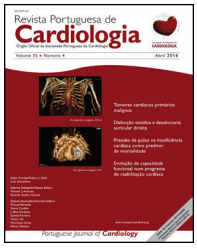
Rev Port Cardiol. 2019;38(12):855–857

Revista Portuguesa de Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org



EDITORIAL COMMENT

Sudden cardiac death in hypertrophic cardiomyopathy: Improved risk stratification strategies are needed

Morte súbita cardíaca na miocardiopatia hipertrófica: é necessário melhorar as estratégias de estratificação de risco

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Hypertrophic cardiomyopathy (HCM) is a common primary myocardial disease, defined as left ventricular hypertrophy in the absence of abnormal loading conditions. It is inherited as an autosomal dominant trait and is caused by mutations in cardiac sarcomere protein genes.[1] The disease is characterized by marked genetic heterogeneity, diverse clinical phenotypes and a highly variable natural history.[2,3]

Sudden cardiac death (SCD) remains the most devastating and feared clinical event for both HCM patients and their cardiologists.[3] Early studies from tertiary centers demonstrated alarmingly high rates of SCD, reaching up to 6% per year, although this was probably due to referral bias.[4] With increased awareness of the disease, lower-risk patients are now more likely to be diagnosed and more recent studies demonstrate an annual SCD rate of 0.5-1% per year. Unfortunately young and asymptomatic patients are often affected.[3,5,6]

SCD in HCM is mainly caused by ventricular arrhythmias. The unpredictable ventricular arrhythmogenic substrate is thought to be the result of the histopathological hallmarks of myocyte disarray, interstitial collagen deposition and replacement fibrosis after myocyte death as a consequence of coronary microvascular-mediated flow dysfunction and ischemia.[3,7]

Effective prevention of SCD with implantable cardioverter-defibrillator (ICD) therapy is the major factor in the significant reduction in HCM-related mortality and has provided HCM patients with the chance of normal life expectancy.[8] Estimation of SCD risk is therefore now an integral part of clinical management of these patients.[9,10]

Patients who have previously experienced aborted SCD and malignant ventricular arrhythmias are at higher risk for further arrhythmic events (10% per year) and both the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and European Society of Cardiology (ESC) guidelines for the management of HCM recommend ICD implantation in such patients.[9–11]

However, the selection of patients to receive an ICD for purposes of primary prevention is more difficult, and the above recommendations differ and to some extent conflict regarding this issue.

In fact, the greatest challenge lies in identifying the minority of patients at sufficiently high risk of SCD to justify the possibility of device-related complications, mainly inappropriate shocks and lead-related complications such as displacement, malfunction, thrombosis or infection.[12] On the other hand, it is important to provide reassurance to those deemed to be at low risk for sudden death.[13]

Research conducted in recent decades has identified a number of phenotypic characteristics associated with the occurrence of adverse events. Different stratification strategies have emerged; however, consistent with the clinical

DOI of original article: https://doi.org/10.1016/j.repc.2019.05.012
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diversity of the disease, none has proved infallible in predicting future adverse events.

Interestingly, in a study conducted by Spirito et al. including 668 HCM patients without conventional risk factors and with no or mild symptoms, the risk of sudden death was not negligible, with an event rate of 0.6% per year.[14] This finding underscores the importance of expanding risk stratification.

Another important consideration is that patient age itself influences the weight that should be given to specific risk factors, which have greater significance in younger patients.[15]

As mentioned above, there are currently two distinct strategies for risk stratifying patients with HCM for ICD therapy (ACCF/AHA and ESC). Of note, no randomized clinical trial has been conducted and the present recommendations are based on observational, retrospective cohort studies.

The 2011 ACCF/AHA primary prevention stratification relies on identification of one or more major risk markers to guide ICD implantation.[9] An individual clinical approach with the flexibility to incorporate emerging risk modifiers (like the presence of apical aneurysms and diffuse/extensive fibrosis identified on late gadolinium enhancement cardiac magnetic resonance study) is proposed.[9]

Since 2014, the ESC has recommended the use of a novel quantitative risk score (HCM Risk-SCD), with an online decision-making tool composed of seven disease-related features, to predict sudden death events over five years.[10] Based on this score, patients are stratified into three subgroups for ICD recommendation for primary prevention: low (<4%, ICD generally not indicated), intermediate (4-6%, ICD may be considered) and high risk (≥6%, ICD should be considered).

To assess the discrimination performance of the 2014 HCM Risk-SCD score, Wang and colleagues recently performed a systematic review and meta-analysis including 13 studies validating the model's usefulness.[16] They concluded that the model has excellent specificity, although it has poor sensitivity when setting a recommended cutoff value of 6% for identifying high-risk patients, indicating that it is likely to miss a subgroup of high-risk patients. Moreover, subgroup meta-analysis based on geographic distribution showed a slightly weaker predictive ability for North America compared with other regions.[16]

On the other hand, the results from a recently published single-center observational longitudinal study including 2094 HCM patients demonstrated that the enhanced ACCF/AHA algorithm for SCD prevention is highly sensitive, resulting in identification of nearly all at-risk patients.[17] In the same study, the ESC risk score was much less sensitive for identifying patients requiring ICD therapy (sensitivity only 34% vs. 95% for ACCF/AHA). However, it was associated with relatively high specificity, suggesting that it could reduce the number of ICD implants in low-risk patients and limit ICD overuse.[17]

Considering the importance of SCD risk stratification and the unsatisfactory results to date, it is understandable that the medical community wishes to pursue research in this field.

The study by Ruivo et al. published in the current issue of the *Journal* sets out to assess SCD risk in Portuguese HCM patients, to develop a new SCD risk prediction model for this population and to compare its accuracy with the current ESC model.[18]

The authors collected data on a cohort of 1022 patients enrolled in the Portuguese nationwide HCM registry (mean age 53.2±16.4 years, 59% male).

During a median follow-up of five years, the observed rate of adverse events, defined as sudden cardiac death, aborted SCD or appropriate ICD shock therapy, was 1.9%.

Four variables were independently associated with the occurrence of adverse events, that were subsequently included in the new five-year SCD predictor model proposed by the authors, which they call SHIFT: unexplained Syncope, Heart failure signs, Interventricular septum thickness ≥19 mm and FragmenTed QRS complex.

Of interest, in this study population, the authors found that heart failure signs and fragmented QRS complex on the surface electrocardiogram (ECG) (as an indirect sign of myocardial fibrosis) provide additional information for SCD risk stratification. These parameters are not considered in the current guidelines.

Intuitively, the presence of heart failure signs may be associated with a more advanced stage of the disease and therefore worse prognosis; the outcome of patients with so-called end-stage HCM is poor, not only due to high rates of heart failure-related complications and mortality but also because of a high incidence of SCD, exceeding 10% per year.[2]

Fragmented QRS complexes on a 12-lead ECG reflect conduction delay from inhomogeneous activation of the ventricles and have high predictive value for myocardial scar and mortality in patients with coronary artery disease, as well as being associated with poor prognosis in patients with non-ischemic cardiomyopathy.[19] However, previous studies regarding the use of the ECG in risk stratification of HCM patients have shown conflicting results, and no ECG pattern can currently be used for clinical decision-making regarding prognosis.[20]

In the study by Ruivo et al., the HCM Risk-SCD model was additionally applied in a subgroup of patients for whom complete data were available on the eight risk factors used to calculate the ESC SCD risk score (349 patients), of whom 2.3% had SCD or an equivalent event during the five-year follow-up. Compared to the ESC model, the new proposed SHIFT model seemed to have better prognostic performance, with a C-index of 0.81 (95% confidence interval [CI]: 0.77-0.83) for SHIFT vs. 0.77 (95% CI: 0.73-0.81) for the ESC model (p=0.246, z: -1.160); D-statistic of 2.38 (95% CI: 0.95-4.35) for SHIFT vs. 1.97 (95% CI: 0.82-3.22) for ESC.[18]

In summary, although most HCM cases have a benign prognosis, identifying patients at the highest risk for sudden death warranting lifesaving prophylactic ICD therapy remains a critical management priority. However, many gray zones remain regarding this topic.

Despite the limitations inherent to the design of the study conducted by Ruivo et al., and the need for future external validation, its results are highly encouraging. The SHIFT model is easy to use and may add prognostic value in SCD risk stratification, especially for the subgroup of Portuguese patients with HCM.

Conflicts of interest

The author has no conflicts of interest to declare.

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