter defibrillator has proven to be effective, providing complete protection and the ability to favorably alter the natural history of the disease. Its efficacy was tested in a nonrandomized retrospective multicenter study that evaluated patients with a high risk profile [16]. In an average follow-up interval of three years, 23% of the defibrillators were activated appropriately with a frequency of 7% per year. The annual discharge intervention rates were as high as 5% for primary prevention models and 11% for secondary prevention. The timeframe between the implant and the first intervention was variable and ranged from four to nine years for 21% of the patients. The results demonstrate that the number of lives saved is well worth the cost and risk involved. On an individual basis the interval between the implant and the first activation is unpredictable since the cardioverter defibrillator can remain inactive for many years.

The study support the recommendation of an implantatable automatic cardioverter defibrillator as an efficient treatment method for secondary prevention and in select cases for primary prevention. In this situation, the available information may not be conclusive.

The clinical criteria used for automatic cardioverter defibrillator indications in HCM are still based on empirical experience and minimize the genetic heterogeneity. Observational studies attest to the efficacy of both the automatic cardioverter defibrillator and amiodarone, but the failure rate appears to be lower with the defibrillator[15,16] . The low rate of long term events and the prolonged periods without intervention make it difficult to plan a study to compare the two methods.

The implantation of an automatic cardioverter defibrillator in HCM is a class I indication for secondary prevention and class IIB for primary prevention in accordance with the guidelines of AHA/ACC/NASPE[59]. Despite its effectiveness it is limited by its high cost and inappropriate discharges. It is the treatment of choice for patients with a history of previous cardiopulmonary arrest or spontaneous sustained ventricular tachycardia[8,14]. For primary prevention, treatment for adults and younger individuals is the same when two or more risk factors exist since mortality in these situations vary from 3% to 6% per year[14,17,21]. There is no real consensus regarding patients with just one risk factor. It is recommended that treatment decisions be individualized according to the patient evaluation taking into consideration the person's age and the risk factor involved[14] (chart 3).

Primary prevention of sudden death using an automatic implantable cardioverter defibrillator is not readily accepted for young age groups. In children there is reluctance to recommend it due to the number of growth related complications and in adolescents due to the the psychological implications. In these conditions, amiodarone is recommended as a bridge for the cardioverter defibrillator[14, 43].

Patients with no risk factors, who represent a significant segment of the population with HCM, usually present a favorable evolution and better prognosis and do not usually require more aggressive therapeutic measures. In these cases, minimal restrictions are required for recreational and work related activities however participation in intense or competitive sports is not advised[14].

In conclusion, sudden death risk stratification is of utmost importance in HCM as it is the main cause of death related to this disease that attacks young people and athletes, among others, and whose victims may be asymptomatic without previous diagnosis. The heterogeneous molecular substrate associated with the great phenotype diversity limits the systematic application of genetic laboratory diagnosis to identify malignant mutations. The marked clinical variation and the complexity of determining sudden death mechanisms make it difficult to individualize risk predictors. Even though, there has been a substantial evolution in the understanding of this disease since its initial description, it is still considered not possible task to identify all susceptible patients. The predictors have proven to be useful since the implementation of effective therapeutic measures result in a favorable clinical evolution and prognosis.

### Potencial Conflict of Interest

No potential conflict of interest relevant to this article was reported.

**Chart 3 – Therapeutic Measures to Prevent Sudden Death in Hypertrophic Cardiomyopathy**

| | | | |
|---|---|---|---|
| Previous cardiopulmonary arrest or spontaneous sustained ventricular tachycardia | 2 or + risk factors | 1 risk factor | No risk factors |
| ↓ | ↓ | ↓ | ↓ |
| Automatic implantable cardioverter defibrillator | Automatic implantable cardioverter defibrillator (amiodarone?) | Individual judgement | Periodic clinical revaluation |

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