Hypertrophic cardiomypathy is an autosomal dominant, genetic heart muscle disease, characterized by ventricular hypertrophy in the absence of any other medical condition causing heart overload. The disease has an estimated prevalence of 1:500 and is a significant cause of sudden death, especially in young individuals, with an annual incidence of approximately 1%. Among the risk markers for the occurrence of malignant ventricular arrhythmias and sudden death in this scenario, we emphasize, in addition to a fatal event that has occurred and was aborted, the family history of sudden death; wall thickness greater or equal to 30 mm; unexplained syncope; presence of non-sustained ventricular tachycardia on Holter; abnormal blood pressure response during exercise testing; and the presence of delayed enhancement on cardiac magnetic resonance. The presence or absence of these markers can define the need or not of an implantable cardioverter-defibrillator to prevent sudden death in these patients. However, there is still much controversy about how these patients should be stratified. It is known that these markers do not have the same weight in predicting who is more likely to suffer a fatal event. This fact becomes particularly important when it is considered that the cardioverter-defibrillator implantation procedure is not free of complications, in addition to the economic impact, in terms of cost, to the health system. The purpose of this article is to carry out a review of the main aspects involved in the sudden death in these patients, from the pathophysiology, risk assessment, prevention and future perspectives.

Introduction

Hypertrophic Cardiomyopathy (HCM) is an autosomal dominant disease characterized by ventricular hypertrophy associated with non-dilated ventricles in the absence of any other condition that leads to heart overload (Figure 1). It has a prevalence of 1:500 individuals, which makes it the most common genetic disease in our country. The presence of this hypertrophy, the result of mutations in genes that encode cardiac muscle sarcomeric components, provides the pathological basis for phenomena that participate in the disease physiopathology, such as diastolic dysfunction and the development of ischemia. These, in turn, lead to several clinical manifestations, such as heart failure, atrial and ventricular tachyarrhythmias. Due to the genetic heterogeneity that determines it, how the disease will manifest in relation to the phenotype and the natural history become unpredictable, as it can develop asymptomatically or even present as Sudden Death (SD) as the only clinical expression of the disease.

The annual incidence of SD in HCM is approximately 1%, which makes it the main responsible for this event in young individuals and competitive athletes. Elderly individuals with the disease may have SD, but the risk is lower. Its manifestation can occur without prodromes and only 50% of the cases occur after performing physical effort.
Physiopathology of Sudden Death in Hypertrophic Cardiomyopathy

The physiopathology of SD in HCM is not fully understood, but several factors seem to be involved in this disease. As the main foundation are the basic characteristics of the disease, which are the myocyte hypertrophy, myofibrillar disarray and fibrosis. The latter has been considerably gaining more attention. Its documentation, through Magnetic Resonance Imaging (MRI) with Gadolinium, was associated with a higher incidence of Non-Sustained Ventricular Tachycardia (NSVT) in ambulatory Holter monitoring, in addition to other more relevant outcomes, as will be seen below (see Sudden Death Risk Assessment).

Another phenomenon that, in many cases, can act as a trigger for arrhythmias is coronary ischemia despite the absence of coronary atherosclerotic disease, but due to vascular remodeling in the intramyocardial branches of these arteries. Considering that the presence of NSVT in Holter monitoring is associated with fatal outcomes in HCM, it is concluded that ventricular arrhythmias are the main cause of SD in these patients.

Other still little known, but important issues are related to specific HCM genotypes. One example is troponin-T mutations, which can cause mild hypertrophy, but a high incidence of SD.

Sudden Death Risk Assessment

All HCM patients should be evaluated for the risk of SD, regardless of phenotype and severity of clinical manifestations. Considering that HCM is a disease that can change with time, this assessment should be periodically repeated (every 1-2 years), searching for the presence of high-risk markers. This involves updating the clinical and family history, physical examination, echocardiography, 24-hour Electrocardiogram Monitoring and exercise testing. Cardiac MRI should also be performed, but repeated only in selected cases, when one believes the disease may be progressing and when its performance can result in treatment changes.

High risk markers

Among the risk markers for SD in this scenario, in addition to a fatal event that has occurred and
was aborted (for instance: reversed cardiac arrest or documented sustained ventricular tachycardia), family history of SD, wall thickness ≥ 30 mm, unexplained syncope, NSVT on Holter, abnormal blood pressure response during exercise testing and significant delayed enhancement in MRI are emphasized.\textsuperscript{1,2,11} The presence or absence of these markers can define the need for an Implantable Cardioverter Device (ICD), considered to be the only effective and safe way to prevent SD.\textsuperscript{12-16}

Of all these markers, family history of SD seems to be the most relevant, despite the low positive predictive value. Dimitrow et al.\textsuperscript{17} demonstrated this fact in a study with 1,306 patients, comparing it to other risk factors, being particularly associated with SD episodes in childhood and adolescence. This marker becomes particularly more important when it occurs in several members of the same family and at an early age, although this situation is unusual.\textsuperscript{18}

Syncope should be considered when deemed to have an unexplained origin. Therefore, the possibility of syncope caused by obstruction or vagal reaction should be ruled out. Its predictive value also increases when it occurs within 6 months of the initial assessment.

Echocardiographic studies also indicate the association between the extent and magnitude of hypertrophy and SD, considering that the ventricular wall thickness > 30 mm is now considered an important risk marker, most commonly found in young individuals with HCM.\textsuperscript{3} The initial studies carried out by Spirito et al.\textsuperscript{19} already indicated this association, even with a low positive predictive value. Subsequently, in a study involving 480 patients, the same authors reported that the incidence of SD practically doubled for each 5 mm increase in ventricular thickness, being 1.8%/year in those with thickness > 30 mm.\textsuperscript{20}

The NSVT, expressed by three or more beats ≥ 120 bpm in 24-hour Holter, is also associated with an increased risk of SD.\textsuperscript{21} This marker has shown to be more important in patients younger than 30 years. The recording of NSVT during or after exercise is rare, but it is also associated with SD.\textsuperscript{22}

The inability to attain a 20 mmHg increase in blood pressure (BP), characterizing an abnormal BP response during exercise testing, occurs in approximately 20 to 40% of patients with HCM and is also associated with increased risk of SD, especially in those younger than 40 years old and with a family history of SD. A BP decrease > 20 mmHg during exercise is also considered an abnormal response.

Other factors, such as age, presence of intraventricular gradient, myocardial ischemia and electrophysiological study were not able to demonstrate a significant association with SD risk for them to be regarded as high-risk markers.

**Cardiac MRI**

Among the latest tools that have been studied aiming to correlate them with increased risk of SD in HCM, undoubtedly the most relevant one is myocardial fibrosis disclosed at cardiac MRI. A recent study found that the percentage of left ventricular mass fibrosis > 15% was associated with a two-fold increase in the risk of SD in patients initially considered to be low risk.\textsuperscript{23} Another finding, less common but very significant, is the apical aneurysm. A classic observational study performed by Maron et al.\textsuperscript{24} demonstrated that its presence was associated with poor prognosis in HCM, with increased risk of SD, sustained ventricular tachycardia and appropriate discharges in individuals with ICD. It is noteworthy that both fibrosis and apical aneurysm remain as risk modifiers, and as highlighted in the American Guideline, they are not sufficient to indicate ICD implantation when they appear alone.

**Strategy according to the number of risk factors and risk prediction models**

Trying to predict which patients have a higher risk of MS remains challenging. Historically, American and European guidelines recommend a strategy based on the number of high-risk markers involved. Some studies supported this trend, for instance, the findings by Elliot et al.,\textsuperscript{25} who showed that, the higher the number of classical risk factors, the lower was patient survival in years, mainly due to SD (Figure 2).

However, multicenter registry data of patients with HCM that received an ICD showed that 35% of patients that had appropriate shocks had only one risk factor. Also, the probability of receiving an appropriate discharge was not different in individuals who had one, two or three risk factors.\textsuperscript{12}

Recently, the European Society of Cardiology based ICD indication on the use of a risk calculator (HCM-Risk SCD), created to offer more accurate stratification.\textsuperscript{2} This calculator was based on a retrospective cohort study involving 367 patients from six European centers.
The derived model used as parameters age, maximum ventricular thickness, left ventricle (LV) outflow tract gradient, left atrial diameter, family history of SD, presence of NSVT and unexplained syncope. The study results show that, for every 16 patients submitted to ICD implantation indicated by the calculator, one life is potentially saved.\(^\text{26}\) Subsequent studies showed controversial results regarding the calculator.\(^\text{27,28}\) We believe it has several limitations: (1) it is not adequate for patients with high muscle thickness (> 35 mm); (2) it uses data from the left atrial diameter, which is traditionally a marker of heart failure and not of SD; (3) and it does not use the data of fibrosis in the cardiac MRI.

**Evolution to dilated cardiomyopathy**

HCM patients that progress to dilated cardiomyopathy usually have a severe condition, with extensive areas of myocardial fibrosis. Their almost inevitable trend is to require cardiac transplantation, despite the treatment for systolic heart failure. It is almost a consensus among several authors that these patients have a higher risk of SD. Thus, the indication of ICD is always something to be considered as a bridge to transplantation.\(^\text{29}\)

**Genetic testing**

Some mutations found in small family series have been correlated with SD. Some examples are the mutation c.2067+1G-->A, related to Myosin Binding Protein C gene and those involving the troponin T gene (TNNT2).\(^\text{30,31}\) However, the behavior of specific genotypes is not always the same in different families, and the wide heterogeneity of the disease (with the number of identified mutations being higher than one thousand in several genes) makes it difficult to use this information for primary SD prevention in this disease.\(^\text{32}\)

**Sudden Death Prevention**

The most basic recommendation to prevent SD in patients with HCM is to avoid competitive sports and high-intensity physical activity, especially in the presence of known risk factors or high intraventricular gradient.\(^\text{33}\)

No drug has shown benefits in reducing the incidence of SD, even antiarrhythmic drugs such as amiodarone, although its use associated with beta-blockers in patients with ICD and recurrent sustained ventricular arrhythmias is reasonable. The same can be said for invasive septal reduction therapy, because neither the myectomy nor the alcoholic septal ablation modified this risk.

The management is based on ICD implantation for high-risk patients.

**Cardioverter Defibrillator**

The best strategy to prevent SD in patients with HCM and high risk for malignant arrhythmias is the ICD...
implantation. In patients with aborted SD or sustained ventricular tachycardia, there is no doubt they should be directly referred to ICD implantation as part of the secondary prevention, despite the absence of randomized trials.\textsuperscript{1,2,34} Regarding primary prevention, the discussion is still surrounded by much controversy and there is a lot of uncertainty about how the stratification should be performed.\textsuperscript{25,35,36} Until recently, the device implantation was virtually a consensus in individuals with more than two high risk markers. However, it is known that the risk markers described in the topic Sudden Death Risk Assessment do not have the same weight in predicting who is most likely to suffer a fatal event. The most recent US guideline on HCM recommends the use of an algorithm that individually applies the aforementioned multiple risk factors, assigning them different status in ICD implantation indication (Figure 3).\textsuperscript{1} As for the European trend, which always indicated the use of two or more risk factors, intuitively more rational, decided in its last version, to adopt the risk calculator (HCM-Risk SCD) to indicate the ICD.\textsuperscript{2}

It is noteworthy that the conduct for ICD indication is not based on randomized clinical trials, but on data from observational studies. However, it is not reasonable to think of evidence in this regard, considering the low prevalence of SD in a disease in which study recruitment is very difficult.

It is particularly important to note that ICD implantation does not occur without complications, such as inappropriate shocks, infection, pneumothorax, lead fractures or dislocations and thrombosis, making the ICD indication a very complex decision. Approximately 20 to 40% of ICD patients experience inappropriate shocks, which has a direct impact on quality of life.\textsuperscript{37,38} A study published by Woo et al. showed that these inappropriate discharges seem to occur more frequently in young individuals and in patients with

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Sudden death (SD) prevention algorithm.}
\end{figure}

\textit{SVT: sustained ventricular tachycardia; ICD: Implantable Cardioverter Defibrillator; BP: blood pressure; NSVT: non-sustained ventricular tachycardia. Source: Adapted from Gersh et al.\textsuperscript{1}}
atrial fibrillation, a scenario often seen in HCM.\textsuperscript{39} Among young individuals, those who suffer the most from this complication are children, due to the high degree of activity in these patients, as well as growth and development particularities, in addition to the long periods when these patients are subject to this complication. Generally, patients undergoing ICD implantation for primary prevention in several populations, experience appropriate therapy with an approximate rate of 1.6 to 4\% a year, lower than that observed in secondary prevention and almost identical to the observed rate of complications, also of 4\% per year.\textsuperscript{7,11,40-45} We also emphasize the economic impact in terms of costs for the health system.

**Perspectives: Development of a Risk Score**

Considering all the evidence, the need to discuss the risks and benefits of ICD implantation for primary prevention of SD in patients with HCM is further increased. Therefore, we decided to perform a systematic review of observational studies evaluating the aforementioned risk markers, aimed at creating an SD risk score for patients with HCM.

Based on the selected articles, we will perform a meta-analysis for the main risk factors and, using the statistical power of each one, we will create the clinical prediction model, which will result in the prognostic score.

The search was carried out in the three databases: MEDical Literature Analysis and Retrieval System Online (MEDLARS\textsuperscript{®}, Medline), Latin American and Caribbean Health Sciences (Lilacs) and Scientific Electronic Library Online (SciELO), seeking clinical trials carried out between 1980 and 2016, prospective and retrospective ones, which assessed the natural history of HCM patients, regardless of gender or ethnicity and had SD, sustained ventricular tachycardia and appropriate shock with ICD as the assessed outcomes. Studies should also report, in addition to classical demographic data, the incidence of SD risk factors in this disease, namely: a family history of SD; ventricular thickness $\geq$ 30mm; presence of unexplained syncope; NSVT on Holter; abnormal blood pressure response to stress test; and presence of obstructive gradient. The presence of fibrosis on cardiac MRI in the studies that used this additional examination will also be analyzed.

To date, the systematic review has followed the flowchart described in Figure 4.

Using these 20 selected articles, we will perform the meta-analysis and, subsequently, will develop the score. With this initiative, we hope to contribute to the study of a subject still involved in considerable uncertainty.

**Author contributions**

Acquisition of data: Bittencourt MI, Cader SA, Salles ALF, Albuquerque FN, Spinetti PPM. Analysis and interpretation of the data: Bittencourt MI, Cader SA, Araújo DV, Rocha RM. Writing of the manuscript: Bittencourt MI, Cader SA. Critical revision of the manuscript for intellectual content: Bittencourt MI, Araújo DV, Albuquerque DC, Rocha RM.

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