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Sudden cardiac death markers in non-ischemic cardiomyopathy

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Abstract Heart failure is an increasingly prevalent disease associated with high morbidity and mortality. In 30–40% of patients, the etiology is non-ischemic. In this group of patients, the implantable cardioverter-defibrillator (ICD) prevents sudden death and decreases total mortality. However, due to burden of cost, the fact that many ICD patients will never need any therapy, and possible complications involved in implant and follow-up, the device should not be implanted in every patient with non-ischemic heart failure. There is an urgent need to adequately identify patients with highest sudden death risk, in whom the implant is most cost-effective. In the present paper, the authors discuss current available tests for risk stratification of sudden cardiac death in patients with non-ischemic heart failure.

Keywords: Sudden death; Risk stratification; Non-Ischemic Cardiomyopathy

Introduction

The prevalence and incidence of heart failure (HF) indicate that it is an important public health problem worldwide. In approximately 30% to 40% of patients with heart failure and low left ventricular ejection fraction (LVEF), the etiology of ventricular dysfunction is non-ischemic. Non-ischemic cardiomyopathy (NIC) is characterized by the absence of major lesions on coronary angiography or by negative findings on imaging studies performed to assess ischemia. Among patients with NIC, the cause of ventricular dysfunction may be either unknown (idiopathic dilated cardiomyopathy) or attributed to one of several causes, including hypertension, exposure to potentially toxic agents (chemotherapeutic drugs and alcohol), Chagas' disease, myocarditis, infiltrative disease, peripartum cardiomyopathy, valvular heart disease, genetic and autoimmune diseases. Epidemiologic studies show frequency variation NIC etiology, being the most common hypertension and idiopathic dilated cardiomyopathy [1]. A different type of NIC related to prolonged strenuous exercise and associated with ventricular arrhythmias has been recently described (Phidippides cardiomyopathy) [2].

Sudden cardiac death (SCD) is an unexpected death from cardiac causes that occurs within an hour of symptom onset. Although advancements in the treatment of NIC have importantly decreased mortality in recent decades, SCD remains an important problem, accounting for approximately 30% of deaths in HF patients. Moreover, patients with aborted SCD experience high levels of cardiac-specific fear and anxiety [3]. Primary prevention of SCD in patients with NIC includes pharmacological treatment and the use of implantable cardioverter-defibrillators (ICD). Randomized clinical trials have demonstrated that the use of beta blockers and aldosterone receptor antagonists (spironolactone and eplerenone) significantly decreased SCD in this group of patients. The Sudden Cardiac Death in Heart Failure Trial (SDC-HeFT), which included patients with both ischemic and NIC with New York Heart Association (NYHA) functional class II-III, indicated that ICD decreased SCD and total mortality [4]. Of patients with an implanted ICD, one third received shocks during five years of follow-up, and approximately a third of them were inappropriate. Moreover, it was observed that the rate of cardiovascular events was significantly lower in patients with HF of non-ischemic etiology.

Undoubtedly, the high costs and the potential complications related to ICD implantation demand a better selection of patients who are at an increased risk of SCD and would benefit the most from ICD implantation. For ischemic HF, in

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addition to LVEF, electrophysiological study identifies patients at an increased risk of SCD, as opposed to NIC, which still needs a better selection of patients. Therefore, this review aims to discuss potential predictors and markers of SCD in NIC (Table 1).

Review

Clinical and laboratory evaluation

Routine clinical and laboratory evaluations provide relevant information that can be used to stratify SCD risk of patients with NIC. The functional class of HF patients is related to distinct SCD risks. Among patients with NYHA class II, SCD is responsible for 64% of deaths, whereas HF progression is responsible for only 12%. Among patients with NYHA functional class III, SCD accounts for 59% of deaths and HF progression accounts for 26%. Finally, among patients with NYHA functional class IV, SCD accounts for 33% of deaths and HF progression accounts for 56%. In patients with Chagas' disease, mortality risk factors include NYHA functional class III-IV, cardiomegaly on chest radiography, ventricular dysfunction on echocardiography, low voltage of the QRS complex on electrocardiography, non-sustained ventricular tachycardia on Holter monitoring and male sex [5]. However, a specific analysis of SCD has not been performed in chagasic patients. Syncope is considered to be an important risk factor for SCD in patients with NIC. In a cohort study involving 491 patients with severe HF, of which 51% presented NIC, the incidence of SCD was 45% among patients with syncope compared with 12% for patients without syncope [6]. Both NYHA class and syncope are considered by international guidelines to be important clinical parameters to define appropriate criteria for ICD implantation in patients with NIC [7].

Several studies have evaluated the prognostic value of routine and specific laboratory tests to stratify risks of NIC patients. Blood tests, including hemoglobin, uric acid, renal function and biomarkers of myocardial stress and fibrosis, such as natriuretic peptides, galectin-3 and ST2, were identified in isolated studies as predictors of mortality and arrhythmic events [8]. Natriuretic peptides are released largely from the ventricles in response to elevation in intraventricular pressure and myocardial stretch [9]. Changes in ventricular pressure and geometry cause electrophysiologic changes that may favor serious arrhythmias. Galectin-3 and ST2 are linked to cardiac fibrosis, which is the main substrate for arrhythmic events [10]. It has also been suggested that low hemoglobin levels and a decreased renal function increase arrhythmia risk in the scenario of left ventricular dysfunction. Considering that these results are still inconsistent, these tests should not be considered as the only tool for risk assessment. Using a risk prediction model based on routine clinical and laboratory variables, patients can be stratified in different levels of risk of appropriate ICD shock, varying from 0.9 to 9.3%/year [11]. However, analyses including NIC patients only are lacking. Basic research to find new laboratory markers of SCD risk and clinical studies to test them are of great importance in NIC patients.

Table 1
Different methods of risk stratification of SCD in NIC patients.

Method	Risk
Clinical Evaluation	
NYHA functional class	Class II: 64% of deaths from SCD Class III: 59% of deaths from SCD
Syncope	With syncope: 45% SCD in 1 year Without syncope: 12% SCD in 1 year
Laboratory tests	BNP, uric acid and hemoglobin included in risk prediction scores
Left Ventricular EF	RR for major arrhythmias: 2.28 for every 10% decrease in EF
Electrocardiogram	Duration of QRS complex and late potentials may increase risk
Holter monitoring	
NSVT	NSVT: RR of 3.2 for SCD NSVT + LVEF < 30%: RR of 8.2 for events
Heart rate variability	Controversial results
Heart rate turbulence	Controversial results
T-Wave Alternans	Controversial results
Cardiopulmonary exercise test	Periodic breathing: HR of 8.4 for major arrhythmic events
^{123}I-MIBG	Altered result: HR of 4.79 for SCD
EPS	Positive EPS: HR of 4.19 for ICD therapy
Genetic Testing	Mutations and polymorphisms associated with increased risk
Cardiac MRI	Fibrosis: HR of 3.2–5.4 for arrhythmic events

Legend: SCD: sudden cardiac death; NIC: non-ischemic cardiomyopathy; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; NSVT: non-sustained ventricular tachycardia; ^{123}I-MIBG: metaiodobenzylguanidine; EPS: electrophysiological study; MRI: magnetic resonance imaging; ICD: implantable cardioverter-defibrillator.

Left ventricular ejection fraction

LVEF can be evaluated using several methods, most commonly by two-dimensional echocardiography. A decrease in LVEF is a major risk factor for SCD and total mortality in HF patients. However, few studies have evaluated LVEF as a risk factor for SCD specifically in patients with NIC. The Marburg Cardiomyopathy Study (MACAS), a prospective cohort study involving 343 patients with NIC, revealed that among patients with sinus rhythm, the relative risk for major arrhythmic events was 2.28 for every 10% decrease in EF [12]. In patients with atrial fibrillation, the relative risk was 4.5.

Moderate to severe left ventricular systolic dysfunction (LVEF ≤ 35%) was an inclusion criterion for the SCD-HeFT trial, a trial that supports ICD indication in patients with NIC. International guidelines consider LVEF ≤ 35% as a criterion for ICD implantation for primary prevention in patients with NIC [7]. However, it should be noted that, although LVEF is considered a major risk factor for SCD, events commonly occur in patients with LVEF >35%. In fact, the absolute number of SCD is significantly higher in patients with more preserved LVEF, considering that these patients represent a much larger subgroup.

Electrocardiography

The electrocardiogram (ECG) is a simple and available tool that provides useful information for risk stratification of