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Sudden cardiac death in nonischemic cardiomyopathy☆

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ABSTRACT

Sudden cardiac death (SCD) is a major cause of mortality in patients with nonischemic cardiomyopathy (NICM). Identifying patients who are at highest risk for SCD is an ongoing challenge. At present, guidelines recommend the use of an implantable cardioverter-defibrillator (ICD) in patients with NICM with a reduced left ventricular ejection fraction (LVEF) and heart failure (HF) symptoms. Some recent data, however, suggest that ICDs may not increase longevity in this population. Conversely, community-based studies have demonstrated that many at-risk individuals who may benefit from ICD therapy remain unprotected. Current recommendations for ICD implantation are continually debated, justifying comprehensive individualized risk assessment. Various promising techniques for further risk stratification are under evaluation, including cardiac magnetic resonance imaging, electrocardiographic assessment of electrical instability, and genetic testing. However, none of these strategies has been fully adapted into guidelines. Hence, clinical risk stratification practice today depends on LVEF and HF symptoms, which have poor sensitivity and specificity for predicting SCD risk.

Contents

Abbreviations and acronyms: MIBG, 123-metaiodobenzylguanidine; CMR, Cardiac magnetic resonance; CRT, Cardiac resynchronization therapy; CM, Cardiomyopathy; CAD, Coronary artery disease; EF, Ejection fraction; ESRD, End stage renal disease; GLS, Global longitudinal strain; GDMT, Guideline directed medical therapy; HR, Hazard ratio; HF, Heart failure; HMR, Heart-to-mediastinum ratio; ICD, Implantable cardioverter-defibrillator; IL-6, Interleukin 6; ICM, Ischemic; LGE, Late gadolinium-enhanced; LV, Left ventricular; MD, Mechanical dispersion; mTWA, Microvolt T-wave alternans; MWF, Midwall fibrosis; NYHA, New York Heart Association; NICM, Nonischemic; pro-BNP, N-terminal pro-B-type natriuretic peptide; PF, Pump failure; fQRS, QRS fragmentation; QTd, QT duration and dispersion; SHF, Seattle Heart Failure; SCD, Sudden cardiac death; TTN, Titin; Tpe, T-peak to T-end interval; VA, Ventricular arrhythmia; WCD, Wearable cardioverter-defibrillator.

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Background

Sudden cardiac death (SCD) is among the most common causes of mortality in the world, especially in patients who have cardiomyopathy (CM),[1] defined as the presence of left ventricular (LV) mechanical and/or electrical dysfunction, which can be classified into two major groups: primary and secondary.[2] Primary CM is predominantly confined to myocardial dysfunction (genetic, non-genetic, acquired), and secondary CM refers to the pathological involvement of the heart as a sequela of systemic diseases.[2] Another frequently used classification of CM is ischemic (ICM) versus nonischemic (NICM). ICM is myocardial dysfunction in the presence of significant obstructive coronary artery disease (CAD), whereas NICM is defined as LV dysfunction in the absence of CAD.[2,3]

NICM is the second leading cause of LV systolic dysfunction, with a predicted incidence of 1 in 400 and with a prevalence of 36 to 40 per 100,000 persons in the United States.[4–6] Chronic myocardial dysfunction can lead to progressive tissue injury and impaired myocardial contractility, which serves as a substrate for ventricular arrhythmia (VA), a major cause of SCD.[6] Three-year mortality rates remain high at 12%–20%, with death typically resulting from heart failure (HF) or VA manifesting as SCD.[7–9] Optimal management of NICM patients includes administration of guideline directed medical therapy (GDMT).

The implantable cardioverter-defibrillator (ICD) has the ability to promptly recognize and treat potentially lethal VA. Current guidelines recommend ICD implantation for primary prevention of SCD in patients with LV ejection fraction (EF) ≤35%, New York Heart Association (NYHA) class II-III HF, and >1 year non-SCD expected survival.[10] However, in reality these criteria are neither sensitive enough nor specific enough to adequately screen at-risk populations.[11] Thus, a large subgroup of NICM patients with normal or mildly reduced LVEF are left still at risk for SCD. For example, in community-based trials among victims of out-of-hospital cardiac arrest, up to 70% had preserved LVEF, and therefore would not have met the current LVEF criterion for ICD prophylaxis.[12] Alternatively, members of the NICM population who meet the criteria for ICDs and receive ICDs may never require therapy from their device.[13] Although the data supporting the use of ICD in ICM are robust, there is conflicting evidence for its use in NICM.[13] Five randomized clinical trials including patients with NICM failed to demonstrate an increase in longevity from ICD implantation, making their routine use somewhat controversial.[8,9,14]

Since the current guidelines fail to capture all high-risk patients, and the role of ICD therapy in the NICM population has been questioned, evidence-based updated recommendations are needed. A comprehensive and algorithmic assessment may better determine SCD risk. Our goal is to provide a brief overview of these candidate techniques, starting from fundamental principles and progressing to more complex screening tools, which have the potential to reshape current guidelines.

Landmark trails examining ICDs in NICM populations

Primary prevention of SCD in NICM patients at high risk for developing life-threatening VA principally involves ICD implantation. Five randomized trials have studied the benefits of ICDs for primary prevention in all types of CM patients (Table 1). The first two trials, Cardiomyopathy Trial (CAT, 2002) and Amiodarone Versus Implantable Cardioverter-defibrillator Trial (AMIOVIRT, 2003), were terminated early due to futility, as mortality rates in both groups were lower than expected, resulting in underpowering.[7,15] The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation Trial (DEFINITE, 2004) enrolled 458 NICM patients with LVEF <36% and premature ventricular complexes or nonsustained VA.[9] In this study, ICD plus GDMT failed to show a significant reduction in all-cause mortality compared to GDMT alone (hazard ratio (HR) 0.65, $P = 0.08$). However, the risk of SCD was significantly reduced with ICD therapy (HR 0.20, $P = 0.006$). Furthermore, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) included patients with LVEF ≤35% due to either ICM or NICM. This was a three-armed primary-prevention study that included antiarrhythmic medical therapy in the form of amiodarone, versus ICD therapy, versus placebo.[8] The authors concluded that amiodarone had no favorable effect on survival, whereas single lead, shock-only ICD therapy reduced overall mortality by 23% (HR, 0.77, $P = 0.007$) and showed an absolute decrease in mortality of 7.2% over 5 years.[13] At that time, SCD-HeFT was the only randomized trial demonstrating a mortality benefit from ICD implantation in both ICM and NICM. Meta-analysis of the NICM groups from these four trials found an all-cause mortality reduction of 31% with ICD therapy (HR, 0.69; $P = 0.002$).[2] Thus, that analysis supported ICD implantation for primary prevention of SCD in NICM patients with LVEF ≤35%.[2,13]

More recently, however, the utility of ICDs in NICM has been challenged. The Danish Study to Assess the Efficacy of ICDs in Patients with Nonischemic Systolic Heart Failure on Mortality (DANISH) investigated ICD therapy versus routine GDMT in symptomatic NICM patients with LVEF ≤35% and N-terminal pro-B-type natriuretic peptide (pro-BNP) >200 pg/mL.[14] In this randomized trial, prophylactic ICD implantation successfully reduced SCD (HR 0.50, $P = 0.005$) but did not significantly reduce all-cause mortality when compared to standard GDMT

Table 1
Randomized trials investigating the benefit of cardioverter-defibrillator implantation for the primary prevention of sudden cardiac death in patients with non-ischemic cardiomyopathy.

Study	n	Inclusion criteria	Ischemic (n, %)/nonischemic (n, %)	Intervention	Follow up (Median) Months	All-cause mortality	Sudden cardiac death
CAT	104	LVEF <30% NYHA II–III	(0, 0%)/(104, 100%)	ICD vs. OMT	23	Terminated early	
AMIOVERT	103	LVEF <30% NYHA II–III NSVT	(0, 0%)/(103, 100%)	ICD vs. Amiodarone	24	Terminated early	
SCD-HeFT	2521	LVEF <30% NYHA II–III	(1311, 52%)/(1210, 48%)	ICD vs. OMT vs. Amiodarone	46	I, 21.4%; C, 27.9% (5 y) HR, 0.73; 95% CI, 0.50–1.07; $P = 0.06$	
DEFINITE	458	LVEF <36% NYHA I–III, NSVT or PVCs	(0, 0%)/(458, 100%)	ICD vs. OMT	29	I, 12.2%; C, 17.4% HR, 0.65; 95% CI, 0.40–1.06; $P = 0.08$	I, 1.3%; C, 6.1% HR, 0.20; 95% CI, 0.06–0.71; $P = 0.006$
DANISH	1116	LVEF <35% NYHA II–III (IV if CRT) NT-proBNP >200 pg/mL	(0, 0%)/(1116, 100%)	ICD vs OMT	68	I, 21.6%; C, 23.4%; HR, 0.87; 95% CI, 0.68–1.12; $P = 0.28$	I, 4.3%; C, 8.2% HR, 0.50; 95% CI, 0.31–0.82; $P = 0.005$

Abbreviations: CAT, Cardiomyopathy Trial; AMIOVIRT, Amiodarone Versus Implantable Cardioverter-Defibrillator; CI, confidence interval; CRT, cardiac resynchronization therapy; DANISH, Danish Study to Assess the Efficacy of ICDs in Patients With Non-Ischemic Systolic Heart Failure on Mortality; DEFINITE, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; HR, hazard ratio; I, implantable cardioverter-defibrillator therapy arm; ICD, LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; NT-proBNP, N-terminal-propeptide brain natriuretic peptide; NYHA, New York Heart Association; OMT, optimal medical therapy; PVC, premature ventricular complex; and SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial.

alone (HR 0.87, $P = 0.28$).[14] This finding implied that in modern practice, which includes improved GDMT and more common use of cardiac resynchronization therapy (CRT), ICD implantation may not be lifesaving. However, an updated meta-analysis including data from DANISH demonstrated 25% reduction in all-cause mortality with ICD therapy compared to GDMT alone (HR, 0.77).[16] Based on these findings, ICD implantation for primary prevention of SCD in symptomatic NICM with LVEF ≤35% remains a Class I, Level of Evidence A indication.[10]

Despite the current guidelines recommending ICD implantation based primarily on LVEF, there are conflicting data which show that this criterion has poor sensitivity and specificity for predicting SCD in NICM.[13] For example, the Maastricht Circulatory Arrest Registry demonstrated that the vast majority of SCD due to out of hospital arrest occurred in patients with LVEF >35%.[12] NICM-specific registries showed increased risk of SCD with reduced LVEF, but patients with only mild to moderate reduction in LVEF also had significant risk of VA/SCD.[17]

Identifying the NICM subpopulation who would most benefit from ICD therapy remains a challenge because the current LVEF- and NYHA-based risk stratification schema for primary prevention of SCD is inadequate. Therefore, a more comprehensive tool, or set of tools, that includes the latest biomarkers, genetic testing, and imaging-based techniques could aid in appropriately stratifying NICM patients by risk for SCD.

Understanding competing risk

Patients with severely symptomatic heart failure (NYHA class IV) and/or noncardiac expected mortality <1 year are at high risk of nonarrhythmic "competing" causes of death, rather than arrhythmic death.[18] The leading cause of mortality in end stage HF is pump failure, rather than VA. In patients at high risk of PF, ICD implantation is not recommended unless advanced cardiac options (e.g., transplant) are planned.[18] In the DANISH trial, a subgroup analysis of the NICM population >68 years of age showed a trend toward increasing mortality despite ICD therapy (HR 1.19, $P = 0.38$), whereas patients <59 years treated with ICD had lower mortality (HR 0.5, $P = 0.02$).[14] Additionally, patients with noncardiac comorbidities can have high risk for non-SCD, thereby leading to shorter life expectancy due to non-cardiac causes and lower likelihood of benefit from ICDs. For example, a matched cohort study examining ICDs for primary prevention in patients with CM and end stage renal disease (ESRD) failed to demonstrate a reduction in mortality, due at least in part to the high non-SCD mortality associated with ESRD.[19,20] When considering ICD implantation for SCD prophylaxis, competing risks should be taken into consideration.

Many different HF scoring models exist to risk stratify and prognosticate patients. The Seattle Heart Failure (SHF) Model is a multi-tier risk stratification scoring system comprising clinical variables with high levels of discrimination. The SHF model is designed to project survival at baseline and after interventions in HF patients by evaluating typically easily obtainable clinical variables.[21] The predicted survival at years 1 and 3 has shown to be very accurate, as is the predicted mode of death.[22] One meta-analysis showed that patients with high SHF scores had a high risk of PF death (87.6%) and a very low risk of SCD: only (6.5%) during a mean follow up of 1.6 ± 0.7 years.[22] These data highlight the fact that even though end-stage HF is associated with VA/SCD, the risk of death from HF in these patients is far greater, rendering ICD implantation ineffective. Other HF scoring systems have also demonstrated effective survival prognostication, but fail to differentiate between SCD and non-SCD causes of mortality.[23] Incorporating HF scoring models as a part of competing risk assessment could discriminate patients who may or may not benefit from ICD therapy.

Markers of myocardial stress

Serum-based biomarkers have the potential to enhance traditional methods of risk stratifying the NICM population. The markers pro-BNP, troponin, galectin-3, interleukin 6 (IL-6), and soluble ST2 can be elevated during inflammation, neurohormonal activation, and/or pathological processes, can be monitored in response to interventions, and can indicate the severity of CM. BNP was investigated in a prespecified subgroup analysis of the DANISH trial. NICM patients with BNP <1177 pg/mL who were randomized to ICD therapy had lower all-cause mortality (HR 0.59, $P = 0.02$) compared to those with BNP >1177 pg/mL, who showed no mortality benefit.[6,14] Another prospective study compared many different electrocardiographic and clinical variables, including biomarkers, and found BNP >1600 pg/ml to be the only independent predictor of all-cause mortality ($P = 0.014$).[24] The Prospective Observational Study of Implantable Cardioverter Defibrillators (PROSE-ICD) enrolled 1189 patients with HF, with the primary endpoint of appropriate ICD shock therapy.[25] In that study, elevated IL-6 levels were associated with increased risk of appropriate ICD shocks. In contrast, C-reactive protein, tumor necrosis factor-a receptor II, and cardiac troponin T demonstrated a linear trend for increased risk of all-cause mortality rather than VA. The combination of these five biomarkers effectively identified patients who were likely to die from non-VA causes. Thus, serum-based biomarkers may be useful for identifying patients who are unlikely to benefit from an ICD.

Markers of electrical instability

Myocardial electrical properties evidenced on the surface electrocardiogram (ECG) have been used to predict the risk of SCD.[26,27] These include QT duration and dispersion (QTd), QRS duration, QRS fragmentation (fQRS), and microvolt T-wave alternans (mTWA). Identifying and understanding the importance of each parameter and its correlated risk of SCD has been challenging, as multiple small studies have had inconsistent methodology, lack uniform data, and have investigated different endpoints.[26] In addition, many of these measurements have yet to be evaluated in NICM specifically.

QRS duration predicts SCD in medically treated hypertensive patients. Over 4.8 ± 0.9 years of follow up of 9193 hypertensive patients, 1.9% suffered SCD. QRS duration was independently predictive of SCD (HR per 10 ms increase = 1.22, $P < 0.001$).[28] Also, QRS duration >120 ms has been identified as an independent risk factor for mortality in patients with HF. A retrospective analysis evaluated this trend in 669 patients with CM.[29] Groups were divided based on QRS duration <120 ms versus ≥120 ms. A prolonged QRS was associated with increased overall mortality ($P = 0.0001$) and SCD in particular ($P = 0.0004$). Interestingly, a subgroup analysis in patients with NICM did not show a QRSd-based difference in survival or increased SCD risk, further adding to the conflicting data between ICM and NICM populations.

Fragmented QRS complexes (fQRS) are characterized by additional spikes within the QRS complex and represent ventricular myocardial fibrosis and/or scar.[30] Strauss et al. published a fQRS scoring system in NICM patients and compared this score with cardiac magnetic resonance for evaluation of myocardial scar. The authors identified increased arrhythmogenesis with higher estimated fQRS scores.[31] In addition, in the ICD arm of the SCD-HeFT trial, patients who did not have ventricular scarring by fQRS scoring had significantly fewer VA events.[32] A large meta-analysis including 45 studies of 6088 NICM patients was performed by Gaetano and Sanzo, who summarized the utility of fQRS for the prediction of arrhythmic endpoints, appropriate ICD discharges, and all-cause mortality.[33] fQRS was found to be the most promising parameter for predicting adverse events (odds ratio [OR] 6.73, $P < 0.001$).[34] Currently, no large studies evaluating fQRS scoring in NICM population have been published. Further investigation in this population is warranted to guide its use in improving risk stratification for SCD.

Microvolt T-wave alternans (mTWA) is a low-amplitude beat-to-beat fluctuation of the surface ECG's T wave amplitude and morphology. Abnormal mTWA is associated with increased ventricular repolarization

dispersion, and has been proposed for additive risk stratification. Cantillon et al. evaluated 286 patients with LVEF ≤35%, both ICM and NICM, who underwent both electrophysiologic testing and mTWA testing due to nonsustained VA and/or syncope, with the primary end point of arrhythmia-free survival.[33] During a mean follow up of 38 ± 11 months, mTWA-negative patients had longer arrhythmia-free survival ($P < 0.001$) and lower total mortality at 2 years ($P = 0.04$). In another study, NICM and ICM patients being treated with beta-blockers had a particularly strong risk of arrhythmic events if they had positive mTWA (HR 5.39, $P < 0.001$).[35] Additionally, an investigation of a NICM population with symptomatic heart failure found that abnormal mTWA was associated with 4-fold higher risk of cardiac death and life-threatening VA.[24] Despite mTWA being a promising marker, the presence of bundle branch block or intraventricular conduction delay, which are commonly found in NICM, decreases mTWA's specificity.[36] mTWA has been more thoroughly studied in ICM populations, with mixed results. The Alternans Before Cardioverter Defibrillator Trial (ABCD) was the first trial to use mTWA to guide prophylactic ICD implantation.[37] Patients who had negative mTWA had a much lower event rate than patients with nonnegative mTWA. Conversely, another large prospective trial in 575 ICM patients found that the risk of VA did not differ according to mTWA classification, further clouding its usefulness for clinical practice.[37]

Finally, the terminal portion of the QT interval, the T-peak to T-end interval (Tpe), is another measure of dispersion of ventricular repolarization. Prolonged Tpe suggests greater dispersion of repolarization, increasing the propensity toward reentrant VA. Rosenthal et al. investigated the relationship of rate-corrected Tpe (Tpe_c) to VA and/or overall mortality in 305 patients with LVEF ≤35% (either ischemic or nonischemic) and an ICD implanted for primary prevention.[38] The study showed that a longer Tpe_c was independently predictive of VA and overall mortality (HR per 10 ms increase: 1.17, $P = 0.01$). A subsequent meta-analysis was performed to evaluate the utility of Tpe_c for predicting VA and/or mortality end points. The authors reviewed 845 studies involving 155,856 patients with a wide variety of CMs and comorbidities, and concluded that prolongation of Tpe_c was a useful tool in predicting arrhythmic or mortality outcomes (OR 1.14; $P < 0.001$). However, as Tpe has not been evaluated in a NICM-only population, it remains unclear whether Tpe is useful in NICM specifically.

The echocardiogram: old tool, new techniques

Echocardiography is used to evaluate LVEF, thereby forming the basis for ICD implantation for primary prevention of SCD. However, newer echocardiographic modalities such as global longitudinal strain (GLS) and mechanical dispersion (MD) using speckle-tracking may be able to provide further information for risk stratification. GLS is the change in peak longitudinal systolic shortening of 16 LV segments, which can be abnormal despite the presence of a preserved LVEF. MD identifies tissue heterogeneity related to myocardial fibrosis, leading to heterogeneous ventricular activation and ventricular contraction. Hauga and colleagues studied 94 NICM patients in whom GLS and LVEF were reduced in patients who suffered VA (HR per 1% increase in strain: 1.26, $P = 0.02$).[39] In the same study, MD also correlated with higher VA, independent of LVEF (HR per 10-ms increase in MD: 1.20, $P = 0.02$). Furthermore, both GLS and MD demonstrated superior predictive value compared with LVEF (area under the ROC curves: GLS, 0.82; MD, 0.80; LVEF, 0.72; $P = 0.05$). Another study with 124 NICM patients undergoing primary-prevention ICD implantation also associated abnormal GLS with appropriate ICD therapy (HR 1.12, $P = 0.032$).[40] Adding these advanced echocardiographic measures to standard LVEF measurement may improve risk stratification of patients with NICM, further informing decisions about ICD implantation.

Cardiac magnetic resonance (CMR) imaging of myocardial scar

A common histological feature of NICM is extensive myocyte necrosis and reactive abnormal growth processes, leading to architectural derangement, with collagen deposition forming myocardial midwall fibrosis (MWF) and scar.[41] Approximately 30% of NICM patients are found to have MWF detected on late gadolinium-enhanced cardiac magnetic resonance imaging (LGE-CMR; see Image A).[42] MWF can provide the electrophysiological substrate for reentrant VT.[43] The interface between MWF and intact myocardium is thought to account for up to 80% of VT.[44] Electrophysiologic studies also demonstrate that scars support sustained and inducible VT, which may be terminable with catheter ablation.[44] NICM and HF lead to activation of the renin-angiotensin-aldosterone system and the beta-adrenergic axis, which contribute to this profibrotic process.[45,46] Hence, early use of GDMT may be able to alter this pathological process.[47]

As discussed above, risk-stratifying patients based on LVEF alone remains suboptimal, and the presence of CMR detected scar and therefore the magnitude of risk might not be perfectly concordant with LVEF. Patients with extensive scar may have relatively preserved LVEF, and conversely, patients with severely reduced LVEF may have no myocardial scar.[48]

Current evidence indicates that MWF on LGE-CMR can provide excellent risk stratification in NICM. The absolute presence or absence of MWF is a particularly appealing criterion. The absence of scar in NICM patients correlates with a low risk of SCD, and therefore it may be useful to add CMR scar imaging during risk stratification for SCD.[48] However, further studies are needed to evaluate whether patients with MWF would benefit from ICD irrespective of LVEF and whether patients without MWF should forgo ICD implantation despite having severe LV dysfunction. LGE-CMR, a routine modality for determining the etiology of NICM, allows non-invasive assessment of myocardial tissue pathology, infiltrative processes, and/or scar, and may help to optimize patient selection for ICD placement in NICM.[49]

Multiple studies have identified MWF in NICM as a predictor of all-cause mortality and cardiovascular hospitalization in addition to predicting VA/SCD events.[41] In a study following 472 patients with

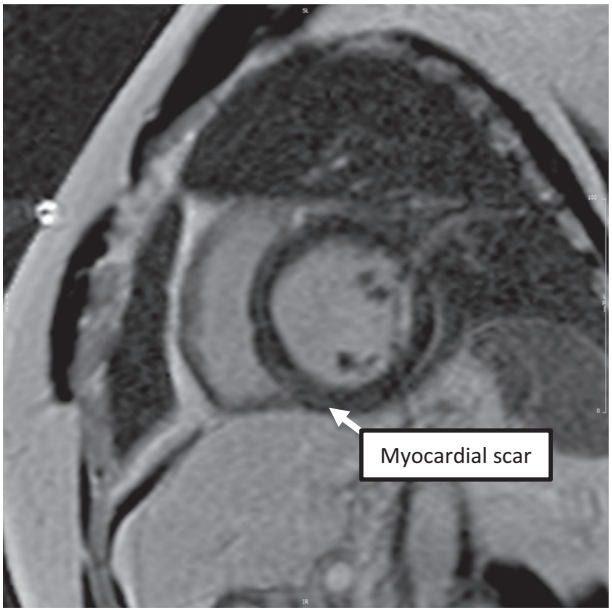

Image A. Cardiac magnetic resonance imaging with delayed gadolinium-enhancement. There is mid myocardial delayed gadolinium enhancement in the ventricular septum in the basal and mid ventricle, consistent with myocardial midwall fibrosis (MWF). MWF has been linked to arrhythmic risk in nonischemic cardiomyopathy.

NICM of any severity for a median of 5.3 years, approximately 30% of patients with MWF reached the composite endpoint of SCD or aborted SCD (defined as appropriate ICD therapy or a nonfatal episode of VA, or VA with hemodynamic compromise requiring cardioversion).[50] In contrast, only 7% of those without MWF had SCD (HR 5.24, $P < 0.001$).[51] The mortality rate in patients with MWF was 26.8% compared to 10.6% in those without MWF (HR 2.96, $P < 0.01$). Most importantly, the presence and extent of MWF predicted arrhythmic events (presence of any MWF: HR 2.43, $P < 0.001$; per 1% absolute increase in extent of MWF: HR 1.11, $P < 0.001$). In another study, Neilan and colleagues studied 162 high-risk NICM patients undergoing ICD implantation, and found a MWF prevalence of 50%.[52] The extent of MWF on LGE was the strongest predictor of VA/SCD requiring ICD therapy (presence of MWF: HR 6.21, $P < 0.0004$; per 1% increase in extent HR 1.16, $P < 0.0001$). Di Marco et al. found a similar association between MWF and VA requiring appropriate ICD therapy, regardless of LVEF. The correlation between LGE and the arrhythmic endpoint remained significant among both patients with left ventricular ejection fraction >35% (odds ratio 5.2, $P < 0.001$) and those with LVEF ≤35% (OR 4.2, $P < 0.001$).[53]

The value of the presence and extent of MWF on LGE-CMR for risk stratification was further validated by a systematic review and meta-analysis comprising 2948 patients with NICM and LVEF 20–43%.[54,55] Gulati et al. concluded that the presence of any myocardial scar was a strong risk factor for SCA, thereby obviating the need to measure the extent of the myocardial scar.[50,56]

Myocardial autonomic dysfunction

Myocardial autonomic dysfunction has been associated with VA.[57] Variable sympathetic myocardial activation leads to heterogeneous conduction velocity and refractory periods, creating a proarrhythmic environment. Noninvasive cardiac sympathetic imaging with 123-metaiodobenzylguanidine (MIBG) may aid in understanding autonomic dysfunction and its deleterious consequences. The distribution of myocardial MIBG is visually assessed and semi-quantified by calculating a heart-to-mediastinum ratio (HMR). Several studies examining myocardial autonomic function have demonstrated a reproducible ability to assess SCD risk in NICM patients. For example, the AdreView Myocardial Imaging for Risk Evaluation in Heart Failure Trial (ADMIRE-HF) studied 961 symptomatic HF patients. Among them, 237 patients experienced VA, with two-year event rates 15% for HMR ≥1.6 and 37% for HMR <1.6 ($P < 0.01$).[58] Additionally, Merlet et al. examined only NICM patients, and found that low HMR predicted all-cause mortality and risk of SCD ($P < 0.0001$).[59] MIBG imaging and its association with autonomic dysfunction could provide incremental prognostic value.

Familial NICM

Over the last few decades, remarkable advances have been made in understanding genetic influences on health and disease processes. Genetic mutations account for a large proportion of NICM. Familial NICM is defined as idiopathic CM occurring in at least two closely related relatives, which can account for 25–50% of cases.[60] More than 60 genes have been associated with familial NICM, with inheritance typically occurring in an autosomal dominant pattern.[2,61,62] Each mutation can have variable expression and penetrance, which can be influenced by environmental factors such as viral triggers, stress, or drugs, which may unmask the adverse phenotype. Ware et al. demonstrated a striking resemblance in genetic makeup between women with peripartum CM and those with non-peripartum NICM, suggesting a genetic contribution to CM of either type.[63]

The most commonly identified genetic mutation is in the gene LMNA, which encodes the proteins lamin A and C, which are part of the inner nuclear envelope. Approximately 200 mutations within the lamin gene have been identified, accounting for 5–8% of familial NICM.[64] LMNA mutation-induced NICM is highly penetrant, and is associated with increased risk of HF leading to VA. Pasotti et al. conducted a longitudinal retrospective observational study of 27 consecutive families, in which 94 members had LMNA gene defects, following them for 57 months.[65] 64% of these family members were phenotypically affected, and all members who reached 60 years of age were affected. Mortality from SCD within 5 years of diagnosis was 40%. Advanced HF, participation in highly competitive sports for >10 years, and splice-type mutations in LMNA, are independent predictors of events. Another cohort demonstrated similar findings, identifying four independent risk factors: non-sustained VA, LVEF <45%, a truncation-type mutation, and male gender.[66] When all four factors were present, patients had up to 50% mortality within 2 years.[66]

Mutation in the titin (TTN) gene is another common cause of familial NICM, occurring in 25% of cases.[67] Two TTN filaments span the sarcomere as a contractile unit in striated muscles, playing an important role in myocardial contraction. Thus, truncating defects in this gene can lead to contractile impairment, which has been associated with NICM and increased risk of SCD.[68,69] Incorporation of sequencing approaches that detect TTN truncations into genetic screening for inherited dilated cardiomyopathy should substantially increase test sensitivity, thereby allowing earlier diagnosis and therapeutic intervention for many patients.[69]

Pedigree evaluation along with advanced genetic analysis may further aid in diagnosis of familial NICM. One registry for organ sharing included 16,091 patients with NICM, of whom only 492 initially carried the diagnosis of familial NICM (3.1%).[70] Further in-depth pedigree investigation of 73 of these patients found that 19 (26%) of them met the definition of familial NICM. Thus, pedigree interpretation has tremendous implications for identification of familial NICM. Furthermore, identifying novel loci in familial disorders may allow appropriate individual risk assessment.[71] Meder and colleagues identified a causative single-nucleotide polymorphism on chromosome 6p21, which underlines the role of genetically driven, inflammatory processes in the pathogenesis of familial NICM.[71] As genetic mapping continues to improve, far more chromosomal loci are being identified. Collaboration between pedigree analysis and gene mapping could help identify causative mutations, which leads to early counseling and potential for therapy, thereby further improving assessment of SCD risk in NICM patients.

Nonfamilial NICM

Determining the etiology of sporadic NICM is often more challenging than in familial NICM. The ideal workup for all CM patients starts with excluding secondary causes, such as ischemia, hypertension, endocrine dysfunction, and valvular disease. This is followed by identifying any causative toxin exposure and/or inflammatory causes, such as alcohol use, infectious processes, and stress, with elimination of these factors perhaps being sufficient for LV recovery.[2,72]

Chemotherapeutic agents such as anthracyclines can result in permanent damage to the myocardium. These drugs may lead to immediate LV dysfunction, which can persist subclinically for years despite withdrawal of the offending agent.[2] Even following LV recovery, these patients may remain at risk for tachyarrhythmias.[2] Some evidence opposes the typical three-month "strategic waiting period" before prophylactic ICD implantation in these patients, as they are at elevated risk during the early phases of their disease process.[73]

GDMT initiation in NICM leads to reversal of myocardial remodeling in up to 30% of patients with NICM, with favorable prognosis pressing the importance of postponing ICD implantation.[74] In a follow up study of the DEFINITE trial, nearly 50% of subjects had LVEF improvement of >5%, with dramatic reduction in mortality compared to those with persistently reduced LVEF (HR 0.09, $P = 0.001$).[75] The Heart Muscle Disease Registry of Trieste investigated 952 NICM patients, of whom 2.1% suffered SCD or malignant VT within the first 6 months of enrollment. In that population, LV end-diastolic diameter, LV end-diastolic volume index, and QRS duration were independently associated with early

occurrence of arrhythmias. The wearable cardioverter-defibrillator (WCD) may be useful during this high-risk period. Roger et al. investigated the WCD as a valuable tool to protect patients at risk for SCD while awaiting possible LVEF recovery.[11] During this crucial waiting period, almost 50% of NICM patients showed improvement in LVEF, thereby reducing the proportion of patients with an indication for primary preventive ICD implantation.[11] Interestingly, in The PROLONG Study, which included 167 NICM patients with newly diagnosed LVEF ≤35%, the NICM subset had delayed LVEF recovery at 3 month follow up.[76] While 12 VA events occurred in 10 patients with 9 appropriate WCD shocks observed, additionally two patients had hemodynamically stable VA, and hence withheld WCD therapy. WCD use may be considered in order to protect patients with newly diagnosed NICM, pending LVEF recovery.

Inflammatory NICM is a complex interplay between infectious agents and autoimmune response leading to LV dysfunction.[77] Felker et al. reported myocarditis as the cause of NICM in 9% of patients.[78] Activation of immunomodulatory cytokines such as IL-6 leads to profound myocardial inflammation, which can be visualized on CMR, as discussed earlier. Studies suggest that ICD implantation should be deferred until resolution of acute myocarditis.[79]

Conclusion

SCD is one of the most common causes of mortality in the world, with a high incidence in the NICM population. ICD implantation, an effective method of preventing SCD in this population, is currently guided by LVEF and severity of HF symptoms. As discussed in this article, these criteria alone show poor sensitivity and specificity, leaving a huge subset of NICM patients undetected and unprotected from SCD. NICM patients should undergo routine cardiac evaluation including EKG, echocardiography, and serum-based biomarkers. After establishing the diagnosis of NICM, determining its etiology and understanding its pathogenesis plays a pivotal role in clinical management, pharmacological treatment, and risk stratification for advanced interventions. The use of LGE CMR, advanced echocardiographic modalities, and genetic testing can aid in risk stratifying patients, but these techniques have not yet been adopted by societal guidelines. An individualized approach to risk stratification, encompassing a comprehensive clinical assessment, is needed. In the meantime, the ICD will continue to be the cornerstone of management of SCD risk in NICM.

Statement of conflict of interest

None of the authors have any conflicts of interests with regard to this publication.

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