Ventricular arrhythmias in nonischemic cardiomyopathy

Fa-Po Chung MD1,2 | Chin-Yu Lin MD1,2,3 | Yenn-Jiang Lin MD, PhD1,2 |
Shih-Lin Chang MD, PhD1,2 | Li-Wei Lo MD, PhD1,2 | Yu-Feng Hu MD, PhD1,2 |
Ta-Chuan Tuan MD1,2 | Tze-Fan Chao MD1,2 | Jo-Nan Liao MD1,2 |
Yao-Ting Chang MD1,2 | Ting-Yung Chang MD1,2 | Chung-Hsing Lin MD1,3 |
Abigail Louise D. Te MD1 | Shinya Yamada MD1 | Shih-Ann Chen MD1,2

1Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan
2Institute of Clinical Medicine, Department of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan
3Department of Medicine, Taipei Veterans General Hospital, Taipei, Yilan County, Taiwan

Correspondence
Shih-Ann Chen, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan.
Email: epsachen@ms41.hinet.net

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Abstract
Nonischemic cardiomyopathies (NICMs) are composed of variable disease entities, including primary and secondary cardiomyopathies. Determining the etiology of NICM provides pivotal roles of not only the understanding of the individual pathogenesis, but also the clinical management, such as risk stratification, pharmacological treatment, and intervention therapies. Despite the diverse causes of NICM, these cases mostly require clinical attention owing to progressive myocardial injury, resulting in ventricular dysfunction and heart failure. The interaction between the diseased ventricular substrates and systemic/neurophysiological factors contributes to the cornerstones responsible for ventricular arrhythmogenesis and sudden cardiac death (SCD). Prevention of SCD and diminishing ventricular tachyarrhythmias are the important mainstays for the management of NICM patients. Given the understanding of the abnormal ventricular substrates and advancement of navigation systems, radiofrequency catheter ablation (RFCA) has become an adjunctive or alternative strategy for NICM patients who experience drug-refractory ventricular tachycardias (VTs). Successful ablation can frequently be achieved at the expense of an epicardial intervention. A recent study has proven the survival benefits for NICM patients who are free from recurrent VTs after a successful RFCA, regardless of the New York Heart Association (NYHA) functional class status or left ventricular ejection fraction. Additionally, recent evidence has highlighted the better delineation of a diseased myocardium through the incorporation of cardiovascular magnetic resonance imaging (CMRI) and 3D mapping systems, which can facilitate the identification of critical ventricular arrhythmogenic substrates in NICM patients.

Keywords
arrhythmogenic substrate, cardiovascular magnetic resonance imaging, catheter ablation, implantable cardioverter-defibrillator, sudden cardiac death

The first two authors contributed equally to the work.

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1 | INTRODUCTION

In contrast to ischemic cardiomyopathy (ICM), nonischemic cardiomyopathy (NICM) consists of a heterogeneous group of diseases, affecting the myocardium without the presence of any significant coronary artery disease. The clinical manifestation varies, including dyspnea, exertional intolerance, or a consequence of ventricular dysfunction and heart failure. Growing evidence has directed the clinical significance to the prevention of sudden cardiac death (SCD) in NICM patients, which is usually attributed to ventricular tachyarrhythmias arising from a diseased ventricular substrate. Therefore, in the risk stratification of NICM patients, given the potential specific therapies and risk prevention strategies for the nonuniform entities of NICM, the identification of the underlying pathogenesis is of clinical relevance. Despite the advancements in the pharmacological treatment of heart failure in recent decades having significantly decreased the mortality in NICM patients, anti-arrhythmic medications and implantable cardioverter-defibrillator (ICD) implantations remain the mainstay for patients with a high risk of SCD or who have experienced episodes of ventricular tachyarrhythmias and aborted SCD. Owing to the improvement in mapping and effective elimination of the VT using radiofrequency catheter ablation (RFCA), ventricular tachycardia (VT) in NICM patients has been recognized as an important issue. A recent study has also proven the promising results of RFCA in preventing VT recurrences, which could improve survival in NICM patients, regardless of the New York Heart Association (NYHA) functional class status or left ventricular ejection fraction. In this review, we will focus on VT in NICM patients, including the identification of the disease entity, risk stratification of SCD, and the management of VT.

2 | CLASSIFICATION AND EVALUATION OF NICM

2.1 | Classification of NICMs

In 2006, the AHA proposed contemporary definitions and classification of NICM, including primary and secondary cardiomyopathies (Figure 1). Primary cardiomyopathy solely or predominantly affects the heart muscle, whereas secondary cardiomyopathy refers to the pathological involvement of the heart owing to systemic diseases. In conjunction with the molecular and genetic fields, the abovementioned classification provides not only the clinical implication for a cardiac diagnosis of NICM, but also an understanding of potentially mixed and heterogeneous groups of diseases based on the associated basic pathophysiological mechanisms.

Primary cardiomyopathies are composed of genetic, mixed, and predominantly nongenetic acquired disorders. Hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and left ventricular (LV) noncompaction contribute to the commonest entities of inherited structural cardiomyopathies, whereas inherited primary arrhythmia syndrome consists of Brugada syndrome (BrS), long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), early repolarization syndrome (ERS), and short QT syndrome (SQTS). Given the heterogeneity of the disease entities, identifying the exact etiology of NICM also provides clues to assess the potential risk of SCD and to decide on its specific management.

2.2 | Initial evaluation of NICM

The initial noninvasive evaluation of NICM patients includes a blood examination, structural assessment using echocardiography or contrast-enhanced cardiovascular magnetic resonance imaging (CMRI), and evaluations of the ventricular arrhythmias (VAs) through a 12-lead electrocardiogram (ECG), ambulatory monitoring, exercise testing, and/or a signal-averaged ECG. Aside from the abovementioned techniques, invasive studies, such as right heart catheterization, ventriculography, electrophysiological (EP) studies, and endomyocardial biopsy should be considered in selected cases for a pretransplantation evaluation, risk stratification of SCD, alternative structural assessment, and clarification of the nature of the disease entity.

2.2.1 | Imaging

Echocardiography can provide basic information regarding the right ventricular (RV) and LV sizes, systolic and diastolic functions, valvular structures, pulmonary artery systolic pressure, and the pericardial abnormalities. In spite of the utility in assessing the ventricular ejection fraction using echocardiography, which is the commonest index of disease severity, there is growing evidence to prove the clinical implication of contrast-enhanced CMRI in NICM patients. In contrast to ICM, which is characterized by an increased gadolinium concentration within the subendocardium, the late gadolinium enhancement (LGE) in NICM is frequently located in the mid-wall or in the subepicardium, which is rarely the coronary arteries are located. Myocardium, with the presence of an LGE identified using CMRI, usually harbors arrhythmogenic substrates that might be responsible for the development of ventricular tachyarrhythmias; the anterosepal and inferolateral scars account for the commonest types of arrhythmogenic substrates in NICM. The abovementioned finding was also evidenced by the facts that a larger extent of transmural scar was associated with inducible VT and an increased risk of SCD. In this regard, the recognition of arrhythmogenic scars using CMRI is of clinical significance.

2.2.2 | ECG

The 12-lead ECG should be scrutinized initially, as it can provide diagnostic information in NICM patients, such as the presence of left ventricular hypertrophy (LVH), existence of myocardial scar resulting in Q wave or fragmentation changes, manifestation of a Brugada phenotype, corrected QT interval, morphologies of VAs, and other clues of structural heart disease. The ECG findings should be delicately interpreted and carefully correlated to the clinical symptoms to exclude the possibility of innocent findings or a misdiagnosis.
Apart from the abovementioned approach, efforts to identify the VA morphologies may also help to localize the arrhythmogenic substrate and distinguish epicardial from endocardial circuits. In spite of the importance of ECG during clinical practice, current evidence does not support the broad application of ECG screening in the general population, owing to the possibility of a misinterpretation. Furthermore, premature ventricular complexes (PVCs) could potentially cause deterioration of the systolic function in NICM patients or result in a PVC-induced cardiomyopathy, and thus, ambulatory monitoring should be considered to assess the PVC burden. Determining the causal relationship between LV dysfunction and the effect of PVCs may be difficult in certain groups of patients. Moreover, the PVC burden or the presence of nonsustained VT provides prognostic information on some NICMs, such as ARVC and HCM.

Exercise testing modalities, including treadmill testing, 6-minute walk test, and cardiopulmonary exercise test, could be useful not only for the diagnosis but also for the quantification of functional capacity before cardiac transplantation in selected NICM patients. The response of PVCs during exercise testing can also provide clues for further investigation, and CPVT should be suspected once the VAs are aggravated.

Additionally, the signal-averaged ECG (SAECG), which exhaustively and noninvasively records slow conduction of the myocardium, has been proven to be a pivotal prognostic tool for patients with NICM. This technique has also been proposed as one of the criteria for the diagnosis of ARVC. Recent studies have also demonstrated the utility of this technique to determine the prognosis of patients with suspected ARVC or patients with ARVC, undergoing a successful catheter ablation of ventricular tachyarrhythmias.

### 2.2.3 EP study

The role of EP study is to mainly assess the potential occurrences of ventricular tachyarrhythmias and the risk of SCD. However, several previous results have demonstrated discrepancies between inducible ventricular tachyarrhythmias using an EP study and the presence of VAs during the follow-up in patients with NICM and heart failure. Moreover, a recent study monitored patients with idiopathic DCM prospectively and found a similar total mortality between the patients with positive and negative inducibility of ventricular tachycardia/ventricular fibrillation (VT/VF) during the follow-up. However, overall ICD therapies were significantly higher in patients with a positive inducibility of ventricular tachyarrhythmias. Despite the predictive value of a positive inducibility, the sensitivity and specificity are not sufficient to prove that the EP study is a perfect surrogate marker for risk stratification. The conflicting reports could result from a heterogeneous population, different programmed stimulation protocols, and nonuniform endpoints. Therefore, the decision to implant ICD based on a positive inducibility of VT/VF during an EP study is not recommended in the current guidelines. Given the limited information, an EP study is also not recommended for risk stratification in patients with LQTS, SQTS, CPVT, and ERS.

Apart from the abovementioned benefit, an EP study can not only provide a diagnostic value for differentiating ARVC from idiopathic RVOT VT, but can also help detect effective algorithms for differentiating the entities of ventricular tachyarrhythmias or anti-tachycardia pacing protocols in patients with an ICD implantation. Future studies will be warranted to clarify the diagnostic and/or prognostic value of EP study for risk stratification in specific groups of NICM patients or carriers of gene mutations using uniform stimulation protocols. In addition, the endocardial unipolar voltage
mapping, created using a 3D navigation system that offers the information of intramural/epicardial fibrosis, can also provide valuable prognostic information to facilitate clinical decisions in NICM patients with LV involvement.31

3 MANAGEMENT OF VT IN NICM

The appropriate therapies for VAs in NICM depend on their type, associated medical conditions that could contribute to or exacerbate triggers, and the risks and benefits posed by the VAs and potential therapies, respectively. The management of VAs in NICM includes pharmacological therapies, implantable devices, ablation or surgical intervention, and heart transplantation to remove or inhibit the potential arrhythmogenic factors/triggers and/or to eliminate the arrhythmogenic substrates. Understanding the pathogenesis and/or substrate characteristics of NICM may help in deciding the clinical strategy to prevent occurrences/recurrences of VAs and SCD.

3.1 Pharmacotherapies of VAs

With the exception of beta-blockers, current randomized clinical trials have not supported the effectiveness of anti-arrhythmic drugs for primary management of life-threatening VAs or the prevention of SCD in NICM patients. However, the OPTIC study demonstrated the additional benefit of amiodarone in combination with beta-blockers for preventing future ICD interventions in those with inducible or spontaneous ventricular tachyarrhythmias.32 Nonetheless, previous reports were frequently confounded by a nonuniform patient population.33,34 One of the randomized trials demonstrated that the mortality and quality of life in NICM patients with a reduced LVEF were similar between those receiving amiodarone, and those with an ICD implantation for nonsustained VT.3 Although anti-arrhythmic drug therapy has never been clearly shown to reduce SCD in NICM patients experiencing life-threatening VAs, amiodarone, rather than sodium channel blockers, reduces the occurrence of VAs without the expense of an increase in the mortality in patients with postmyocardial infarction and heart failure.35,36 In patients with an ICD implantation, amiodarone, especially in conjunction with beta-blockers, significantly reduces ICD interventions.37 Sotalol, a rapid delayed rectifier potassium current inhibitor with beta-blocker properties, is effective in suppressing VAs in patients with coronary artery disease without LV dysfunction, but less effective in NICM patients.38,39 Ranolazine in combination with other anti-arrhythmic agents has been explored to suppress VT in otherwise drug-refractory cases. Careful monitoring of the ECG and cardiac function is needed to detect any deterioration in the LV function and/or signs of pro-arrhythmic effects of anti-arrhythmic drugs in NICM patients. Additionally, the identification of disease entities helps in the selection of certain anti-arrhythmic drugs, such as quinidine for BrS and short QT syndrome and verapamil for left fascicular VT.20,41 With the lack of clinical evidence, combinations of different classes of anti-arrhythmic drugs, such as sodium channel blockers and potassium channel blockers (eg, mexiletine and sotalol, or flecainide/proprafenone and amiodarone), should be reserved for patients with frequent VTs, which cannot be satisfactorily suppressed by a single-agent anti-arrhythmic drug therapy. An attempt to improve the LV function by angiotensin-converting enzyme5 inhibitors, angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and angiotensin-neprilysin inhibitor could also be helpful to reduce SCD and potential occurrences of VT through reverse remodeling in patients with NICM and a decreased LVEF.42-44 In general, anti-arrhythmic agents may be effective as an adjunctive therapy for the management of VAs in NICM patients. However, the anti-arrhythmic drugs should be used with caution, and careful monitoring for any potential adverse effects should be performed.

3.2 ICDs

Nearly all NICMs were associated with a risk of SCD due to the structural and/or functional abnormalities of the ventricular myocardium. Three trials have been conducted for patients suffering from a cardiac arrest or life-threatening VAs. These 3 trials have demonstrated a consistent result that an ICD implantation, rather than anti-arrhythmic drugs, mostly amiodarone, significantly reduced the arrhythmic mortality or total mortality.45-47 Therefore, the current guidelines suggest an ICD implantation for (i) NICM patients who experience an aborted SCD, unexplained syncope, or hemodynamically unstable VT/VF, (ii) primary prevention for DCM patients with NYHA functional classes II-III and a decreased LVEF of <35% in spite of ≥3 months of optimal pharmacological treatment, (iii) HCM patients who are classified as a high risk of SCD, (iv) patients with Chagas cardiomyopathy and an LVEF of <40%, and (v) ARVC patients with well-tolerated sustained VTs, after balancing the risk of ICD therapy.20 However, there is no adequate evidence to support the benefits of an ICD implantation for asymptomatic patients (NYHA class I) with systolic dysfunction (LVEF ≤ 35-40%), patients with HF and a preserved LVEF (>40-45%), and patients with an NYHA class IV.20

3.3 Catheter ablation in NICM

The advancement of navigation and mapping systems, improved energy penetration of irrigated catheter, and better understanding of the underlying pathogenesis have driven the application of catheter ablation as an important treatment option for VT in NICM patients experiencing frequent ICD interventions. Recently, an International VT Ablation Center Collaborative Group study demonstrated that a successful catheter ablation can render nonrecurrences of VT and decrease further mortality and heart transplantsations regardless of the NYHA class or LVEF in NICM patients.7 For the abovementioned reasons, the amount of VT ablation in NICM has increased proportionally, especially in East Asia.5,48 Nonischemic VTs in different disease entities could result from nonuniform arrhythmogenic substrates, which can lead to
heterogeneous ablation outcomes. The inconsistent ablation outcome could also vary between different groups depending on disease severity, composition of the disease entities, and ablation strategies. Furthermore, there are limited reports for certain NICMs, such as LQTS, SQTS, CPVT, and ERS. In general, a previous study demonstrated a worse VT ablation outcome in patients with NICM than in those with ICM.49 However, a recent retrospective study showed a similar effectiveness of catheter ablation for electrical storms in patients with NICM or ICM during the long-term follow-up.50 A future prospective study focusing on the specific diseases will be warranted to elucidate the VT ablation prognosis and effectiveness in NICM patients.

### 3.3.1 Preprocedural assessment

The first step is to localize the VT origin and identify the potential regions of arrhythmogenic substrates. The VA morphologies provide not only the clues to the origin, but also the potential need for an epicardial approach.16 Standardized echocardiography or an image assessment using intracardiac echography during the procedure helps in delineating the valvular apparatus and ventricular systolic function, and in excluding any intracardiac thrombus.51 Computed tomography (CT) and cardiac magnetic resonance imaging (CMRI), especially with an LGE, can localize the regions of fibrosis or scarring (Figure 2).10,12,13 The distribution and extent of the scar are useful for deciding the

**FIGURE 2** Delayed enhancement in a patient with DCM. A 62-year-old woman with idiopathic dilated cardiomyopathy who experienced syncope and several episodes of nonsustained VT. The CMRI demonstrated dilated LV with a decreased LVEF of 34% and patchy delayed myocardial enhancement at mid-wall of the basal anteroseptal, basal anterior, and basal anterolateral regions, as well as the subepicardial part of the mid-anteroscpetal region of the LV, which was compatible with the origin of VAs

**FIGURE 3** Integration of a 3D reconstruction of a cardiac CT and electroanatomic mapping to prevent potential injuries to coronary arteries during an epicardial catheter ablation. A, A diagnostic catheter in conjunction with a coronary angiogram (gray) was used to confirm the accuracy of the 3D reconstruction of the cardiac CT (yellow). B, Two white lines represent the safe margin at a distance of 1 cm from the coronary arteries (yellow). Late potentials were recorded in the area close to the left circumflex and right coronary arteries. Preprocedural detailed image processing helps to prevent incidental coronary artery injury.
ablation strategy, such as an epicardial approach, transcoronary venous ablation, alcohol ablation, or simultaneous bipolar ablation. The integration of the reconstructed images obtained from CT, MRI, and 3D navigation mapping systems can aid in the illustration of the structural complexity and avoidance of damage to the critical regions, in terms of vascular or nervous structures (Figure 3).

3.3.2 | Substrate characteristics and electrogram properties in NICM

With the exception of ARVC and BrS, the arrhythmogenic substrates in NICM that could be identified using electroanatomic mapping are mostly located in the basal or perivalvular region of the LV, which is distinct from the ischemic substrates along the territories of the coronary arteries. Both endocardial or epicardial diseased substrates in NICM could exist and contain critical isthmuses for a successful ablation. These abnormal substrates frequently harbor fibrotic and scar tissue that lead to slow conduction and fractionated electrograms in human tissue experiments. Aside from the electroanatomic mapping, CMRI can help to delineate the scar distribution as well.

Furthermore, Nakahara et al investigated the electrogram differences between NICM and ICM. A higher prevalence of very late potentials (>100 ms after QRS) in ICM than in NICM for both the endocardial and epicardial substrates was reported, which may explain the less favorable outcomes in NICM patients receiving an LP-targeted ablation strategy.

3.3.3 | Mapping and ablation strategies

In our laboratory, quadripolar catheters are placed at the RV apex and the bundle of His for pacing and excluding VTs involving the fascicular system. Mapping is usually initiated from the diseased chamber based on the preprocedural examination. Unlike the direct approach of the RV, the endocardial LV can be accessed retrogradely across the aortic valve or antegradely with a transseptal puncture. The transseptal approach is effective in reaching most of the LV endocardium, whereas the retrograde aortic approach is more effective in accessing the basal septum, basal inferior, and basal lateral segments, and the aortic outflow tract. For conditions where entry into the LV is difficult, a percutaneous interventricular septal access, an epicardial approach, or a percutaneous transapical procedure will be considered.
serve as a rescue procedure for those with mechanical aortic or mitral valves. Steerable long sheaths can also provide additional support for difficult endocardial mapping and epicardial procedures. Epicardial access can be achieved using a standard subxiphoid puncture under fluoroscopic guidance or in conjunction with electroanatomic mapping. A recent report also demonstrated the feasibility and safety of the “needle-in-needle” epicardial access and novel EpiAccess Needle and System with real-time pressure monitoring, which could potentially minimize the procedural complications.

The innovation of navigation systems and multi-electrode catheters leads to the era of ultra-high-density mapping. Given small and closely spaced electrodes, these multi-electrode catheters, such as the Livewire duodecapolar catheter (St. Jude Medical, Saint Paul, MN), Orion mapping catheter (Boston Scientific, Marlborough, MA), and Pentaray mapping catheter (Biosense Webster, Diamond Bar, CA), not only increase the speed and point acquisition of electroanatomic mapping, but also improve the resolution of the scar and provide better discrimination of late potentials (Figure 4). Ablation guided through high-density multi-electrode mapping can also result in a shorter radiofrequency ablation time.

During sinus rhythm mapping, a cutoff value of the bipolar voltage between 0.5 and 1.5 mV has been traditionally set up to define the endocardial substrates, whereas a voltage threshold of 1.0-1.5 mV is used for the setting for epicardial bipolar voltage mapping. It is notably crucial to recognize and acquire the location of

**FIGURE 5** Stepwise approaches of localization and ablation of VTs in patients with NICM in our laboratory. For hemodynamically stable VTs, both activation mapping and entrainment provide an accurate identification of the critical isthmus, whereas substrate mapping based on the complete elimination of any abnormal electrograms is the most acceptable strategy for those with nontolerable VT. Single and a combination of substrate modification strategies are used to achieve complete elimination of abnormal electrograms.
fractionated signals and/or isolated late potentials using electroanatomic mapping, which frequently are potentially responsible for the VT isthmus (Figure 4). Pacing maneuvers resulting in directional influences can lead to different substrate characterizations and potentially facilitate the recognition of delayed components of electrograms.70

Remarkably, endocardial voltage mapping of the RV and LV can help in evaluating the extent of epicardial abnormalities with a cutoff value of 5.5 mV and 8.3 mV for the RV and LV, respectively.71,72 Arrhythmic potentials or local abnormal ventricular activity potentials can be adjusted objectively through a novel quantification analysis, such as simultaneous amplitude frequency electrogram transformation (SAFE-T) maps.73 An attempt to map hemodynamically tolerable VTs using entrainment and/or activation mapping should be made, whereas pacemapping or substrate-based ablation strategies could be applied in those in whom delicate mapping cannot be achieved. The flowchart of the mapping and ablation in our hospital is shown in Figure 5.

3.3.4 | Difficult ablation target of VTs in NICM

Clinical hurdles persistently exist for directly accessing the intramural arrhythmogenic substrates. Furthermore, complex histo-anatomical structures composed of fat or fibrotic tissue may impede the energy penetration and prevent an effective lesion formation. Alternative strategies including bipolar radiofrequency ablation, needle ablation, and intracoronary ethanol injections have been described.74 Additionally, a previous report also demonstrated that rare VT circuits cannot be approached using percutaneous ablation techniques in certain patients with NICM; thus, surgical cryoablation or hybrid approaches through the assistance of endoscopic robotic epicardial ablation might be the final solutions with or without the guidance of pre/intra-operative electroanatomic and EP mapping.75,76 Future work is required to identify patients who could benefit from these novel procedures and the associated long-term prognosis.

3.3.5 | Clinical outcomes of VT ablation in NICM

As mentioned earlier, the disease entity and nonuniform pathogenesis could result in a heterogeneous prognosis. In one retrospective study on 226 NICM patients undergoing ablation for drug-refractory VT, the survival was achieved, with no further requirement for heart transplants and readmissions for VT recurrences, in 173 (77%) patients. In that study, the patients with ARVC had better outcomes than those with DCM, whereas the patients with sarcoidosis had the worst outcomes.48,77 Another recent retrospective study on 282 NICM VT patients yielded consistent results in achieving a long-term freedom from VT in 69% of cases.78 The Prospective Heart Centre of Leipzig VT study echoed that the long-term outcomes in NICM patients were significantly worse than those in ICM patients (40% and 57% freedom from VT at 1-year follow-up for NICM and ICM patients, respectively),79 which was echoed by a substrate-based approach.79 Additionally, patients with scar involving the inferolateral aspect of the LV, which frequently requires an epicardial approach, usually have a better prognosis than those with anteroseptal scar.80 The progressive disease entities and involvement of intramural and epicardial substrates might contribute to a worse prognosis in certain groups of patients.

4 | CONCLUSIONS

VTs contribute to a significantly increased risk of morbidity and mortality in NICM patients. The identification of the underlying causes of NICM is of clinical importance. Furthermore, the management of VT in NICM remains a clinical challenge for physicians, especially in terms of catheter ablation, ICD implantations, and anti-arrhythmic drugs. The appropriate therapies for NICM patients rely on a non-invasive assessment before any invasive interventional procedures, particularly under the assistance of the new imaging modalities and individual consideration of the pathological differences. A future investigation is needed to focus on improving the cardiac function and novel ablation strategies such as surgical or hybrid interventions for VTs, originating from intramural myocardium, that cannot be eliminated currently through conventional ablation interventions.

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CONFLICT OF INTEREST

Authors declare no Conflict of Interests for this article.

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