

Catheter Ablation of VT in Non-Ischaemic Cardiomyopathies: Endocardial, Epicardial and Intramural Approaches



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Non-ischaemic cardiomyopathy (NICM) encompasses a heterogeneous group of disorders that includes genetic, idiopathic, post viral and inflammatory cardiomyopathies. NICM is associated with an increased risk of ventricular arrhythmias (VAs), namely in the form of ventricular tachycardia (VT). Although implanted cardiac defibrillators (ICD) may prevent sudden death from VA, NICM patients may suffer from recurrent symptoms and ICD therapies, and anti-arrhythmic drug side effects. Catheter ablation is highly efficacious in NICM, however poses unique challenges when compared to post myocardial infarction substrates. NICM substrates are fundamentally different in scar location, extent, and transmural which results in variable electrophysiologic properties and less apparent ablation targets during sinus rhythm, compared to ischaemic cardiomyopathy. NICM substrates can be intramural and/or epicardial, posing challenges to accessibility, which likely accounts for the observed higher rates of arrhythmia recurrence following ablation. Substrate location is influenced by the underlying aetiology (inflammatory, genetic), and can be gleaned from a combination of unique 12-lead electrocardiogram VT patterns, distribution of late gadolinium enhancement on cardiac magnetic resonance imaging, and electroanatomic voltage mapping. With the high proportion of intramural substrate in NICM, novel techniques have become increasingly common in recent years, including sequential, simultaneous or bipolar ablation on opposite myocardial surfaces to achieve greater lesion depth; use of half normal saline for irrigation; use of a novel retractable needle within an endocardial catheter; and transcatheter/venous ethanol ablation to target more inaccessible regions. Epicardial approaches have also been improved in recent years, with advents such as the needle-in-needle technique to reduce the risk of pericardial bleeding and phrenic nerve displacement, and hybrid surgical approaches to facilitate epicardial access in the presence of adhesions. Non-invasive cardiac radiation holds promise for the future. This state-of-the-art review will summarise the incidence, mechanism, multimodal assessment and catheter ablation-based management of VA in NICM.

Keywords

Nonischaemic cardiomyopathy • Ventricular tachycardia • Catheter ablation • epicardial
• Intramural

Abbreviations: cMRI, cardiac magnetic resonance imaging; DCM, dilated cardiomyopathy; EGM, electrogram; ICD, implanted cardiac defibrillator; ICM, ischaemic cardiomyopathy; LMNA, lamin A/C mutation; LV, left ventricle; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NICM, non ischaemic cardiomyopathy; PVC, premature ventricular contractions; RF, radiofrequency; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia

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Introduction

Classically, non-ischaemic cardiomyopathy (NICM) has been defined as left ventricular (LV) dilatation and/or dysfunction in the absence of coronary artery disease or abnormal loading conditions (e.g., valve disease) [1]. This broad definition thereby encompasses multiple distinct morphologic and functional phenotypes that include disease processes driven by genetic predisposition (e.g., hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, some forms of ventricular non-compaction and familial dilated cardiomyopathies) and acquired disorders in the context of infiltration, inflammation (e.g., myocarditis, sarcoidosis), metabolic disease (e.g., Fabry's), toxin-mediated (e.g., excess alcohol injection or chronic amphetamine use) and valvular heart disease [2]. In the context of catheter ablation, NICM generally refers to patients with dilated cardiomyopathy (DCM). Advances in genetics, imaging (with cardiac magnetic resonance imaging [cMRI]), nuclear imaging (CT-positron emission tomography), biopsy and biomarkers have allowed diagnosis of early cardiomyopathies before LV systolic dilatation and dysfunction, and allowed for more refined classification of NICM subtypes. Beyond their association with progressive heart failure, many of these conditions have a distinct proclivity for ventricular arrhythmias (VA), ranging from premature ventricular complexes (PVC), ventricular tachycardia (VT) and, less often, ventricular fibrillation (VF).

The occurrence of VA in NICM may be considered a harbinger for arrhythmic mortality that has been increasingly ameliorated with the insertion of implantable cardioverter-defibrillators (ICDs). Whilst anti-arrhythmic drugs (AADs) may be used as a means of suppressing VA, they are frequently limited by failure and significant toxicities that carry considerable morbidity. Radiofrequency ablation is being increasingly utilised as a primary and/or adjunctive treatment for the elimination of VA in NICM, achieving greater arrhythmia-free survival rates, reducing anti-arrhythmic burden/toxicity [3]. Patients with NICM have not been enrolled in published randomised trials of VT ablation but preliminary data suggests benefit of ablation over anti-arrhythmic drugs [4]. Growing operator experience and technological developments have resulted in advances in the mapping, characterisation and ablation of arrhythmic substrate in recent decades.

Due to advances in imaging and substrate characterisation with combined epicardial and endocardial mapping, it has become apparent that: (a) NICM has important differences in the location, topography and electrophysiologic properties of scar compared to post-infarction substrates; and these differences influence the accessibility of substrate, putative ablation targets, anticipated outcomes and complications; (b) different aetiologies of NICM exhibit characteristic scar patterns and distribution; (c) long-term outcomes are influenced by the natural history of the underlying disease; the aetiology should be elucidated when possible with multi-modality imaging, genetics and biopsy. This state-of-the-art review

will summarise the contemporary knowledge and ablation approaches relevant to the treatment of VA in NICM in the contemporary era.

Incidence of Ventricular Arrhythmias

Compared with individuals without underlying structural heart disease, those with NICM have higher rates of VA, with up to 90% having PVCs [5,6], and over 40% having non-sustained VT [7]. Ventricular arrhythmias contribute to persistent cardiac symptoms, poor quality of life, may cause or exacerbate ventricular systolic dysfunction (PVC-induced cardiomyopathy) or cause cardiac arrest/sudden cardiac death. In patients with NICM, LV ejection fraction (LVEF) $\leq 35\%$ and New York Heart Association (NYHA) heart failure class II–IV undergoing cardiac resynchronisation therapy, the implanted cardioverter-defibrillator (ICD) provides anti-tachycardia pacing for VT in 17.4%, and a shock for VT or VF in 11.5% of patients over a median follow-up of 67.6 months [8]. In a large, real-world series of patients with NICM, 32.5% of patients experienced VA over a mean of 50 months (annual event rate 0.8 events/patient), and 6.9% experienced electrical storm (≥ 3 VA episodes/24 hours) [9]. The frequency of VA varies according to disease type; some forms of NICM are more prone to arrhythmias. In a recent series of patients with lamin A/C cardiomyopathy (*LMNA*), the event rate for appropriate ICD therapies was 3–7%/year [10], compared to other forms of NICM ($\sim 2\%$ /year) [11], arrhythmogenic right ventricular cardiomyopathy ($\sim 5\%$ per year) [12]; and, hypertrophic cardiomyopathy $\sim 2\%$ per year [13]. *LMNA* is an unusual condition where the majority of patients who experienced VA had relatively preserved LVEF ($\geq 45\%$ in 82% of patients). [10] Of the acquired causes of NICM, sarcoidosis warrants particular attention with its high rate of subclinical cardiac involvement (up to 70% in one observational study [14]), and a considerable frequency of VA in those with overt cardiac involvement with sustained VAs occurring at a rate of 15%/year in those patients who have an ICD implanted [15]; and, the presence of sustained monomorphic VT is a significant predictor of mortality [16].

Mechanism of Ventricular Arrhythmias

There are fundamental differences in the scar location and topography between ICM and NICM substrates that ultimately dictate the technical challenges and success rates of catheter ablation in these two substrates (Table 1). Whilst the pathophysiology of VA in NICM is dependent on the specific aetiology of the underlying condition, it has been shown that over 80% of VTs are due to scar-mediated myocardial re-entry [17]. The specific arrhythmia substrate is postulated to involve regions of interstitial fibrosis interspersed with healthy myocardium [18]. This results in poor myocyte

Table 1 Differences between substrate and ablation targets between ischaemic and non-ischaemic cardiomyopathy.

	Ischaemic cardiomyopathy	Non-ischaemic cardiomyopathy
Scar distribution	<ul style="list-style-type: none"> Geographically dependent on blood supply (eg. anterior with prior infarct in the left anterior descending coronary) Size of endocardial scar larger than epicardial scar 	<ul style="list-style-type: none"> Anteroseptal (intramural) and inferolateral (epicardial) subtypes Underlying aetiology governs scar location (predominantly endocardial, epicardial, intramural) Some phenotypes with unusual scar locations (apical in HCM, over non-compacted myocardium in LVNCM)
Scar layering	<ul style="list-style-type: none"> Compact fibrosis Subendocardial (\pm intramural, transmural) distribution 	<ul style="list-style-type: none"> Patchy, diffuse or interstitial fibrosis Basal perivalvular location (around aortic, mitral, tricuspid and pulmonary valves) Anteroseptal (intramural) Inferolateral (epicardial) Isolated RV Isolated epicardial (myocarditis, certain genetic cardiomyopathies)
Ablation targets	<ul style="list-style-type: none"> Abundance of targets Surrogates for VT substrate: low bipolar voltage scar, late potentials, channels, sites with pace mapping-induced delay. 	<ul style="list-style-type: none"> Sparse ablation targets Surrogates for VT substrate: abnormal unipolar voltage, epicardial low bipolar voltage, early potentials, late potentials infrequent (more common in epicardium)
Challenges	Intramural/epicardial extension of scar may be difficult to target due to prior cardiac surgery; or limited coronary targets for transcatheter or transvenous ethanol ablation	Deep septal substrate; proximity to His (anteroseptal subtype); proximity to coronaries, phrenic, fat inhibiting energy delivery (inferolateral subtype)
Techniques to overcome challenges	<ul style="list-style-type: none"> Pre-procedural substrate identification with LGE-cMRI High power, long duration RF ablation; half normal saline Sequential, simultaneous unipolar RF on directly opposed sites Bipolar ablation Epicardial ablation (esp. inferior scars) Surgically assisted epicardial access (epicardial window: if prior cardiac surgery or myocarditis) Intramural needle ablation Non-invasive stereotactic whole-body radiation Phrenic nerve displacement (epicardial inferolateral substrate) 	

Abbreviations: cMRI, cardiac magnetic resonance imaging; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LVNCM, left ventricular non-compaction; RF, radiofrequency; RV, right ventricle; VT, ventricular tachycardia.

coupling and promotes regions of slow conduction, leading to functional and anatomic conduction block and subsequent re-entrant excitation. The critical parts of these circuits can potentially span all three myocardial layers in a three-dimensional manner [19]. The slow conduction in these regions may be enhanced by alterations in connexin protein expression and distribution, and VA may be further promoted by increased sympathetic activation [20]. Ventricular tachycardias originating from the His-Purkinje system also occur, of which bundle branch re-entrant VT is the classic form.

The differences between infarct-related scar substrate and that found in NICM have been demonstrated in necropsy and histopathology studies. In ICM, scar distribution follows

the territory of coronary vascular supply and the wavefront of necrosis progresses from subendocardial to transmural. In contrast, substrate in NICM involves more patchy areas of fibrosis with a much lower proportion having macroscopically visible scar and most (91%) patients having septal involvement [21]. Moreover, fibrosis in NICM may be progressive, unlike that found in ICM, with particular involvement of the mid-myocardium and epicardium over time [22]. Liuba *et al.* demonstrated the progressive nature of scar in NICM clinically in their series of 13 patients in whom endocardial electroanatomic maps were obtained 32 months apart, demonstrating an increase in endocardial unipolar low voltage (a marker of intramural/epicardial scar) from

6% to 46%, accompanied by a significant decline in systolic function over time [22].

Glashan et al. recently described postmortem/post-transplant human heart histological findings from eight DCM patients with a dominant antero-septal substrate for VT [23]. The classic midwall or subepicardial fibrosis patterns described in imaging studies were seen in only 36% of all transmural biopsy samples; 30% showed a subendocardial pattern, and a transmural pattern was seen in 28%. A patchy fibrotic architecture was the most common dominant architecture, followed by diffuse and interstitial fibrosis, with a combination of two or three architectures in 90% of all transmural biopsy samples. Compact fibrosis was the dominant architecture in only 3%, and never extended transmurally [23].

Two distinct phenotypes of dense scar distribution have been recognised in NICM (Figure 1) [24–26]. The first is basal antero-septal subtype where scar involves the basal antero-septum, peri-aortic LV, aortic mitral continuity, aortic cusps and right ventricular septum. The scar often extends intramurally, and epicardial mapping and ablation is of limited utility as the RV outflow tract overlies the area superiorly, and fat and proximal coronary arteries are present in the leftward basal region. The second pattern consists of basal inferolateral scar, which can be predominantly epicardial. While an epicardial mapping and ablation approach is often useful, proximity of the substrate to the phrenic nerve, thick epicardial fat, and the proximal left coronary arterial tree limits the ability to deliver radiofrequency (RF) energy delivery in some patients. The scar location can be predicted by 12-lead ECG in sinus rhythm, morphology of induced VTs and advanced imaging techniques such as cMRI [24,25,27]. Each scar location poses unique technical challenges and success rates are lower for the septal scar VTs than for the lateral wall VTs [27].

Diagnostic Evaluation

12-Lead Electrocardiogram

A 12-lead ECG can be used to predict scar location and scar extent. The location of scar as antero-septal or infero-septal may be inferred from the 12-lead ECG in sinus rhythm. A PR interval <170 ms, QRS voltage in the inferior leads <0.6 mV, or a lateral Q wave has a 92% sensitivity and 90% specificity in predicting an inferolateral scar pattern in patients with a preserved LVEF. An antero-septal scar pattern may be predicted by a four-step algorithm, which includes a PR >230 ms, QRS >170 ms, $r \leq 0.3$ mV in lead V_3 [27]. Moreover, the extent of prolongation in PR and QRS interval correlates to the extent of intramural scar in the antero-septum, whereas a progressively lower mean voltage in the limb leads corresponds to greater scar in the inferolateral epicardium in the inferolateral subtype [27].

Studies have analysed the relationship between 12-lead ECG morphology of spontaneous VTs and their associated substrate location in NICM. Basal antero-septal subtypes were associated with VT with a right bundle-branch block

(RBBB), left/right inferior axis with positive concordance, or a left bundle-branch block (LBBB), left/right inferior axis and early ($\leq V_3$) precordial transition. Basal inferolateral scar patterns are associated with RBBB, right inferior/superior axis with a late ($\geq V_5$) precordial transition (Figure 1) [25]. These two scar patterns were also seen in a series of 87 patients with VT in NICM performed by Oloriz et al. [24]. Ventricular tachycardia with a LBBB morphology and inferior axis had a 100% positive predictive value for antero-septal scar, whilst a RBBB pattern with superior axis had a positive predictive value of 89% for inferolateral scar.

Other unique 12-lead ECG patterns for septal substrate have also been recognised, and are worthy of consideration when planning VT ablation in NICM [26]. A LBBB pattern with inferior limb discordance (positive in lead II, negative in lead III, with positive in avL) is likely exiting from the basal midseptal parahisian region (LV or RV side). A reverse discordance pattern (RBBB, negative in II, positive in III) exited out of the LV side of the basal midseptal region. Another common morphology is a ‘pattern-break’ type where there is qR/Rs in lead V_1 and V_3 , but reversal of this in V_2 with an inferior axis. These can be exiting out of the LV summit endocardially or epicardially, the anterior interventricular vein or the left coronary cusp [26].

Epicardial exits may potentially be predicted by a 12-lead ECG of the VT. Epicardial activation results in slurring of the QRS complex, and in general, greater time to peak Q or R wave on a 12-lead ECG, compared to endocardial activation. This feature has been used to differentiate endocardial vs. epicardial exit of VTs. In RBBB VTs, a stepwise approach including (1) absence of q waves in inferior leads, (2) a pseudo-delta wave (defined as the interval from the earliest ventricular activation [or from the stimulation artefact] to the onset of the earliest fast deflection in any precordial lead) ≥ 75 ms, (3) a maximum-deflection index of ≥ 0.59 (defined as the interval measured from the earliest ventricular activation [or from the stimulation artefact] to the peak of the largest amplitude deflection in each precordial lead (taking the lead with shortest time)) divided by the QRS duration; and the presence of (4) a Q-wave in lead I was highly specific (95%) for an epicardial basal-superior/lateral exit site [28]. These criteria, however, have limited discriminatory value in the setting scar-related VT compared to idiopathic PVCs. Anti-arrhythmic drugs (AADs) and subjectivity in determining QRS onset during faster VTs are likely factors that limit epicardial exit site prediction [29,30].

The extent of scar extension is also reflected in the VT QRS morphologies. Left BBB VT with precordial transition $\geq V_5$ or RBBB VTs with precordial transition $\leq V_3$ (referred to as apical VT) have been associated with larger low-voltage areas extending to the apex [31].

Cardiac Magnetic Resonance Imaging

Pre-procedural identification and characterisation of scar substrate with late gadolinium-enhanced (LGE) cMRI is increasingly important for the diagnosis of NICM and for pre-procedural planning in VT ablation. Canine studies have

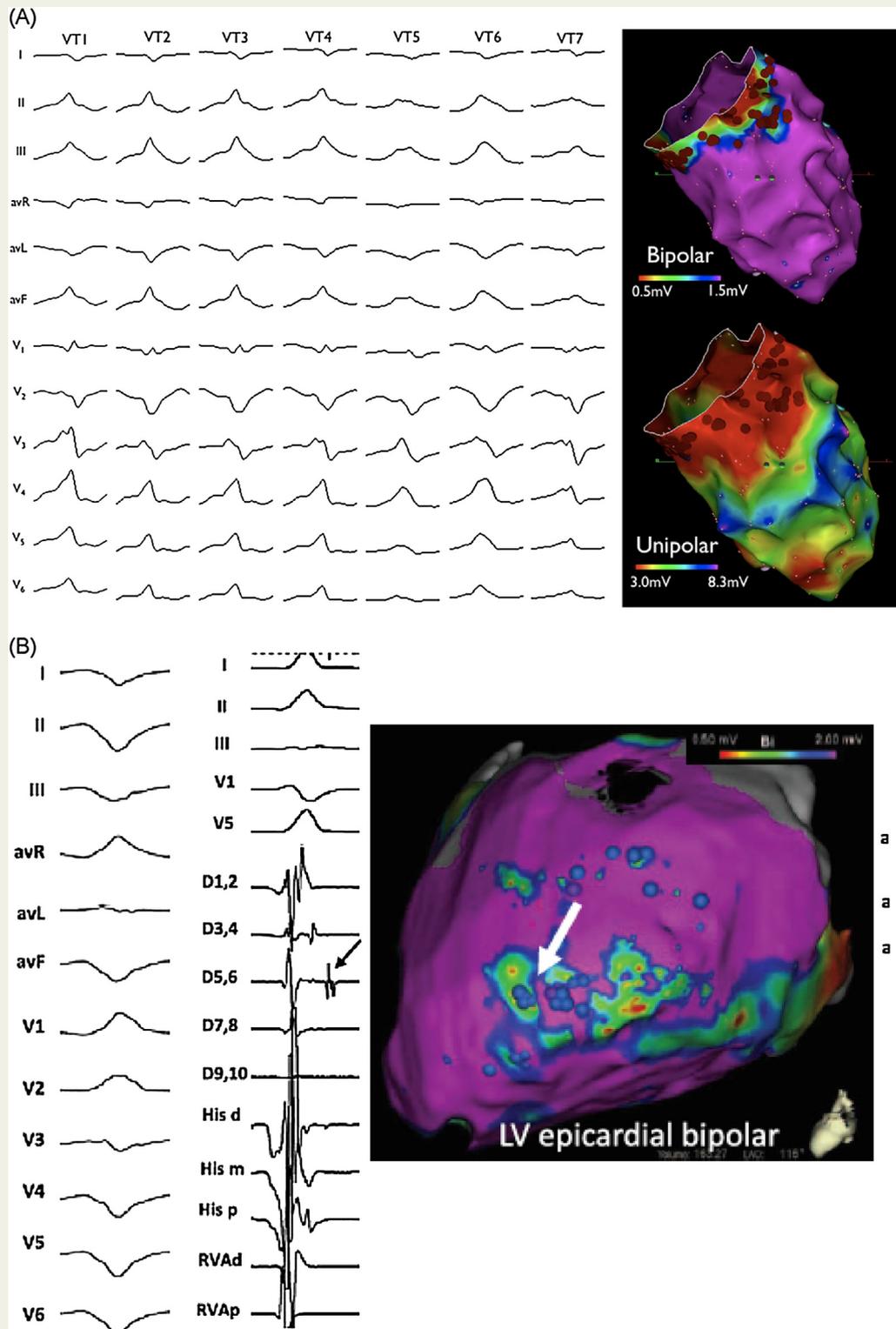


Figure 1 Examples of anteroseptal (A) and inferolateral subtype of NICM scar (B).

(A): Example of typical anteroseptal scar in NICM. Multiple inducible VTs of intramural origin were present. Classical VTs of left bundle, early transition ($\leq V_3$) inferior axis are inducible. 3D cardiac maps show a classic feature of anteroseptal NICM with a small bipolar scar (subendocardial scar; top panel, red area) but a much larger extensive intramural scar on unipolar map (bottom panel). Derived from Kumar *et al.*, with permissions (license number 4444120634072) [52]. (B) Example of typical inferolateral epicardial scar in NICM (green zone on 3D map on the right panel). Classic VT of right bundle superior axis is seen (left panel). Late potentials after the QRS are seen on mapping (middle panel). Derived from Kumar *et al.*, with permissions (license number 4444120794106) [101]. Abbreviations: 3D, three dimensional; VT, ventricular tachycardia; NICM, non ischaemic cardiomyopathy.

demonstrated the ability to correlate cardiac magnetic resonance imaging (cMRI) scar with histological assessment [32]. cMRI has also been shown to be safe and helpful in patients with pre-existing ICDs. Dickfield et al. studied 22 patients; 14 patients were able to have successful three-dimensional reconstruction of their scar, achieving $\geq 11/12$ pace map sites through early identification of the MRI border zone combined with 12-lead ECG morphology, even before detailed voltage mapping [33]. Crucially, intramural scar that may contribute to clinical VT can remain undetected via traditional bipolar voltage mapping if there is >2 mm of surrounding surviving endocardium, as was the case with 60% of patients in this study. Even when intra-cardiac devices are present, cMRI allows for partial, if not full, assessment of LGE to guide ablation, using a novel wide-band LGE technique [34]. Emerging evidence indicates that cMRI can be performed safely in patients with intra-cardiac devices, even in the presence of devices that are not considered MRI-conditional [35].

Late gadolinium enhancement-cMRI may allow for pre-procedural planning and likelihood of success in that it will identify anteroseptal vs. inferolateral subtypes. Piers et al. described that 42% of NICM have a basal anteroseptal scar, often extending to the sub-aortic region whereas 47% have a dominant basal inferolateral scar with variable extension to the mid-lateral wall segments (Figure 1). Anteroseptal scar had a higher transmural extent than inferolateral scar; the latter were often located subepicardially [25]. Identification of the scar pattern allows avoidance of epicardial access in the anteroseptal subtype where ablation will be limited by close proximity of coronary arteries, great cardiac and anterior interventricular vein and prominent epicardial fat. In contrast, first-line epicardial access may be advisable for basal inferolateral substrate. Furthermore, in patients with inferolateral subtype of scar, LVEF may be normal and the substrate may be confined to the subepicardium alone. Epicardial scar can be missed by unipolar voltage mapping in some such patients [36,37], but is easily identified by LGE-cMRI, allowing critical pre-procedural planning. Beyond LGE, cardiac T1 mapping, which reflects changes of the intracellular and extracellular component of the myocardium, and post contrast T1 mapping, which allows assessment of the extracellular volume fraction, can be used as a potential marker for myocardial fibrosis in NICM.

Electrophysiologic and Electroanatomic Substrate

In the absence of gadolinium-enhanced cMRI, electroanatomic voltage contact mapping is considered an important indicator of scar substrate and tissue viability. Low voltages are known to correlate macroscopically with areas of scar on histopathology [38]. Unipolar and bipolar voltage mapping may be performed. Bipolar voltage mapping detects sub-endocardial scar, wherein unipolar mapping has been traditionally felt to have a larger field of view and the ability to detect intramural and epicardial substrate. Normal values

for unipolar mapping were based on a mapping study of six healthy control subjects all of whom, who had with 95% of all their voltages, >8.27 mV [39]. Using the LGE-based scar, different cut-off values for endocardial scar (bipolar <1.78 mV, unipolar <5.64 mV) [40] and intramural scar have been reported (bipolar <1.55 mV, unipolar <6.78 mV) [41]. Classically, NICM is characterised by a small scar on bipolar voltage map and large scar on unipolar mapping (Figure 1). Recently, the utility of using fixed voltage cut-offs for scar have been called into question, suggesting that tissue characteristics such as wall thickness (hypertrophy), presence of epicardial fat, and the very nature of fibrosis can influence identification of scar on voltage mapping [23,42].

Beyond voltages, the characteristics of electrograms (EGMs) can further indicate scar presence and, potentially, areas of discontinuous conduction, with abnormal EGMs being a marker of VA substrate. Abnormal EGMs are believed to be consistent with delayed activation of channels of surviving myocytes within scar during sinus rhythm. These surviving myocytes are poorly coupled, capable of slow and discontinuous conduction that support re-entrant VT. Poorly coupled myocytes thereby manifest as fractionated, split, and late potentials and are considered a surrogate for such a VT substrate. Ischaemic cardiomyopathy patients without clinical sustained spontaneous VT, compared to those with VT, have fundamentally different electroanatomic and electrophysiologic substrate [43]. Those without VT have a higher, mean voltage of low-voltage zones, fewer fractionated, isolated, and very late potentials, with lower density of these scar-related electrograms per unit low-voltage area, fewer conducting channels that support VT, and less VT inducibility [43]. These areas of fractionated, isolated and late potentials, and conducting channels can be targeted for ablation.

In NICM substrates, however, there are fewer apparent ablation targets. NICM, compared to ICM have smaller and less dense endocardial low voltage scar, and fewer fractionated, isolated and late potentials [44]. Indeed late potentials cannot be identified in $>50\%$ of patients with DCM and are particularly scarce in those with non-inflammatory and anteroseptal scar [30,44]. The lack of abnormal EGMs has also been attributed to deep intramural substrate location and patchier scars that may not result in fixed conduction block regions that delay local activation. Furthermore, compared to ischaemic scars, NICM patients exhibit fewer surrogate markers of critical pathways that support VT that are identifiable by pace-mapping. NICM patients have fewer sites where pace mapping identifies best “matches” with the clinical spontaneous VT with stimulus-QRS delays (identifying potential channels that support VT). The lack of substrate targets (making empiric substrate-based ablation approach more difficult) and the presence of concealed intra-mural substrate likely contributes to the higher recurrence rate of NICM, compared with ICM, especially with the anteroseptal subtypes [10,44,45].

Several studies have documented the electroanatomic distribution of VA substrate in NICM. The recently described anteroseptal intramural and basal-lateral epicardial phenotypes have already been described [24,25]. In the earlier series, Hsia *et al.* in a series of 19 patients with NICM demonstrated VT originating from areas of low voltage on mapping, with even small areas being capable of supporting multiple re-entrant VTs [17]. The basal peri-valvular regions of the LV including adjacent to the aortic and mitral annuli are a classic location of substrate for NICM [46]. Haqqani *et al.* further highlighted the presence isolated intramural septal substrate in NICM that can remain undetected on bipolar voltage mapping, hence supporting the role for unipolar mapping and cMRI guidance [26]. Indicators of septal substrate may include (a) an apically displaced transmural breakthrough with a delayed transmural conduction time (>40 msec); and (b) fractionated, late, split, and wide (>95 msec) bipolar EGMs whilst pacing from the basal RV septum and recording at the LV septum [47].

Distribution of Substrate According to Underlying Disease

The distributions and characteristics of VA substrate, and subsequent outcomes of catheter ablation, are strongly influenced by the underlying pathophysiologic process specific to the disease. Some characteristic scar patterns and locations are recognised (Figures 2 and 3). In inflammatory NICM, sarcoidosis has been well studied. The substrate for VA in cardiac sarcoidosis is highly dependent on the anatomical location of inflammation and ensuing fibrosis within the myocardium. In a series of 21 patients with cardiac sarcoid-related VT, electroanatomic mapping revealed confluent RV epicardial (7 of 8) and endocardial (16 of 18) scar, with more patchy involvement of the LV endocardium around the septum (11 of 15), anterior wall (7 of 15) and perivalvular regions (5 of 15) [48]. Notably, intramural VT circuits were found to be the greatest contributor to recurrence and/or procedure failure. The subepicardium may be more involved

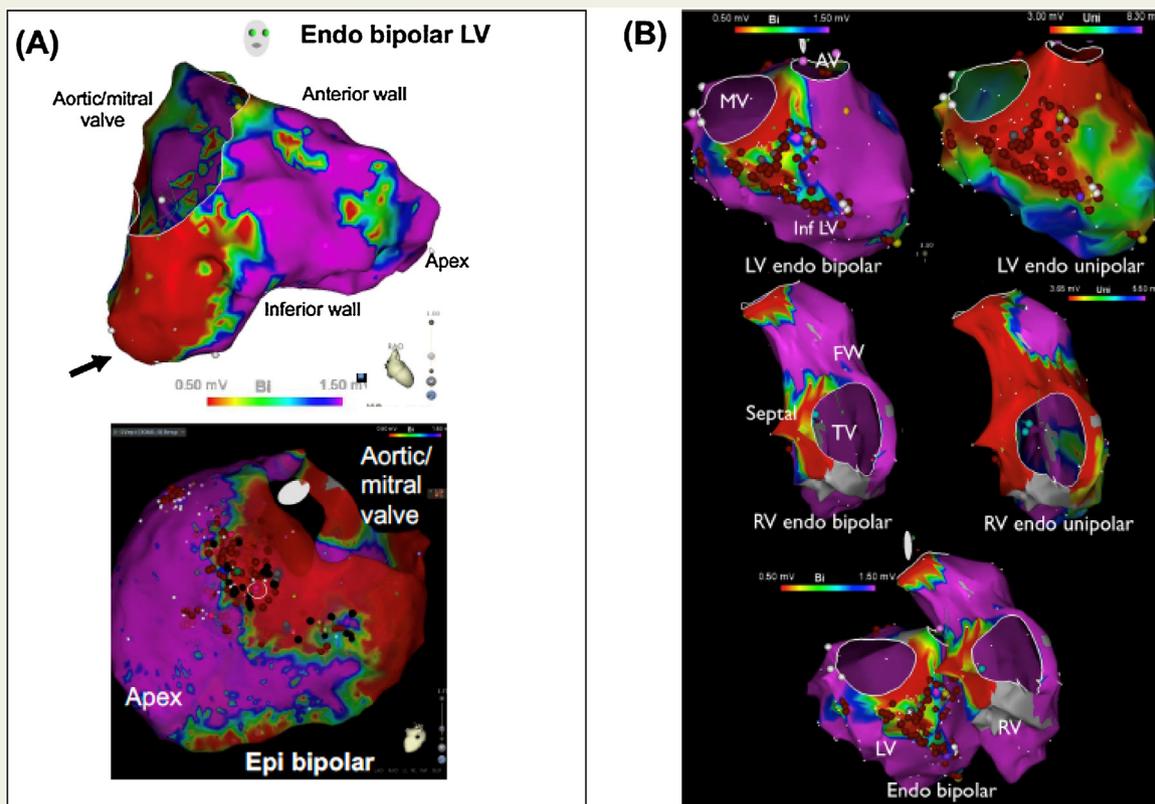


Figure 2 Classic features of sarcoid-related scar and LMNA-related scar.

(A) Example of voltage map of the endocardial bipolar voltage map of the LV (top) and epicardial bipolar map of the LV in a patient with cardiac sarcoidosis. Low voltage scar (red area) is seen in the inferior wall associated with an inferior wall aneurysm (arrow). Corresponding extension of the infero-lateral epicardium (red zone, bottom panel) is seen.

(B) Example of biventricular voltage maps in a patient with LMNA cardiomyopathy. Scar regions (red/green areas) are seen much more extensively on unipolar maps of the LV and RV involving the basal-apical septum and inferior wall. Adapted from Kumar *et al.* [52], with permissions (license number 4444120932542).

Abbreviations: AV, aortic valve; Endo, endocardial; Epi, epicardial; LV, left ventricle; MV, mitral valve; RV, right ventricle; LMNA, lamin A/C mutation.

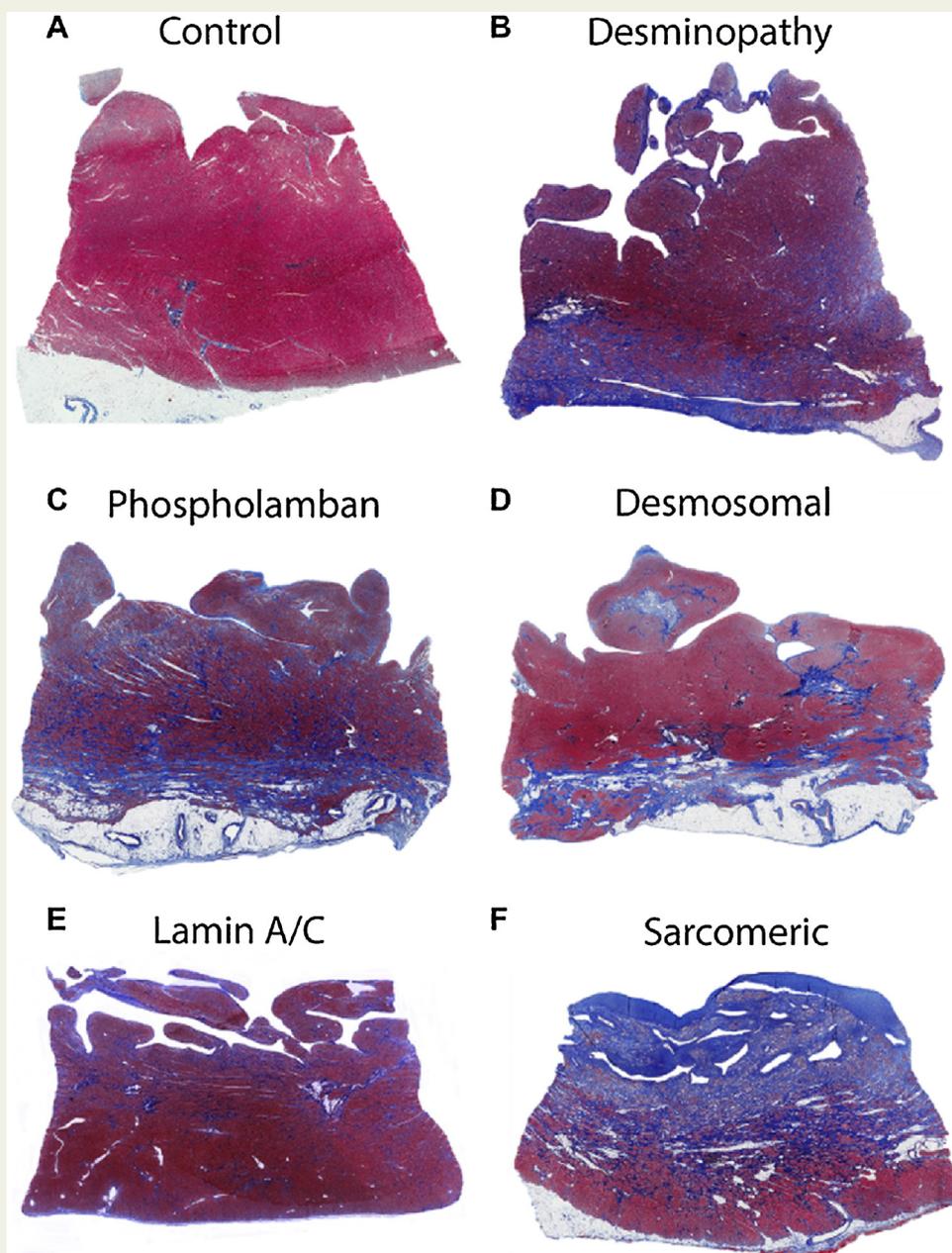


Figure 3 Histopathologic findings in non ischaemic cardiomyopathy (NICM) with pathogenic mutations. Masson's trichrome staining with fibrosis in blue, cardiomyocytes in red and adipocytes in white of A: Control heart with almost no fibrosis; B: desminopathic heart, C: phospholamban, and D: desmosomal mutations with fibrosis in the outer layer of the myocardium. Hearts with a mutation in the genes encoding E: lamin A/C and F: sarcomeric proteins with trabecular fibrosis and fibrosis in the inner layer of the compact myocardium. Adapted from Sepehrkhoy et al. [51], with permissions (license number 444121171614).

than the mid-myocardium and endocardium, which might explain the limited diagnostic yield (<25%) of endomyocardial biopsy.

In healed myocarditis-related VT, scar tends to be exclusively subepicardial (sometimes the only location with scar) [36,37]. Ventricular tachycardia may be inducible only by stimulation from the epicardium (seen in 33–42% of patients) [36,37]. Outcomes of catheter ablation appear to be excellent

if late potential channel elimination and VT inducibility can be achieved [36,37,49]. Late potentials can be recorded in up to 92% of such patients and were abolished in 50–82% of patients with 10–25% having recurrent VT during a median follow-up of 23–28 months [24,36,50].

Genetic NICM have key scar distribution patterns [51]. Prominent epicardial fibrosis is classically seen with phospholamban mutations, but also in mutations within the desmin

filament network (desminopathies), and desmosomal mutations, affecting the posterolateral LV and RV. Endocardial and intramural fibrosis is seen classically with *LMNA* mutations and sarcomeric mutations (e.g. titin; Figure 3) [51].

Mutations in the *LMNA* gene resulting in cardiomyopathies have a distinct preponderance to VA and have been extensively characterised in a series of 25 consecutive patients [52]. Almost all (95%) patients had low-voltage endocardial scar in the LV and 72% in the RV, with a particular concentration of substrate in the basal septal and basal perivalvular regions of both ventricles (Figure 2). The combination of a predominantly septal substrate with more extensive endocardial unipolar than bipolar voltages is consistent with the presence of intramural septal scar in this group of patients.

Catheter Ablation

Outcomes

Catheter ablation for VA is increasingly utilised in NICM [4,53–55]. Procedural success rates, often defined as non-inducibility of any VT at the end of the procedure, range from 38% to 74%, with VT recurrence rates between 29% and 58% during a median follow-up of 9 to 22 months [17,44,46,56–58]. The recurrence of VT is heavily dependent on the aetiology of NICM, with outcomes being worse for sarcoidosis and non-ischaemic dilated cardiomyopathy and best for arrhythmogenic right ventricular cardiomyopathy (ARVC) [55]. Muser *et al.* reported a large series of 282 consecutive patients with non-ischaemic dilated cardiomyopathy, who had failed a median of two anti-arrhythmic drugs prior to referral, including amiodarone in 59% of patients VT-free survival was 69% at 60 months [59]. The therapeutic benefit of VT ablation in NICM, as in ICM, extends beyond recurrence of VT alone. Amongst 21% of these patients with VT recurrence, ablation resulted in a significant reduction of VT burden with 53% having only isolated VT episodes (1–3 episodes) in 12 months (range, 4–35 months) after the procedure. Moreover, ablation resulted in reduction and/or discontinuation of AADs with 45% of patients left only on beta blockers or no treatment, 15% left on sotalol or class I anti-arrhythmic drugs and 22% on amiodarone [59]. Catheter ablation of storm in non-ischaemic dilated cardiomyopathy is highly effective, with only 5% experiencing recurrence of storm at a median follow-up 45 months [60]. It is notable that the inferolateral subtype of patients with NICM have better outcomes than those with anteroseptal subtype, likely due to greater recognition of abnormal substrate (late potentials, fractionated electrogram) and lack of concealed intramural substrate [24,58].

When compared to ICM, outcomes of patients with NICM are consistently worse [44,56,57,61]. Proietti *et al.* revealed, in their series of 142 patients (55 of whom had NICM), a significantly lower acute procedural success rate of 53% in NICM compared with 69% in ICM ($p = 0.03$) [61]. Dinov *et al.* went on to demonstrate a higher rate of VT recurrence

with NICM (HR 1.62, $p = 0.01$), and lower VT-free survival (40.5% vs 57%) [56]. In a propensity-matched analysis of hospital outcomes in the United States, catheter ablation was associated with a lower mortality compared to AAD in NICM (adjusted odds ratio 0.53; 95% CI, 0.43–0.66) [4].

Earlier referral for catheter ablation from the onset of VT has been shown to reduce VT recurrence and improve recurrence-free survival [62], a finding that was further affirmed in a recent meta-analysis by Kumar and colleagues (VT recurrence RR 0.69, $p < 0.001$) [63]. The standard definition of early referral for catheter ablation remains unclear. Frankel *et al.*'s study of 96 patients with structural heart disease used a definition of ≥ 2 episodes of VT for late referral and demonstrated a 1-year survival benefit with earlier referral [3]. In contrast, Romero *et al.* defined early referral as ablation performed within failure of one anti-arrhythmic drug (class I or III), revealing an increased risk of VA recurrence (HR 1.6, $p = 0.01$) and mortality (HR 2.6, $p = 0.008$) [64]. Dinov *et al.* further highlighted the value of achieving acute non-inducibility at the end of each procedure by demonstrating both a mortality benefit and a reduced risk of future VT recurrence [45]. Combining endocardial and epicardial ablation is likely associated with better outcomes, especially if scar is identified on the epicardial surface prior to the procedure [65].

More recently, the largest single-centre retrospective series on catheter ablation in NICM was performed with 695 consecutive patients, of which 239 had NICM [57]. This study further affirmed the high risk of VT recurrence in NICM, when compared with those with ICM and no structural heart disease (37% vs 54% vs 77%, respectively), where factors that were more predictive of VT recurrence included lower systolic function, number of anti-arrhythmic drug failures, acute non-inducibility and the need for epicardial ablation. Whilst mortality was found to be highest in those with ICM, requirement for transplantation (11%) and mortality (25% by 6 years) were remarkably high in NICM. These findings are most likely attributed to the greater comorbidity burden in those with ICM contributing to increased all-cause mortality. Indeed, the consistently higher rates of VT recurrence and lower acute procedural success rates in NICM allude to the greater prevalence of intramural and epicardial substrate that warrants more comprehensive mapping and ablative strategies, including the use of adjunctive measures [66,67].

Overcoming Challenges of Ablation in NICM

There are a number of reasons for VT ablation procedural failure (Table 2). In NICM, the most important reasons for failure are inadequate mapping, ineffective ablation, the presence of intramural substrate, close proximity to critical structures such as the coronary arteries, the AV node or the phrenic nerve, and anatomic barriers that prohibit effective lesion formation such as predominant epicardial fat [68,69]. The likelihood of intramural substrate is higher in NICM

compared with ICM and may necessitate alternative or adjunctive approaches, where a traditional endocardial approach may fail due to insufficient lesion depth with contemporary ablation technologies.

Expanding Lesion Size Using Existing Technologies: Targeting Intramural Substrate

When VA originates from a deep intramural location, failure can be because of inability to achieve sufficient lesion depth with contemporary RF ablation technologies. Catheter ablation is usually performed with open-irrigated ablation, targeting a maximum impedance drop of 12 to 18 Ohms with power up to 50 W. At sites suspected of intramural substrate, power up to 60 W and lesion duration ≥ 3 minutes may be necessary to expand lesion size [24,59]. This technique has been useful for targeting septal substrate and for targeting epicardial substrate with endocardial ablation [70]. It is clinically more useful during ablation of the VT from the LV summit, where ablation from adjacent sites such as the left or right sinuses of Valsalva, the septal right ventricular outflow tract or below the aortic-mitral continuity may abolish the arrhythmia even when activation and pace-mapping from these sites suggest a suboptimal location [68,71,72]. Another alternative is to relocate the dispersive patch electrode from the standard location on the back to the front of the chest, when targeting LV summit VAs, in order to re-direct the current toward the anatomical site being targeted, a technique recently described [73].

Alternatively, deep intramural substrate may be targeted through sequential or simultaneous unipolar or bipolar ablation at two sites directly opposite from the target area. Traditional RF ablation is in unipolar configuration (current flow between catheter tip to a patch placed on patient's skin). Bipolar ablation is a configuration where current will flow between two sequentially opposed catheters, with both catheters attached to the same generator (power supply) and delivering energy simultaneously. Sequential unipolar ablation means ablation of two opposing sides sequentially, one at a time e.g., left, then the right side of the interventricular septum, or endocardial followed by epicardial ablation on the juxtaposed sides. Simultaneous unipolar ablation is performed with two juxtaposed catheters that deliver energy simultaneously through two different generators. In experimental models, bipolar ablation creates lesions that are larger and more likely to be transmural than sequential unipolar lesions, even in tissue up to 25 mm in thickness [74–76]. In a small case series of nine patients, bipolar ablation with this technique was shown to be effective when sequential unipolar ablation had failed (VT 78%), although VT recurred in 50% of patients [77]. Caution must be taken with bipolar ablation, with suggestions of an increased risk for thromboembolism, steam pops and ventricular septal defect formation [69].

Simultaneous unipolar RF may also be feasible. A potential advantage of simultaneous unipolar ablation is that it allows individual power titration at both ablation catheters. Limited experience with simultaneous unipolar RF suggests its

Table 2 Reasons for Acute Failure with Contemporary Catheter Ablation Techniques. Adapted from Kumar et al. [69].

Reasons for acute failure
Suboptimal previous endocardial or epicardial ablation
Non-endocardial VA origin but inaccessible epicardium
Previous cardiac surgery
Previous pericarditis
Failed attempt at epicardial access
Intramural substrate
Septal
Free wall
VA origin in close proximity to critical structures
Endocardial: His bundle
Epicardial: phrenic nerve, coronary arteries
Inability to deliver adequate energy to VA target site
Great cardiac vein or anterior interventricular vein
Anatomic barriers prohibiting lesion formation
Prominent trabeculations (eg, right ventricle)
Epicardial fat (eg, LV summit)
Suspected nonendocardial VA origin, but epicardial access not undertaken because of anticipated cardiac surgery for other conditions, such as valve replacement or LVAD insertion, where VA surgery will also be performed
Acute complications
Ventricular perforation and tamponade
Other catastrophic complications (eg, refractory cardiogenic shock, stroke, electromechanical dissociation)

Abbreviations: LV, left ventricle; LVAD, left ventricular assist devices; VA, ventricular arrhythmia.

excellent utility in elimination of ventricular arrhythmias from the LV outflow tracts, with elimination of arrhythmia in all 14 patients over long-term follow-up [78].

Traditional irrigated RF ablation is delivered using normal saline as an irrigant. Changing to half normal saline, as recently described, may increase lesion size and effectiveness of catheter ablation for deep intramural substrate [79–81]. Compared to 0.9% saline, half normal saline has decreased osmolarity and charge density which results in increased RF energy delivery to tissue, resulting in larger lesions for both open and closed irrigated ablations. Lesion size with unipolar half normal saline resembles that of bipolar ablation using normal saline [79]. A recently published multi-centre experience with half normal saline for refractory VA appears promising with a high acute non-inducibility rate of 83% in patients in whom standard normal saline ablation had failed, with no complications [81].

Another technique for characterising and targeting intramural substrate is the use of a retractable needle within an endocardial catheter, a technique that has progressed beyond experimental studies and is garnering increasing clinical evidence as an effective tool. This was demonstrated in a novel study of eight consecutive patients who had failed at

least one previous catheter ablation [82]. The needle catheter can allow traditional mapping techniques, including intramural pacing and recording of potentials, as well as the delivery of radiofrequency ablation. Attesting to the ability to map closer to the VA exit point, intramural semi-bipolar EGMs had two-and-a-half times greater amplitudes and were consistently earlier than corresponding endocardial bipolar EGMs. Ventricular arrhythmia was able to be successfully terminated at 12 of 28 sites (43%). Further studies incorporating correlation with LGE on cMRI and long-term follow-up are needed. Intramyocardial RF delivery has also been recently described for deep septal VA, using an intracoronary wire mapping and a coronary re-entry system. In this technique, a chronic total occlusion guidewire Stingray LP device (Boston Scientific, Marlborough, MA, USA) is used to perforate a small septal perforator that supplies the exit site of the VA, through which RF energy is then delivered into the intramyocardial tissue [83].

Trans-coronary ethanol ablation (TCEA) is an adjunctive measure that may be utilised for intramural substrate

or epicardial substrate with prohibitive epicardial access (Figure 4). The aim is to achieve complete vascular occlusion in the injected arterial wall, resulting in transmural myocardial necrosis with a minimal rim of surviving subendocardium [84]. TCEA has traditionally been used in VA associated with ICM following failure of more conventional approaches [68]. In one series of 42 patients, of which 22 had NICM, TCEA was used to target mostly septal regions (74%), eliminating at least one inducible VT in 71% of cases, and terminating VT storm in 70%. Whilst VT recurrence was high at 82% by 12 months, there was a significant reduction in the burden of ICD shocks (median of 6 to 3, $p = 0.001$) and a reduction in anti-arrhythmic burden between 1 and 6 months post-procedure (median of 3 to 2, $p = 0.04$). The rate of complications was relatively high (32%), predominated by expected AV block when targeting basal septal substrate. The presence of multiple collaterals can increase the risk of damage to non-target myocardium, precluding up to 14% of patients from consideration of TCEA [69]. Coil embolisation has

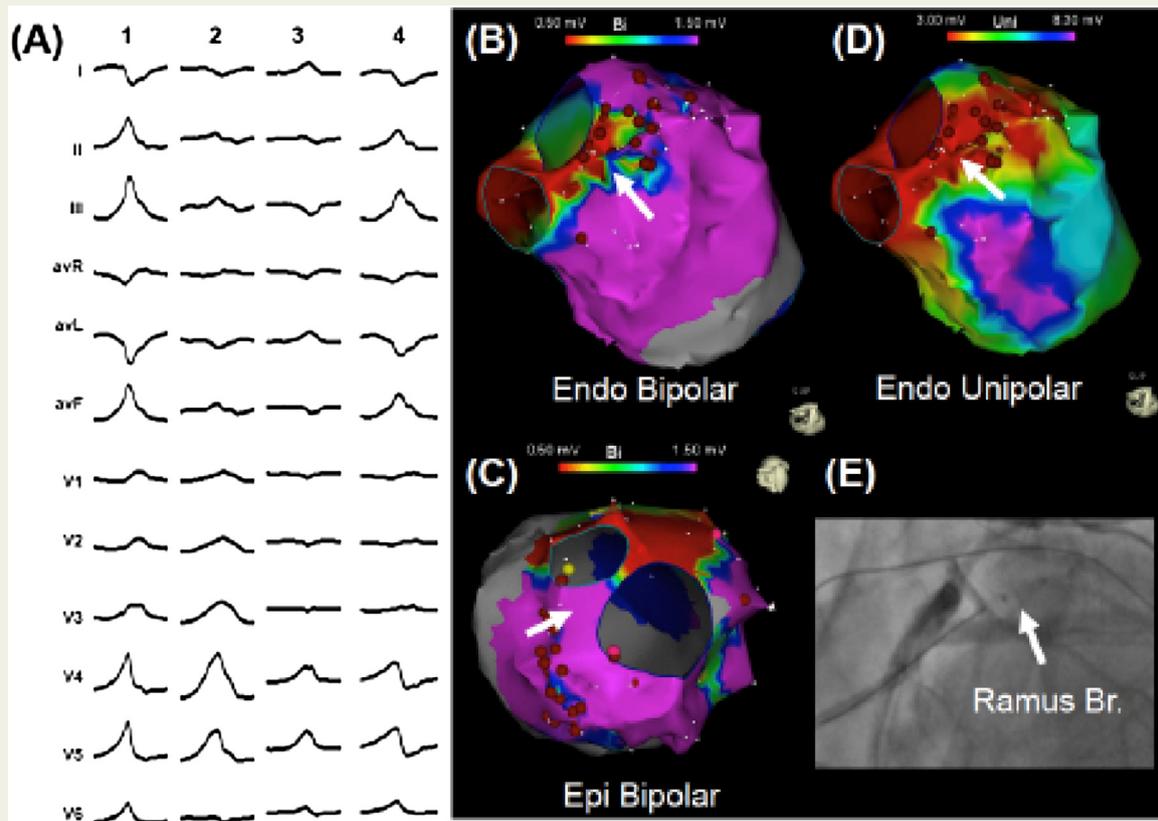


Figure 4 Example of transcatheter ethanol ablation.

Example of NICM patient with basal intraseptal substrate identified by unipolar mapping capable of supporting multiple VTs (A). There was a small scar (red/green zone) on bipolar mapping (B, C), but was extensive on unipolar mapping (D). Ablation of the endocardium had failed to abolish all inducible VTs, prompting use of transcatheter ethanol ablation. Coronary angiography identified a small ramus branch that subtended the area of scar (arrow) that was targeted for ethanol ablation (E). Adapted from Kumar *et al.* with permissions (license number 4444121338176) [68].

Abbreviations: Br, branch; Endo, endocardial; Epi, epicardial; NICM, non ischaemic cardiomyopathy; VT, ventricular tachycardia.

been trialed on an individual case-based level and found to be a feasible alternative in such situations [85].

The coronary venous system offers many advantages over the arterial system for alcohol ablation, including relatively unobstructed access to the capillary bed, even in the presence of severe coronary artery disease, as well as a lower risk of arterial complications related to femoral arterial cannulation and instrumentation, and a lower collateral arterial damage. Furthermore, the coronary veins are amenable to electrophysiologic mapping. Despite these perceived advantages, trans-venous ethanol ablation (TVEA) has remained relatively under-studied, with only limited experience reported. In one, small observational series Kreidieh et al. involved seven patients with prior failed ablation attempts [86]. Five of these patients had ablation of septal branches of the anterior interventricular vein to target substrate within the LV summit. TVEA facilitated elimination of VA in all cases, however four of seven patients had recurrence within 2 years of follow-up, all of which were subsequently eliminated with further procedures. Although promising, major disadvantages are that there is limited control over the extent of ablation, which may be large, and limitations in venous anatomy may still limit access to target site.

One clear impediment to the use of the above techniques is that it requires a well-defined target area, which may be facilitated by real-time image integration, high-density activation and entrainment mapping (sometimes requiring haemodynamic support if VT is not haemodynamically tolerated), and/or high density substrate and pace mapping techniques. Scars themselves can be large, and the critical isthmus for the VT circuit may be small. Hence, empiric targeting of large scar areas may result in extensive collateral damage. Despite this however, extensive scar homogenisation has been shown to be superior to limited ablation of substrate [87].

Percutaneous Epicardial Approach

Combined endocardial-epicardial substrate homogenisation, compared to limited substrate ablation has been shown to be beneficial in ischaemic [88] and non-ischaemic cardiomyopathy [87] in two randomised studies, and confirmed by a recent pooled meta-analysis of all published series with such an approach [65]. A significant proportion (47%) of substrate for re-entrant VT in NICM originates from the epicardium, especially with an inferolateral scar pattern [25]. Epicardial infero-lateral substrate is often associated with prior myocarditis [36,37,49]. Isolated epicardial scar may be the only finding [36]. Epicardial scar is larger than anteroseptal subtypes and there is a higher proportion of late potential targets, compared to the anteroseptal subgroup. Therefore, outcomes of catheter ablation are better in the epicardial inferolateral subtype than the anteroseptal subtype. An appreciation of the complexities, complications and limitations of an epicardial approach is paramount.

The traditional technique for nonsurgical epicardial access for electroanatomic mapping is that which has been described by Sosa et al. [89], which involves a 17-gauge

(G) or 18G Touhy needle for combined percutaneous and pericardial puncture. A major procedural risk is inadvertent puncture or laceration of the RV, resulting in significant (>80 mL) pericardial bleeding, with a reported incidence ranging from 3.7% to 10% [90,91]. One multi-centre non-randomised study explored the efficacy and safety of a novel “needle-in-needle” (NIN) technique involving a short 18G needle for percutaneous puncture, followed by a longer 21G needle inserted through the former [92]. Rates of pericardial bleeding were similar but non-significant (9%), likely attributed to the prominent difference in cohort sizes (316 Sosa technique procedures versus 23 “needle-in-needle”). In a subsequent study, Gunda et al. confirmed the above results in 404 consecutive patients undergoing epicardial access [93]. Whilst there was no significant difference in the incidence of inadvertent puncture of myocardium between group (traditional 7.6% versus NIN 6.8%, $p = 0.76$), the rate of large pericardial effusions was higher with traditional vs. NIN (8.1% versus 0.9%; $p < 0.001$), including a numerically higher rate of open heart surgery to repair cardiac laceration (6 versus 0), injury to liver (1 versus 0), coronaries (1 versus 0), and superior epigastric artery requiring surgical exploration (0 versus 1) with the traditional approach [93]. Other techniques of epicardial access including use of a needle incorporating a real-time pressure/frequency recording [94]; and, use of carbon dioxide insufflation after creating a controlled (small) coronary venous perforation have recently been described [95].

Ablation within the epicardial space produces greater shallow and flatter lesions compared to the endocardium, which may also be larger due to absence of heat sink effect of the circulating blood [96]. As irrigated catheters are commonly used with epicardial ablation, significant volume may be delivered in the epicardial space (up to 30 mL/min of RF ablation with some catheters). The presence of intrapericardial fluid hinders lesion formation, hence regular drainage of pericardial fluid will improve the efficiency of RF ablation in the epicardial space [97].

A potential complication related to an epicardial approach is inadvertent left phrenic nerve injury. With respect to VA ablation, foci arising from the basal inferolateral LV epicardium lie in close proximity to the path of the left phrenic nerve [98], with a distance of <3 mm from the epicardial surface in up to 36% of patients [99]. Phrenic nerve injury can vary in clinical manifestation from being asymptomatic through to frank respiratory failure, with up to 33% of patients experiencing long-term morbidity beyond 28 months from their procedure [90,100]. This may be avoided intra-procedurally, as demonstrated in one small case series where two different strategies were used in five patients undergoing VT ablation for NICM [101]. The use of a vascular or oesophageal balloon in the pericardial space averted phrenic nerve injury and facilitated successful ablation in all patients, with one patient developing a pleuro-pericardial fistula and moderate pericarditis. Whilst air insufflation and saline infusions have been attempted as alternative means of phrenic nerve displacement, they have been hampered by

lower success rates [102], or safety issues from tamponade with saline or an inability to externally defibrillate with air [103,104]. These results were confirmed by a series by Okubo *et al.* [105] who studied 363 patients undergoing epicardial access, in whom 7% had substrate coursing the phrenic nerve. The most common cause was myocarditis; large balloon was able to displace the phrenic nerve and allow complete late potential abolition in 9/13 patients (69%). Without phrenic nerve displacement, nerve injury was seen in 3/12 patients (25%), and late potential abolition was achieved in only one patient (8%).

One major limitation of ablation in the epicardial space is the presence of epicardial fat, which hinders myocardial lesion formation [69]. This may be overcome with higher contact forces (greater catheter pressure) in the epicardial space [106], albeit at a higher risk of collateral arterial or nerve injury, or surgical dissection [68,107]. In one series of VA from the LV summit, fat dissection and displacement of the left anterior descending coronary by a cardiac surgeon allowed successful lesion delivery for PVCs originating in the anterior interventricular vein [107].

Another major limitation of epicardial ablation is injury to the coronary arteries. A distance of at least 5 mm between the ablation catheter and coronary arteries is advised to avoid acute vessel closure [108], and/or chronic vascular changes resulting in stenosis [109,110]. Routine coronary angiography is advised to delineate the relationship between vessel anatomy and the anticipated lesion set.

Operators must be cognisant of the complications of epicardial access and ablation which include inadvertent RV puncture (incidence, ~4.5–17%), pericardial bleeding (incidence, ~10–30%, which tends to be mild and self-limiting, and ~4.5% reported to have bleeding >80 mL), injury to the subdiaphragmatic vessels (~0.5%), coronary vessel damage (~0.6%), as well as phrenic nerve injury, pneumopericardium, pericarditis and pleuritis [111]. Unusual complications related to epicardial access/ablation such as intra-abdominal bleeding, related to puncture of the left lobe of the liver, lacerated venous structures (middle cardiac vein), right-ventricular-intra-abdominal fistula, pleuro-pericardial fistula, coronary vasospasm, and retained wire fragments, have also been described [112].

Surgical Approaches

One of the most commonly encountered issues with epicardial access relate to anatomical barriers, including pericardial adhesions from previous surgical intervention and dense epicardial fat (especially in the region of the LV summit). Indeed, in a series of 518 patients, suspected pericardial adhesions resulting in an inaccessible pericardium was the most commonly cited reason for acute ablation failure [113]. In such situations, a hybrid surgical approach with the creation of an epicardial window (Epi-Window) by a cardiac surgeon in the electrophysiology lab may be used and has been found to be effective [68,114]. Using this technique, the surgeon establishes a subxiphoid pericardial window through a pericardiotomy, followed by manual lysis of

adhesions and placement of a sheath to facilitate mapping and ablation of the inferior, anterior and lateral epicardial LV walls [115]. In one case series by Soejima *et al.*, four of six patients who underwent an Epi-window-assisted procedure after previous failed ablation achieved VA elimination with no recurrence on a mean follow-up of 13 months [114].

Alternatively, a dedicated surgical approach in the operating theatre may be performed with surgical cryoablation, especially if there is a requirement for concomitant cardiac surgery (e.g., revascularisation or valvular intervention). In one small case series of eight consecutive patients with recurrent VT and failed percutaneous approach, surgical cryoablation facilitated a significant reduction in VT burden through a reduced number of ICD shocks (6.6 to 0.6 shocks; $p = 0.026$). Surgical cryoablation may also be advantageous in its ability to achieve much cooler temperatures than catheter cryoablation, thereby creating larger lesions [69]. It must be remembered that VA can be more difficult to induce under general anaesthesia and cardioplegic conditions [69], thereby highlighting the need for appropriate preoperative imaging and electroanatomic mapping. Consideration should be given to “marking” sites of earliest activation to assist with surgical dissection and cryoablation, as described in one case of VA from the anterior interventricular vein where a coronary sinus lead was deployed at the site of earliest activation and suture to the skin to allow the surgeon to identify the VA exit during open heart surgery (Figure 5) [116]. Overall, whilst surgical hybrid approaches may be valuable in reducing the VA burden of patients with difficult epicardial access and otherwise limited options (VA-free survival, 49–67%) [68,115,117], complications have been shown to occur in up to 36% of patients, including thromboembolism, infection and coronary or phrenic nerve injury [69]. However, surgical approaches lead to significant reduction in VA burden and anti-arrhythmic drug use in patients in whom anti-arrhythmic drugs and exhaustive attempts at endocardial and epicardial catheter ablation have otherwise failed [68].

Neuraxial Modulation

The basis of techniques under the umbrella of neuraxial modulation is to ameliorate high sympathetic tone and input to the ventricular myocardium, thereby reducing β -adrenergic-induced automaticity, increasing repolarisation times and prolonging refractory periods [118]. These techniques are traditionally reserved as a “bail-out” strategy for electrical storm (incessant VA) [119], when more conservative measures with catheter ablation are unsuccessful. Thoracic epidural analgesia with bupivacaine aims to reduce sympathetic outflow from T1 to T5, thereby non-selectively blocking afferent and efferent signals to the heart. It is typically used as a bridging measure due to its short-lived therapeutic effects. Its appeal can be seen through ease of access, rapid onset of action and lack of adverse haemodynamic response [69]. The same can be said for left stellate ganglion blockade with local anaesthetic, which provides a similar short-lived sympathetic block to a wider region, including the head, neck and diaphragm [118].

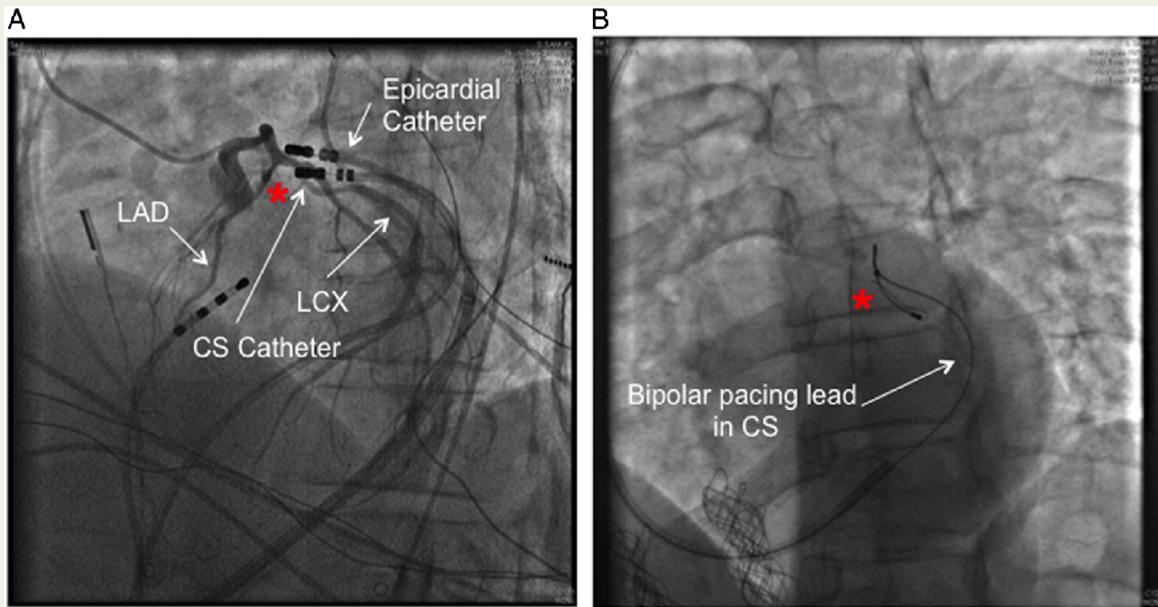


Figure 5 Use of surgical ablation for ablation of ventricular arrhythmias from sites considered inaccessible with percutaneous catheter ablation.

Case of a ventricular arrhythmia originating from the anterior interventricular vein. Mapping is performed in the anterior interventricular vein (coronary sinus [CS] catheter; A and the epicardial space (epicardial catheter, A) showing close proximity to the left anterior descending (LAD) and the left circumflex coronary artery (LCX). Owing to the close proximity to the arteries and veins, the patient was referred for surgical epicardial ablation. A bipolar pacing lead was placed in the CS and sutured to the skin (B). Surgical dissection was then performed allowing precise localisation of the site of origin and cryoablation. Derived from Choi et al., with permissions (license number 4444130246118 [116]).

More definitively, surgical cardiac sympathetic denervation (CSD) involves resection of the lower half of the left or bilateral stellate ganglia and thoracic ganglia from T2–T4 [118]. Left CSD has been shown to be effective in suppressing VA associated with long QT syndrome [120] and catecholaminergic polymorphic VT [121]. However, only modest results have been seen in structural heart disease, with 56% of patients achieving a complete or partial response, and 44% experiencing VA recurrence within 15 months [119], with greater efficacy achieved with bilateral CSD [122]. Renal denervation may also allow control of VA storm [123].

Stereotactic Beam Radiation Therapy

A recently described technique of stereotactic beam radiation shows promise in complete substrate abolition [124]. The procedure involves complete substrate identification using a novel anatomical and electrophysiologic mapping system (non-invasive electrocardiographic imaging) with pre-procedural computed tomography (CT) or cMRI. Completely non-invasive stereotactic body radiation therapy is then delivered precisely to the target region whilst the patient is completely awake. Preliminary data in five high risk patients with refractory VT showed significant reduction in arrhythmia burden after treatment. During the 3 months before treatment, the patients had a combined history of 6,577 episodes of ventricular tachycardia. After a 6-week “blinking period”, there

were only four episodes of ventricular tachycardia over the next 46 patient-months, resulting in a 99.9% reduction in VA burden, with no changes in LVEF and only mild inflammatory lung changes at 3 months, which had resolved by 1 year. Additionally, one patient died and another required repeat ablation. The technique holds promise for future substrate-based approaches in patients with concealed intramural or large substrates with high VA burden, but further data on safety and efficacy are needed.

Conclusion

Ventricular arrhythmias in patients with NICM are a major source of morbidity and mortality. There are many fundamental differences in scar location, topography, electrophysiologic and electroanatomic properties between patients with NICM and ICM. Two predominant substrate phenotypes of NICM, the anteroseptal intramural and inferolateral epicardial have been well-described. Scar location, accessibility and visibility of ablation targets during mapping determine the worse outcomes in NICM, especially with the anteroseptal subtype. Key scar patterns specific to subtypes of NICM, inflammatory and/or genetic, are recognised. Pre-procedural imaging with LGE-cMRI may aid in identification of substrate and planning the optimal mapping and ablation

approach. The greater proportion of previously inaccessible epicardial and intramural substrate has fueled the advent and development of novel ablative techniques. With growing evidence supporting the importance of arrhythmia control in NICM, these technologies will hopefully improve safety and efficacy of catheter ablation for NICM.

Disclosures

No disclosures.

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