Stratification of the Risk of Sudden Death in Nonischemic Heart Failure

Maurício Pimentel¹,², Leandro Ioschpe Zimerman¹,², Luis Eduardo Rohde¹,²
Curso de Pós-graduação em Ciências Cardiovasculares - Universidade Federal do Rio Grande do Sul¹; Serviço de Cardiologia do Hospital de Clínicas de Porto Alegre², Porto Alegre, RS - Brazil

Abstract

Despite significant therapeutic advancements, heart failure remains a highly prevalent clinical condition associated with significant morbidity and mortality. In 30%–40% patients, the etiology of heart failure is nonischemic. The implantable cardioverter–defibrillator (ICD) is capable of preventing sudden death and decreasing total mortality in patients with nonischemic heart failure. However, a significant number of patients receiving ICD do not receive any kind of therapy during follow-up. Moreover, considering the situation in Brazil and several other countries, ICD cannot be implanted in all patients with nonischemic heart failure. Therefore, there is an urgent need to identify patients at an increased risk of sudden death because these would benefit more than patients at a lower risk, despite the presence of heart failure in both risk groups. In this study, the authors review the primary available methods for the stratification of the risk of sudden death in patients with nonischemic heart failure.

Introduction

The prevalence and incidence of heart failure (HF) indicate that it is an important public health problem. Data from the city of São Paulo indicate high rates of hospitalization in the elderly population, in addition to high treatment costs and a mortality rate approaching 15%. In 30%–40% patients with heart failure accompanied by a decreased ejection fraction (EF), the etiology of ventricular dysfunction is nonischemic. Data from the I Brazilian Registry of Heart Failure (BREATHE registry) indicate that HF is nonischemic in 70% hospitalized patients (Graph 1). Nonischemic HF (NIHF) 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 NIHF, the cause of ventricular dysfunction—designated as idiopathic dilated cardiomyopathy—may be unknown; alternatively, it can be attributed to several causes, including hypertension, exposure to potentially toxic agents (chemotherapeutic drugs and alcohol), Chagas disease, myocarditis, infiltrative disease, peripartum cardiomyopathy, valvular heart disease, and genetic and autoimmune diseases.

Sudden cardiac death (SD) is an unexpected natural death from cardiac causes, and it usually occurs within an hour of symptom onset. Considering that advancements in the treatment of NIHF have brought about a significant decrease in mortality in recent decades, SD remains a significant problem, accounting for approximately 30% deaths. The primary prevention of SD in patients with NIHF involves pharmacological treatment and the use of implantable cardioverter–defibrillators (ICD). Randomized clinical trials have demonstrated that the use of beta-blockers and spironolactone significantly decreased SD in this group of patients. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which included patients with both ischemic and nonischemic HF of New York Heart Association (NYHA) functional class II–III, indicated that ICD decreased SD and total mortality in patients with NIHF. Moreover, an analysis of all patients with implanted ICD revealed that 33.2% received some level of shock by the defibrillator, 22.4% received appropriate defibrillator shocks, and 10.7% received only inappropriate shocks. Undoubtedly, the costs and potential complications related ICD implantation demand a better selection of patients who are at an increased risk of SD and would benefit the most from ICD implantation. For ischemic HF, in addition to EF, electrophysiological studies identified groups of patients at an increased risk of SD, as opposed to NIHF, which still requires a better selection of patients. Therefore, this study aimed to review the primary available options for the stratification of SD risk in patients with NIHF (Table 1).

Clinical and laboratory evaluation

Routine clinical and laboratory evaluations provide information that can be used for the risk stratification of patients with NIHF. The functional class of patients with HF is related to distinct SD risks. Among patients with NYHA functional class II HF, SD is responsible for 64% deaths, whereas HF progression is responsible for 12% deaths. Among patients with NYHA functional class III HF, SD accounts for 59% deaths and HF progression accounts for 26% (Table 2). Among patients with NYHA functional class IV HF, HF progression accounts for 56% deaths and SD accounts for 33%. Chagas disease, NYHA functional class III–IV HF, cardiomegaly on chest radiography, ventricular dysfunction on echocardiography, low voltage of the QRS complex on electrocardiography, nonsustained ventricular tachycardia on Holter electrocardiography, and male sex are
### Graph 1 – Etiology of HF: BREATHE registry data. HF: heart failure; BREATHE: I Brazilian Registry of Heart Failure.

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<th>Marker/Risk</th>
<th>Comment</th>
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<td><strong>Clinical Evaluation</strong></td>
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<td>NYHA functional class</td>
<td>NYHA class II → 64% deaths from SD</td>
<td>Associated with different risks of SD</td>
</tr>
<tr>
<td></td>
<td>Class III → 59% deaths from SD</td>
<td></td>
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<tr>
<td>Syncope</td>
<td>With syncope → 45% SD in 1 year</td>
<td>In patients with advanced HF (NYHA class III and IV)</td>
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<tr>
<td></td>
<td>Without syncope → 12% SD in 1 year</td>
<td></td>
</tr>
<tr>
<td>Laboratory tests</td>
<td>BNP, uric acid, and hemoglobin</td>
<td>Included in risk prediction scores</td>
</tr>
<tr>
<td>LVEF</td>
<td>→ RR for major arrhythmic events was 2.28 for every 10% decrease in EF</td>
<td>Major risk factor for SD Validated in ICD cohorts and trials</td>
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<td>ECG</td>
<td>Duration of the QRS interval and late potentials</td>
<td>QRS was not associated with risk of SD in NIHF. Late potentials with conflicting results</td>
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<td>NSVT</td>
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<td>123I-MIBG</td>
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<td>Cardiac MRI</td>
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<td>Fibrosis increases risk of SD in patients with NIH</td>
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SD: sudden death; HF: heart failure; NIHF: nonischemic heart failure; NYHA: New York Heart Association; ICD: cardioverter-defibrillator; LVEF: left ventricular ejection fraction; NSVT: nonsustained ventricular tachycardia; MIBG: metaiodobenzylguanidine; MRI: magnetic resonance imaging; TWA: T-wave alternans; ECG: electrocardiogram; HRV: heart rate variability; SD: sudden death; RR: relative risk; SDNN: standard deviation of normal-to-normal R-R intervals; EPS: electrophysiological study; BNP: basal natriuretic peptide; HR: hazard ratio.
risk factors for total mortality. However, a specific analysis of SD has not been performed. Both Brazilian and international guidelines include functional classes among the criteria for ICD implantation for the primary prevention of NIHFr12,15.

Syncope is considered to be an important risk factor for SD in patients with NIHFr. In a cohort study involving 491 patients with severe HF, 51% of whom experienced NIHFr, Middelkauff et al. demonstrated that the incidence of SD was 45% among patients with syncope compared with 12% for patients without a history of syncope. A cohort study of patients with NIHFr who received ICD indicated that the administration of appropriate therapies was similar for patients with syncope and those who experienced resuscitated SD. Phang et al. followed 108 patients with NIHFr and syncope and 71 patients with NIHFr and sustained ventricular arrhythmia and observed that the incidence of ventricular arrhythmia, SD, and total mortality was similar in both groups. The occurrence of syncope is contemplated in the guidelines as an indication for ICD in patients with NIHFr. In addition to NYHA functional class and syncope, other clinical factors associated with an increased risk of arrhythmic events include the lack of use of beta-blockers and systolic blood pressure.

Several studies have evaluated the prognostic value of routine screening procedures for the risk stratification of patients with NIHFr. Blood tests, including those for hemoglobin, uric acid, and atrial natriuretic peptide (ANP), were identified in isolated studies as predictors of mortality and arrhythmic events. However, considering that these results are still inconsistent, these tests cannot be considered in isolation for risk assessment. Using risk prediction models derived from the Seattle score on the basis of routine clinical and laboratory variables, Levy et al. classified the patients in the SCD-HeFT into 5 risk groups. In group I patients, ICD significantly decreased the relative risk of SD by 88%, whereas in group V, the decrease was 24%. However, these differences were not significant. With regard to total mortality, the absolute decrease in risk after ICD implantation, in risk quintiles I to V, was 6.6%, 8.8%, 10.6%, 14%, and −4.9%, respectively. However, an analysis including only patients with NIHFr was not performed.

**Left ventricular ejection fraction**

Left ventricular EF (LVEF) can be evaluated using several available methods, the primary one being echocardiography. The decrease in EF is considered to be a major risk factor for SD and total mortality in patients with HF. However, few studies till date have evaluated EF as a risk factor for SD specifically in patients with NIHFr. The Marburg Cardiomyopathy Study (MACAS), a prospective cohort study involving 343 patients with NIHFr, revealed that in patients with sinus rhythm, the relative risk for major arrhythmic events was 2.28 for every 10% decrease in EF. In patients with atrial fibrillation, the relative risk was 4.5.

EF ≤ 35% was an inclusion criterion for the SCD-HeFT, a trial that serves as the basis for ICD indications in patients with NIHFr. Both Brazilian and international guidelines consider EF ≤ 35% as a criterion for ICD implantation as the primary preventive measure in patients with NIHFr. However, we should note that, although EF is considered a major risk factor for SD, several other events occur in patients with EF > 35%. In addition, the relative risk of SD is significantly higher in patients with EF ≤ 35% than in those with EF > 35%. However, the absolute number of SD cases is higher among patients with more preserved EF, considering that these patients represent a much larger subgroup. Data from the Maastricht study indicate that, among patients for whom EF was measured before an SD episode, 52% had EF > 30% and 32% had EF > 40%.

**Electrocardiography**

The electrocardiogram (ECG) is a simple, readily available tool that provides useful information for the risk stratification of patients with NIHFr. The rate of prolongation of the QRS interval in patients with HF ranges from 20% to 50%. In specific cohort studies involving patients with NIHFr, no correlation was found between the presence of bundle branch block and the increased risk of SD. In the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE), a clinical trial involving patients with NIHFr, ICD decreased the arrhythmic causes of SD without causing a significant decrease in total mortality, and no correlation was found between the QRS duration and total mortality. In the SCD-HeFT, an increased benefit from ICD implantation was observed in patients with QRS > 120 ms. However, a specific analysis was not performed for the group with NIHFr. Another study indicated that fragmentation of the QRS complex (default RSR’ and a duration of < 120 ms in two contiguous leads) was associated with a higher incidence of arrhythmic events in patients with NIHFr. However, this finding warrants further investigation. In addition, observational studies indicate conflicting results for the association between the measured QT interval and mortality from HF, and a specific analysis was not performed in patients with NIHFr. Furthermore, the dispersion in the QT interval (maximum difference between the QT intervals on a surface...
ECG) was evaluated in patients with NIHF. Although previous studies have indicated a positive correlation, recent studies have found no association between QT interval dispersion and an increase in major arrhythmic events\textsuperscript{39}.

The high-resolution ECG (HRECG) is a useful tool for the amplification and processing of ECG signals. It evaluates the presence of late potentials at the end of the QRS complex and the duration of the QRS interval. Previous studies on the role of HRECG in the risk stratification of patients with NIHF have revealed conflicting results. The presence of late potentials using HRECG was identified in 27% patients with NIHF and was associated with an increased cardiovascular mortality and arrhythmic events\textsuperscript{39}. However, in other studies, this method could not stratify the risk of arrhythmic events in patients with NIHF, despite similar variations in HRECG\textsuperscript{19,30}.

**Holter electrocardiogram (ambulatory electrocardiographic monitoring)**

Holter ECG is a widely available diagnostic tool used for risk assessment of patients with NIHF, taking into consideration the presence of nonsustained ventricular tachycardia (NSVT) and the analysis of measures of autonomic activity, including heart rate (HR) variability (HRV) and HR turbulence (HRT).

The incidence of NSVT (Figure 1) in patients with NIHF ranges from 30%–79%; therefore, its use in the risk stratification of arrhythmic events is considered controversial\textsuperscript{11}. In a prospective study involving 179 patients, Iacovielo et al. revealed that the presence of NSVT was associated with a relative risk of 2.96 [95% confidence interval (CI), 1.17–7.49; \( p = 0.022 \)] for the occurrence of major arrhythmic events\textsuperscript{32}. In the MACAS, the presence of NSVT alone was not significantly correlated with an increased risk of arrhythmic events\textsuperscript{19}. However, a combination of NSVT with EF < 30% was associated with an 8.2-fold increase in the risk of arrhythmic events (95% CI, 3.1–22.6; \( p = 0.0001 \)). In this same cohort, a subsequent analysis was performed after taking into consideration the duration of and HR in NSVT. The incidence of arrhythmic events was 2% per year in patients without NSVT, 5% per year in patients with NSVT lasting from 5 to 9 beats, and 10% per year in patients with NSVT lasting > 10 beats (Table 3)\textsuperscript{11}. With regard to HR in NSVT, there was no significant difference between groups with and without arrhythmic events. Meta-analysis data indicated that the presence of NSVT was associated with a 3.2-fold increase in the risk of SD (95% CI, 2.12–4.89; \( p < 0.05 \))\textsuperscript{14}. In patients with NIHF who were implanted with ICD, the presence of NSVT was associated with a 7.8-times increase in the risk of appropriate therapy for ICD (95%CI, 1.8–33.7; \( p = 0.006 \)). The presence of NSVT or \( \geq 10 \) ventricular extrasystoles per hour on Holter ECG was an inclusion criterion in the DEFINITE\textsuperscript{26}. A combined analysis of these results demonstrates that the detection of NSVT can indicate an increased risk of major ventricular arrhythmias. However, these results do not allow us to justify the clinical decision on ICD implantation on the basis of NSVT detection.

HRV is a measure of autonomic activity that takes into consideration the beat-to-beat variation in the R-R interval. HRV analysis can be performed as a function of time or frequency. In clinical practice, the most commonly used measure is the standard deviation of normal-to-normal R-R intervals (SDNN), which represents the standard deviation in R-R intervals. A decreased HRV is associated with an increased risk of death from HF progression, but not an increased risk of SD\textsuperscript{36,37}. In the MACAS, no association was found between a decreased HRV and an increased risk of arrhythmic events\textsuperscript{19}. Moreover, an analysis of the DEFINITE reveals that patients with preserved HRV exhibit a good prognosis and may not benefit from ICD implantation\textsuperscript{18}.

HRT is a measure of autonomic activity that takes into account variations in R-R intervals that manifest after the occurrence of ventricular extrasystoles. During follow-up of patients from the MACAS, there was no significant correlation between HRT and arrhythmic events, similar to the finding observed in the study by Klingenheben, who evaluated a series of markers of autonomic activity\textsuperscript{11,19}.

**T-wave alternans**

T-wave alternans (TWA) can be defined as the beat-to-beat alternation in morphology, amplitude, and/or polarity of T-waves. Considering that these changes are measured in microvolts, specific processing programs are available for the detection of specific TWA. The T-Wave Alternans in Patients with Heart Failure (ALPHA) study prospectively monitored 476 patients with NYHA functional class II and III NIHF\textsuperscript{40}. Of these, 44.8% had positive TWA, 34.6% had negative TWA, and 20.6% were undetermined. The primary outcome (cardiac death in addition to serious arrhythmias) occurred in 6.5% patients with altered TWA (positive or indeterminate) and 1.6% patients with normal TWA. According to multivariate analysis, the relative risk was 3.2 (95% CI, 1.12–9.20; \( p = 0.013 \)). The negative predictive value for this outcome after 18 months was 97.3% (95% CI, 93.9–99.3). However, the positive predictive value was only 9% (95% CI, 5.9–13.0).

In contrast, in the MACAS study, TWA was not able to stratify patients with an increased risk of arrhythmic events\textsuperscript{19}. The event rate was 13% in patients with positive TWA, 10% in those with negative TWA, and 24% in those with indeterminate TWA, without significant differences between groups. In a meta-analysis that evaluated major arrhythmic events combined with death from any cause, the relative risk for altered TWA (abnormal or indeterminate) was 2.99 (95% CI, 1.88–4.75), with a negative predictive value of 96.2\%\textsuperscript{17}. In the assessment of TWA in the SCD-HeFT, no significant differences were observed in major arrhythmic events.

### Table 3 – Incidence of major arrhythmic events and NSVT on 24-h Holter ECG (*)

<table>
<thead>
<tr>
<th>NSVT</th>
<th>Major arrhythmic events (% per year) (†)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of NSVT</td>
<td>2</td>
</tr>
<tr>
<td>NSVT of 5–9 beats</td>
<td>5</td>
</tr>
<tr>
<td>NSVT of ≥ 10 beats</td>
<td>10</td>
</tr>
</tbody>
</table>

NSVT: nonsustained ventricular tachycardia (*); ECG: electrocardiogram. Adapted from reference 33. (†) \( p < 0.05 \).
events among patients with normal, altered, or undetermined TWA. Therefore, these studies with conflicting results and the absence of clinical trials that addressed TWA as an inclusion criteria preclude TWA from being included in the guidelines as a criterion for the selection of patients eligible for ICD implantation.

**Cardiopulmonary exercise test**

The cardiopulmonary exercise test is recommended for the evaluation and follow-up of patients with HF. Meta-analysis data indicate that variables derived from cardiopulmonary exercise testing and oxygen consumption (VO\textsubscript{2}) slope, and the occurrence of periodic breathing, in isolation, indicate an increased risk of combined events, including total mortality, cardiac death, heart transplantation, hospitalization, and the need for ventricular assistive devices. A national database of patients using beta-blockers indicated that peak VO\textsubscript{2} ≤ 10 ml/kg/min indicates an increased risk of cardiovascular events, peak VO\textsubscript{2} between 10 and 16 ml/kg/min represents a moderate risk, and peak VO\textsubscript{2} > 16 ml/kg/min indicates a lower risk. In addition, a VE/VCO\textsubscript{2} slope of > 34 was associated with an increased risk. Patients with NIHF accounted for 68% of the sample. However, a stratified analysis on the etiology of HF was not performed.

Guazzi et al. assessed the performance of the cardiopulmonary exercise test variables in relation to the risk of SD. Patients without complications exhibited a peak VO\textsubscript{2} of 16.8 ± 4.5 ml/kg/min, a VE/VCO\textsubscript{2} slope of 32.8 ± 6.4, and a 20.3% prevalence of periodic breathing. Patients who developed SD exhibited a peak VO\textsubscript{2} of 13.58 ± 3.2 ml/kg/min, a VE/VCO\textsubscript{2} slope of 41.5 ± 11.4, and a 100% prevalence of periodic breathing. According to multivariate analysis, the only variable associated with an increased risk of SD was the development of periodic breathing. In this study, patients with NIHF represented 37% of the sample (n = 156). However, a stratified analysis according to the etiology of HF was not performed. These findings warrant further investigations involving a larger number of patients that can analyze the etiology of HF.

**Myocardial scintigraphy with iodine-123-metaiodobenzylguanidine**

Myocardial scintigraphy with iodine-123-metaiodobenzylguanidine (\textsuperscript{123}I-MIBG) can evaluate the function of the sympathetic nervous system in patients with HF. Recent data indicate that a low late heart-to-mediastinum ratio and an increased washout rate of \textsuperscript{123}I-MIBG were associated with an increased incidence of cardiovascular events. In a cohort study with 106 patients, 44% of whom had NIHF, patients with abnormal \textsuperscript{123}I-MIBG scintigraphy results exhibited a significantly higher risk of SD (hazard ratio, 4.79; 95% CI, 1.55–14.76; p = 0.006). In another study that monitored 116 patients with ICD, those with alterations in \textsuperscript{123}I-MIBG exhibited a higher rate of ICD therapy (52% versus 5%, p < 0.01). In both studies, no specific analysis was performed in patients with NIHF. Considering these promising findings, it is estimated that other prospective studies will be conducted with a larger number of patients, with the view to performing a stratified analysis of the etiology of HF, and will enable the inclusion of \textsuperscript{123}I-MIBG in the guidelines for the risk stratification of patients with NIHF.

**Electrophysiological study**

In a group of patients with ischemic HF, an electrophysiological study (EPS) with programmed ventricular stimulation was able to identify patients at a higher risk of major arrhythmic events. However, the results are controversial for patients with NIHF. Poll et al. conducted EPS involving 20 patients with NIHF and observed the induction of ventricular tachyarrhythmia in 30% of patients. Of these, 50% had ventricular tachyarrhythmia during follow-up. Among those with negative EPS, 36% experienced arrhythmias. In the 1990s, Brembilla-Perrot et al. conducted EPS involving 92 patients with NIHF and observed the induction of ventricular tachyarrhythmia in only 8%. The incidence of ventricular arrhythmias in this group was 50%; however, it was only 4% in the group with negative EPS findings. In another study involving 34 patients, Grimm et al. induced ventricular tachyarrhythmia in 38%. The incidence of ventricular arrhythmias in this group was 30% compared with 24% in the group with negative EPS findings. Nonetheless, these studies...
involved a small number of patients, adopted heterogeneous methodologies, and were conducted before the widespread use of beta-blockers for HF treatment.

Recent studies have re-evaluated EPS conducted in these conditions. In a subanalysis of the DEFINITE EPS findings were positive in 14% of patients, and 34% of these patients presented with ventricular arrhythmias. Among patients with negative EPS findings, the incidence of ventricular arrhythmias was 12%. The positive and negative predictive values of EPS for determining the requirement of ICD therapy were 34% and 88%, respectively. Gatzoulis et al. prospectively monitored 158 patients with NICF undergoing EPS for the primary prevention of SD. EPS findings were positive (induction of ventricular tachycardia or ventricular fibrillation) in 44 patients (28%) and negative in 114 (72%). ICD implantation was performed in 41 patients from the positive EPS group and 28 patients from the negative EPS group. However, the total mortality during a follow-up of 46.9 months was not significantly different between patients with positive or negative EPS. In patients implanted with ICD, the rate of administration of therapies for ICD (e.g., shock or anti-tachycardia stimulation) was 73.2% for those with positive EPS and 17.9% for those with negative EPS (p = 0.001). Positive EPS was the only prognostic factor for the administration of ICD therapy (hazard ratio, 4.19; 95% CI, 1.467–11.994; p = 0.007). Considering the overall results of these studies, the guidelines do not recommend the routine performance of EPS for the risk stratification of patients with NICF. Therefore, future studies using a larger number of patients, optimal pharmacological therapies, and more uniform protocols for ventricular stimulation can better assess the role of EPS in this group of patients.

Genetic evaluation

Several studies have evaluated the association between genetic mutations and the pathophysiology and prognosis of patients with NICF, particularly those with familial diseases. Among the best investigated conditions are mutations in the lamin A/C (LMNA) gene. Pasotti et al. demonstrated that patients with NICF carrying LMNA mutations have a high incidence of major arrhythmic events (40%–67%), and the risk factors included NYHA functional class, type of mutation, and practice of competitive physical activity. In the study by van Rijssing et al., the incidence of major arrhythmic events was 18%, and the risk factors included NSVT, EF, male sex, and type of mutation. Furthermore, mutations in the SCN5A sodium channel gene have been associated with an increased risk of arrhythmic events. Mutations in the RBM20 gene, which is responsible for regulation of the splicing process in cardiac tissue, were identified in 2.8% patients from a cohort with NICF and ICD and were not associated with an increased risk of ventricular arrhythmias. Considering the prevalence and the important prognostic implications, the investigation of mutations in the LMNA gene may be considered in all patients with idiopathic NICF, particularly when there is significant impairment in the conduction system. In Brazil, this genetic evaluation is not yet available for routine clinical use.

Moreover, analysis of the presence of genetic polymorphisms has been evaluated as a tool for the risk stratification of patients with NICF. In a cohort study, the presence of the Gly389 allele in the polymorphism of the β1-adrenergic receptor Arg389 Gly was associated with a lower incidence of ventricular arrhythmias. In addition, a national cohort study including patients with ICD identified a protective effect of the presence of the Gly389 allele. However, a stratified analysis of patients with NICF, which corresponded to 41% of the study group, was not performed. The AT1R-1166CC genotype of the polymorphism associated with the renin–angiotensin–aldosterone system was correlated with a two-fold increase in the requirement of ICD therapies in patients with CI. In this same study, circulating levels of the microRNA miR-155 were associated with an increased risk of ICD therapies. In addition, 23% patients who received ICD therapy presented with NICF. Therefore, the analysis of genetic polymorphisms is very promising, and future studies may lead to the identification of patients with genetic patterns associated with greater risk and patients who may benefit the most from ICD implantation.

Cardiac magnetic resonance imaging

The presence of myocardial fibrosis is an important arrhythmogenic substrate in patients with NICF. The detection of myocardial fibrosis using serum markers of collagen metabolism or imaging methods could identify high-risk patients. Kanoupakis et al. demonstrated that patients with NICF and changes in serum markers of collagen metabolism exhibited a higher rate of appropriate ICD therapies. Cardiac magnetic resonance imaging (MRI) using the delayed enhancement technique is the primary imaging method used to detect and quantify the extent of myocardial fibrosis. Approximately 30% patients with NICF exhibited myocardial fibrosis on MRI (Figure 2).

Several studies have evaluated the relationship between the presence of fibrosis on MRI and the occurrence of major arrhythmic events in patients with NICF. In a pioneering study, Nazarian et al. evaluated 26 patients with NICF subjected to EPS and MRI. The presence of fibrosis covering 26%–75% of the wall thickness was associated with a nine-fold increase in the risk of ventricular arrhythmia according to EPS. In a cohort study with 101 patients, Assomull et al. revealed that fibrosis was an independent predictor of SD associated with ventricular tachycardia (hazard ratio, 5.2; 95% CI, 1.10–32.2; p = 0.04). In a study by Lehrke et al. involving 184 patients, the presence of fibrosis was considered to be an independent predictor of the combined events of cardiac death, appropriate ICD therapy, and hospitalization (hazard ratio, 3.4; 95% CI, 1.26–9.00; p = 0.015). In this cohort, a fibrosis rate of > 4.4% of the left ventricular (LV) mass was associated with a worse prognosis, and the prognostic value of the presence of fibrosis was restricted to patients with EF < 30%. However, these findings were not confirmed in the study of Hombach et al., who monitored 151 patients and found no association between the presence of fibrosis and the combined events of cardiac death and SD. MRI variables associated with the event were cardiac index, index of the end-diastolic volume of the right ventricle, and the presence of QRS > 110 ms and diabetes.
Gulati et al. recently published the results for the largest cohort of patients with NIHF examined on MRI. In this study, 472 patients were monitored, with a median follow-up of 5.3 years. The primary outcome of total mortality occurred in 26.8% patients, and myocardial fibrosis occurred in 10.6% patients without fibrosis. After multivariate analysis with adjustment for EF and other prognostic factors, the presence of fibrosis represented a hazard ratio of 2.43 (95% CI, 1.50–3.92; p < 0.001), and the extent of fibrosis represented a hazard ratio of 1.11 (95% CI, 1.06–1.16; p < 0.001). Combined events of SD and aborted SD were observed in 29.6% patients with myocardial fibrosis and 7.0% patients without fibrosis. For this event, the presence of fibrosis represented a hazard ratio of 4.61 (95% CI, 2.75–7.74; p < 0.001), and the extent of fibrosis represented a hazard ratio of 1.10 (95% CI, 1.05–1.16; p < 0.001). These results, together with those from previous studies, indicate that MRI can be a useful technique for the risk stratification of patients with NIHF. The usefulness of MRI needs further confirmation through prospective multicenter studies designed specifically for this purpose.

**Author contributions**

Conception and design of the research: Pimentel M, Rohde LE; Acquisition of data: Pimentel M; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Pimentel M, Zimerman LI, Rohde LE.

**Potential Conflict of Interest**

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**Study Association**

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Figure 3 – Risk stratification of sudden death in patients with nonischemic heart failure

EF: ejection fraction; EPS: electrophysiological study; MRI: magnetic resonance imaging; HRV: heart rate variability; TWA: T-wave alternans.

References


