Chapter 4: Left ventricular endocardial unipolar voltage abnormalities in patients with ventricular tachycardia

4.1 Preface to This Chapter

Patients with NICM have deep intramural substrate abnormalities that can lead to ventricular tachycardias (VT). These mid myocardial and epicardial substrate abnormalities can be best studied with invasive electro-anatomical mapping (EAM) tools. It is well known that endocardial unipolar low voltage zones (LVZs) can be picked up by EAM. However, the extent of spread of these endocardial unipolar LVZs that correlate with VT is not known. It will be useful to perform EAM on patients with VT and to study the cut-offs for the extent of distribution of these unipolar LVZs. Hence, a prospective EAM analysis on NICM patients was designed to address this knowledge gap. ***Hypothesis:*** LV Endocardial unipolar voltage has better correlation than bipolar electrogram characteristics with LV ejection fraction and for prediction of VT substrate.

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Abstracts from this research presented to International Societies- 2

Indian Heart Rhythm Society, 2023: Defining cut-offs for endocardial unipolar voltage abnormalities in non-ischemic cardiomyopathy presented under 'Young Investigator award' category

Heart Rhythm Society, 2024: Risk prediction of ventricular tachyarrhythmias in non-ischemic cardiomyopathy using unipolar low voltage zones in the left ventricle

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Correlation of extent of left ventricular endocardial unipolar low-voltage zones with ventricular tachycardia in nonischemic cardiomyopathy

Deep Chandh Raja, MD, DM,[1,2] Jenish Shroff, MD, DM,[1,2] Anugrah Nair, MD, DM,[1,2] Sreevilasam P. Abhilash, MD, DM,[1,2] Lukah Q. Tuan, BSc,[1,2] Abhinav Mehta, BSc,[1] Walter P. Abhayaratna, MBBS, FRACP, PhD,[1] Prashanthan Sanders, MBBS, FRACP, PhD, FHRS,[3] David S. Frankel, MD, PhD, FHRS,[4] Francis E. Marchlinski, MD, PhD, FHRS,[4] Rajeev Kumar Pathak, MBBS, FRACP, PhD, FHRS[1,2]

ABSTRACT

BACKGROUND Endocardial electrogram (EGM) characteristics in nonischemic cardiomyopathy (NICM) have not been explored adequately for prognostication.

OBJECTIVE We aimed to study correlation of bipolar and unipolar EGM characteristics with left ventricular ejection fraction (LVEF) and ventricular tachycardia (VT) in NICM.

METHODS Electroanatomic mapping of the left ventricle was performed. EGM characteristics were correlated with LVEF. Differences between groups with and without VT and predictors of VT were studied.

RESULTS In 43 patients, unipolar EGM variables had better correlation with baseline LVEF than bipolar EGM variables: unipolar voltage ($r = +0.36$), peak negative unipolar voltage ($r = -0.42$), peak positive unipolar voltage ($r = +0.38$), and percentage area of unipolar low-voltage zone (LVZ; $r = -0.41$). Global mean unipolar voltage (hazard ratio [HR], 0.4; 95% confidence interval [CI], 0.2–0.8), extent of unipolar LVZ (HR, 1.6; 95% CI, 1.1–2.3), and percentage area of unipolar LVZ (HR, 1.6; 95% CI, 1.1–2.3) were significant predictors of VT. For classification of patients with VT, extent of unipolar LVZ had an area under the curve of 0.82 (95% CI, 0.69–0.95; $P < .001$), and percentage area of unipolar LVZ had an area under the curve of 0.83 (95% CI, 0.71–0.96; $P = .01$). Cutoff of >3 segments for extent of unipolar LVZ had the best diagnostic accuracy (sensitivity, 90%; specificity, 67%) and cutoff of 33% for percentage area of unipolar LVZ had the best diagnostic accuracy (sensitivity, 95%; specificity, 60%) for VT.

CONCLUSION In NICM, extent and percentage area of unipolar LVZs are significant predictors of VT. Cutoffs of >3 segments of unipolar LVZ and >33% area of unipolar LVZ have good diagnostic accuracies for association with VT.

KEYWORDS Electroanatomic mapping; Bipolar voltage; Unipolar voltage; Ventricular tachycardia; Nonischemic cardiomyopathy; Low-voltage zone

(Heart Rhythm 2024;■:1–8)

4.2 Introduction

Sudden Cardiac Death (SCD) is responsible for nearly 35% of deaths in patients with non-ischemic cardiomyopathy (NICM).[86,104] Though left ventricular ejection fraction (LVEF) is a standard risk prediction tool for SCD in NICM,[105] the DANISH study using LVEF for risk-stratification in NICM failed to show reduction in all-cause mortality.[9,106] While search is on for additional risk markers for SCD in NICM, invasive tools such as electroanatomical mapping are useful and reliable in predicting abnormal electrical substrate causing ventricular tachycardia (VT) and SCD.[51] Electrogram (EGM) characteristics derived from electroanatomical mapping have been studied in NICM.[39,40,42,46,47,48] However, there is paucity of data on quantitative correlation of extent of distribution of these electrogram abnormalities with occurrence of VT in NICM. Therefore, our study was designed to study the various electrogram characteristics in NICM and analyse their correlation with LVEF and with VT, in patients with NICM. Further, we have derived cut-offs for the extent of electrical abnormality to predict VT.

4.3 Methods

All patients with NICM undergoing invasive electrophysiology study along with electroanatomical mapping from November 2018 to November 2021 were screened for inclusion. The primary objective of the study was to corelate intracardiac EGM characteristics with LVEF in NICM patients. The secondary objective was to evaluate the association of EGM characteristics with VT. The following categories of NICM were excluded: congenital heart diseases; hypertrophic cardiomyopathy; arrhythmogenic right ventricular cardiomyopathy (ARVC); and LV noncompaction. In addition, pacing-dependent patients, persistent/ long standing atrial fibrillation patients were excluded for the study. Patients with severe coronary artery disease (≥75% stenosis in one of the epicardial vessels or ≥50% in the

left main vessel) detected by coronary angiogram were excluded. Those patients with incomplete hospital records limiting collection of any meaningful clinical data were also excluded. The study was conducted as per the ethical guidelines of the Declaration of Helsinki and was approved by the Human Research and Ethics Committee of the Canberra Hospital. (2019/ETH13256) A systematic protocol, as detailed in the supplementary material, was followed for electrophysiology study, electroanatomical mapping of left ventricle (LV), and analysis of EGM characteristics.

4.3.1 Study definitions

Patients were classified under the group of VT, if they met one of the following: history of documented sustained monomorphic VT on ECG or Holter recordings or appropriate ICD therapies; inducible sustained monomorphic VT during electrophysiology study in those with history of palpitations or syncope. NICM was defined as those patients with either LV systolic dysfunction (LVEF <50%) or with documented late gadolinium enhancement (LGE) in cardiac MRI, without significant CAD as assessed by on coronary angiography (CAG) and with no history suggestive of myocardial infarction (MI). After corroborative evidence from electrocardiography, echocardiography, cardiac MRI, and genomic assessment, the aetiopathogenesis of NICM was assigned. As per our previously published study,[110] the term mixed CMP was used to categorise patients with LV systolic dysfunction (<50%), a documented non-ischemic aetiology and with moderate CAD (≥50% and <75% stenosis) in one or more of left anterior descending artery (LAD), left circumflex artery (LCX), right coronary artery (RCA), or 30-50% stenosis involving the left main coronary artery. Categorisation of heart failure patients based on LVEF was performed resulting in three distinct categories; heart failure with reduced ejection fraction (HFrEF, LVEF<40%), heart failure with mid-range ejection fraction

(HFmrEF, LVEF between 40-49%), heart failure with preserved ejection fraction (HFpEF, LVEF ≥ 50).[88] The other study definitions are elaborated in the supplementary material.

4.3.2 EGM characteristics:

The following bipolar EGM characteristics were analysed globally and in each of the 17-segments within the LV model: voltage, EGM duration and impedance. The following unipolar EGM characteristics were analysed globally and in each of the 17-segments: voltage, peak positive voltage, peak negative voltage and dv/dt. According to conventional LV endocardial voltage criteria, bipolar voltage <1.5mV was considered as 'Bipolar' low voltage zone (LVZ) and unipolar voltage <8.3mV was considered as 'Unipolar' LVZ.[40,111] Endocardial bipolar voltage <0.5mV was considered as Bipolar scar zone. Extended EGM characteristics namely the percentage area of LVZ and the extent of LVZ were derived based on the above-mentioned EGM variables. Global proportion (%) of abnormal areas (bipolar LVZ<1.5mV, unipolar LVZ<8.3mV, EGM duration>40ms, EGM duration>60ms) at the applied cut-offs to the total LV endocardial surface area was derived automatically from the software. Extent of bipolar LVZ and bipolar scar was defined as number of segments with mean LV endocardial voltage <1.5mV and <0.5mV, respectively. Extent of unipolar LVZ was defined as the number of segments with mean LV endocardial unipolar voltage <8.3mV.

4.3.3 Statistical analysis

Continuous variables which were normally distributed were expressed as mean±SD. Categorical variables were presented as proportions and percentages. MAGGIC score was computed for each patient based on 13 clinical variables.[127] Correlation between continuous variables was tested using Pearson's coefficients (r values). Correlation values were ranked as mild (0-0.3), moderate (0.4-0.6) and high (0.7-1.0). Groups with and without VT were

compared with Chi-square test for categorical variables and Student-t test for continuous variables. Logistic regression analysis was performed for predictors of ventricular tachycardia, considering two covariates per model. Hosmer-and-Lemeshow test was applied to study the goodness of fit for the logistic regression models. Receiver-operating-characteristic (ROC) curves for correct classification of patients with VT, were constructed and the respective area-under-curves (AUC) were analysed. Youden index was used to obtain the cut-offs with best diagnostic accuracies. Differences, correlation-coefficients, and the hazards ratio were considered statistically significant at the two-sided $p<0.05$ level. All the analyses were performed using SPSS Statistics (version 27, IBM, Armonk, New York).

4.4 Results

Prospectively, between November 2018 and November 2021, 69 patients with NICM were referred for evaluation of heart failure symptoms, syncope or cardiac arrest. Of them 58 patients underwent invasive electrophysiological studies with electroanatomical mapping. (Supplementary figure 1) Based on the exclusion criteria for this study, 15 patients were excluded: pacing-dependent (n=3); persistent atrial fibrillation (n=3); hypertrophic cardiomyopathy (n=3); ARVC (n=2); congenital heart disease (n=2); noncompaction (n=1); inadequate segmental voltage mapping (n=1). The characteristics of the 43 patients included in this study are summarized in Table 1. VT was prevalent in 46% (n=20) patients, of which 12 patients had clinically documented VT and 8 patients with history of syncope had inducible sustained monomorphic VT in the electrophysiology study. The EGM characteristics are shown in Table 2. The most common locations of bipolar or unipolar LVZ were basal anteroseptal (63%), followed by basal inferolateral (53%), basal anterolateral (42%), and mid anterior (32%) segments. Only unipolar voltage (r=+0.36), peak negative unipolar voltage (r=-0.42) and peak

positive unipolar voltage (r=+0.38) had good correlations with baseline LVEF. (Supplementary table 1) Among the extended electrogram characteristics, only percentage area of unipolar LVZ (r=-0.41) had good correlation with LVEF. (Supplementary table 2)

All demographic and clinical variables were compared between patients who presented with and without VT. (Table 3, Supplementary Table 3) The mean LVEF was significantly less in patients with VT (38±10% vs 49±9%, p<0.001). The proportion of patients with HFrEF was significantly higher in patients with VT (55% vs 17%, p=0.009). Whereas the proportion of patients with HFpEF was significantly higher in patients without VT (61% vs 5%, p<0.001). (Figure 1A) Patients with VT had significantly lower mean bipolar voltage (2.6±1.4mV vs 3.1±1.6mV, p=0.02), lower mean unipolar voltage (8.3±2.8mV vs 11.5±3.5mV, p<0.001), lower mean peak negative unipolar voltage (-5.2±1.9mV vs -7.2±2.3mV, p<0.001) and lower mean positive unipolar voltage (3.1±1.4mV vs 4.3±1.4mV, p<0.001) than patients without VT. Percentage area of bipolar LVZ (33.5±21% vs 21±13%, p=0.02) and unipolar LVZ (56±20% vs 30±18%, p<0.001) were significantly different between both groups. There was significant difference in the mean extent of unipolar LVZ (8±4 vs 3.1±1.6 segments, p=0.02).

Logistic regression analysis was performed for the predictors of VT. (Table 4) The MAGGIC clinical risk score and the unipolar EGM variables were considered as covariates. MAGGIC score was a significant predictor for VT. Among the unipolar EGM variables, percentage area of unipolar LVZ (HR 1.1 (1.02-1.2)), extent of unipolar LVZ (HR 1.6 (1.1-2.3) and mean unipolar voltage (HR 0.4 (0.2-0.8)) were significant predictors of VT.

ROC-curves for correct classification of patients with VT, were constructed for the extent of bipolar and unipolar LVZ, and for percentage area of bipolar and unipolar LVZ. (Figure 1B; Supplementary table 4; Supplementary figure 1) Extent of unipolar LVZ had AUC of 0.82 (95% CI 0.69-0.95; p<0.001), and percentage area of unipolar LVZ had AUC of 0.83 (95% CI

0.71-0.96; p=0.01). While the differences between the AUC of both these variables were not significant (p=0.61), both these variables had significant differences in AUC as against the extent of bipolar LVZ (0.04 and 0.03 respectively). (Supplementary table 4) The cut-off of 33% for percentage area of unipolar LVZ had the best diagnostic accuracy (sensitivity- 95%; specificity- 60%; Youden index- 0.5) for correct classification of patients with VT. The cut-off of >3 segments for extent of unipolar LVZ had the best diagnostic accuracies (sensitivity- 90%; specificity- 67%; Youden index- 0.6). (Figure 1B) Representative electroanatomical maps in two patients of NICM and VT are shown in Figure 2 and Supplementary figure 2.

In a post-hoc analysis of cardiac MRI parameters in 19 patients of this cohort, there was significant correlation between percentage abnormality detected by longitudinal and circumferential with percentage unipolar LVZ (r=+0.5, p=0.02). While the concordance rates for LGE to localise LVZ was 63%, the concordance rates were better for circumferential strain (79%) and longitudinal strain (95%) derived from cardiac MRI.[103]

4.5 Discussion

Our study demonstrates that in patients with NICM 1) Among the various LV EGM characteristics which were analysed, the unipolar EGM characteristics namely–voltage, peak negative voltage and peak positive voltage had good correlations with baseline LVEF; 2) Global mean unipolar low voltage, extent of unipolar LVZ and percentage area of unipolar LVZ were significant predictors of VT; 3) Cut-offs of >3 segments extent of unipolar LVZ and >33% area of unipolar LVZ had good diagnostic accuracy to classify a NICM patient with VT.

4.5.1 Electrical Arrhythmic Substrate and Endocardial Electrogram characteristics in NICM

While using the binary cut-off of LVEF 35% seems to identify patients who might benefit from ICD therapies in ischemic cardiomyopathy, extending the utility of LVEF for risk stratification in NICM did not result in mortality reduction.[9,106] The inadequacies of using LVEF as a lone risk-stratification tool in NICM has been highlighted in literature.[31,104] Electroanatomical mapping, though an invasive tool, gives immense insight into the altered electrical substrate in NICM. Distribution of scar in NICM is often patchy, involving the mid-myocardium and epicardium.[40,53] Studies have consistently shown that endocardial unipolar voltage, over bipolar voltage, is more representative of deeper intramural substrate abnormalities of NICM found in mid-myocardium and epicardium detected either by CMR-LGE or epicardial mapping.[42,49] In a previous study, unipolar peak-negative voltage independently predicted presence of epicardial LVZ and epicardial dense scar in RV cardiomyopathy patients. In the same study, bipolar voltage and bipolar EGM duration could not predict epicardial dense scar.[50]

In our study, while unipolar EGM characteristics showed good correlation with LV systolic function and for prediction of VT, bipolar EGM characteristics such as voltage, impedance and EGM duration did not show good correlation. Measuring bipolar EGM duration is a good surrogate for understanding slow conduction in the myocardium, and hence could be a useful measure in ischemic cardiomyopathy.[109] However, our study revealed that bipolar EGM duration had a poor correlation with LVEF and VT in NICM. This is conceivable as deeper substrate abnormalities in NICM may not be represented by endocardial bipolar EGM.[37]

4.5.2 Prognostic implications of unipolar low voltage zones in NICM

A study on 24 patients with NICM, showed a cut-off of 32% area of unipolar LVZ was derived to identify irreversible cardiomyopathy.[41] In another study, endocardial unipolar LVZ >54% area of LV predicted cardiac mortality and VT recurrence.[51] In our study, endocardial unipolar LVZ >33% area of LV had a sensitivity of 95% to correlate with occurrence of VT. In addition, extent of unipolar LVZ >3 segments had a sensitivity of 90% to correlate with occurrence of VT.

4.5.3 Search for novel risk-stratification tools

In a subset of patients recruited in this study, we had shown strong association of CMR-strain with endocardial unipolar voltages.[103] Similarly, CMR T1 mapping values has been shown to have a strong correlation with unipolar low voltage areas in a study on NICM patients undergoing VT ablation.[48] We are in the era where there is an extensive search for a risk-stratification tool that could serve as an alternative and better marker than LVEF to predict SCD such as certain genetic mutations,[3] LGE assessment by CMR,[44] newer CMR modalities like T1 mapping, ECV estimation and Fast-strain encoded CMR.[33,55,113]

4.5.4 Clinical implications

Our study highlights those parameters measuring the distribution of unipolar LVZ such as global mean unipolar voltage, extent of segments involved, and percentage area of involvement have significant association with VT. This can help choose the high ventricular arrhythmic-risk patients who will benefit from ICD therapy irrespective of underlying LVEF. Moreover, noninvasive tools like body surface mapping and cardiac MRI can be validated against the parameters mentioned in this study for prediction of VT.[103]

4.5.5 Limitations

The results must be interpreted in the background of a small sample size, limited power, and observational cross-sectional study design. Cut-offs of bipolar and unipolar voltage, though have been adopted by conventional criteria, can be variable depending on the myocardial thickness, mapping catheter used and density of mapping. Association between EGM variables and long-term outcomes like all-cause mortality, ventricular arrhythmias, sudden cardiac death, heart transplant, and heart failure hospitalizations could not be performed as the events were very less in the short follow-up of 12 months. The presence of VT does not necessarily reflect the risk of SCD and the indication for ICD in patients with NICM.

4.6 Conclusion

Our study concludes that in patients with NICM, unipolar electroanatomical parameters namely the global mean unipolar voltage of LV endocardium, the extent of distribution and the percentage area of unipolar low voltage zones have good correlation with LVEF and strong association with VT. These tools can be useful surrogates for risk stratification. They can also be used to validate noninvasive markers like cardiac MRI parameters.

4.7 Figure legends

Figure 4-1: Panel A shows the distribution of heart failure patients according to categories of ejection fraction in patients of non-ischemic cardiomyopathy with and without ventricular tachycardia, HFrEF- heart failure with reduced ejection fraction; HFmrEF- Heart Failure with mid-range ejection fraction; HFpEF- heart failure with preserved ejection fraction. Panel B is the Receiver-Operating-Characteristic (ROC) curve for extent of bipolar and unipolar low voltage zones (LVZ) for prediction of ventricular tachycardia, the area-under-curve (AUC) and the best diagnostic accuracies for the curves are shown in the inset

Figure 4-2: Electro-anatomical maps of a 54-year female with sarcoid-related non-ischemic cardiomyopathy, mid-range ejection fraction and presentation with ventricular tachycardia. Bipolar voltage map is shown on the left and unipolar voltage map on the right, respective polar plot maps of the 17-segment left ventricular model are shown in the bottom row,

sample points with bipolar and unipolar electrograms (EGM) and respective voltages are shown with white arrows, extent and percentage area of LVZ is mentioned next to the polar plots.

Table 4-1: Baseline variables in 43 patients of Non-ischemic cardiomyopathy

Variables	Frequency	Variables	Frequency
Age (years)	62±12	Dyspnoea	22 (51)
Male	24 (56)	Syncope	9 (21)
Female	19 (44)	Cardiac arrest	6 (14)
Cardiac MRI	23 (54)	Diabetes	11 (26)
NYHA Class I	12 (28)	Hypertension	10 (23)
NYHA Class II	21 (49)	CAD	3 (7)
NYHA Class III	10 (23)	CKD	2 (5)
NICM- Idiopathic	20 (47)	OSA	5 (12)
NICM- Sarcoid	4 (9)	Familial	4 (9)
NICM- Genetic	4 (9)	Hemoglobin (g/dl)	13.9±1.6
NICM- Mixed	3 (7)	Creatinine (mg/dl)	0.84±0.19
NICM- Others	12 (28)	NT-proBNP (pg/ml)	201±126
Atrial arrhythmias	8 (19)	Heart rate (per minute)	80±13
Ventricular tachycardia	20 (46)	Systolic blood pressure (mmHg)	127±17
Documented VT	12 (28)	Betablockers	38 (88)
Inducible VT	8 (19)	Spironolactone	36 (84)
RFA for AT/AF	5 (12)	SGLT2 inhibitors	22 (51)
RFA for PVC/ VT	22 (51)	ACEi/ ARNi/ ARB	43 (100)
LVEF (%) (baseline)	44.9±12	Antiarrhythmics	5 (12)
LVEF (%) (6 months)	45±8	Device	36 (84)
LVEF (%) (1 year)	51±9	ICD	21 (48)
LVEDVi	85±8	CRT-d	15 (36)
LVESVi	41±16	QRS duration	119±28
RVEF (%)	51±5	QTc interval	438±46
LAVi	33±7	MAGGIC score	30±14
PA systolic pressure (mmHg)	49±7	HFrEF	15 (35)
Grade of Tricuspid regurgitation	1.7±0.5	HFmrEF	13 (30)
Grade of Mitral regurgitation	1.2±0.4	HFpEF	15 (35)

- P values <0.05 have been denoted as * for the significant differences between ICM and NICM groups, + for the significant differences between mixed CMP and ICM groups, $ for the significant differences between Mixed CMP and NICM groups
- Categorical variables are presented as frequencies (proportions in % within parenthesis), Continuous variables are presented as mean ± standard deviation with 95% confidence intervals
- MRI- Magnetic Resonance Imaging; NYHA- New York Heart Association classification; ICD-Implantable Cardioverter-Defibrillator; CRT-d Cardiac Resynchronisation Therapy with defibrillator; VT- Ventricular tachycardia; AT- Atrial tachycardia; AF- Atrial fibrillation; RFA- Radiofrequency Ablation; LVEF- Left Ventricular Ejection Fraction; LVEDVi- left ventricular end diastolic volume index; LVESVi- left ventricular end systolic volume index; RVEF- right ventricular ejection fraction; LAVi- left atrial volume index; PA- pulmonary artery; CAD- Coronary Artery Disease; CKD_ Chronic Kidney Disease; OSA- Obstructive Sleep Apnoea; NT- proBNP- NT pro Brain Natriuretic Peptide; ACEi- Angiotension Converting Enzyme inhibitor; SGLT2- Sodium Glucose cotransporter-2; ARNi- Angiotensin Receptor and Neprilysin inhibitor; ARB- Angiotensin Receptor Blocker; HFrEF- heart failure with reduced ejection fraction; HFmrEF- Heart Failure with mid-range ejection fraction; HFpEF- heart failure with preserved ejection fraction

Table 4-2: Bipolar and Unipolar Electrogram characteristics in the 43 patients with Non-ischemic cardiomyopathy

Variables	Frequency	Variables	Frequency
Total points	964±574 (410-3500)	No. of pts. with Bipolar LVZ	29 (67)
LV Area (sq.mm)	146±130 (87-236)	No. of pts. with Unipolar LVZ	37 (86)
Map density (points per sq.mm)	7.5±7 (range: 0.73-30)	Extent of Bipolar LVZ (per 17 segments)	3.1±2.1
Bipolar voltage (mV)	2.9±1.5	Extent of Unipolar LVZ (per 17 segments)	5.3±4.4
EGM duration (ms)	44±5	% Area of Bipolar LVZ	27±18
Impedance (ohms)	148±14	% Area of Bipolar Scar	5.4±7
Unipolar dv/dt	-1.2±0.6	% Area of Unipolar LVZ	43±23
Unipolar voltage (mV)	9.9±3.2	% Area of EGM duration >40ms	62±41
Peak Negative Unipolar voltage (mV)	-6.2±2.2	% Area of EGM duration >60ms	0.8±1.2
Peak Positive Unipolar voltage (mV)	3.7±1.3		

- Categorical variables are presented as frequencies (proportions in % within parenthesis), Continuous variables are presented as mean ± standard deviation with 95% confidence intervals
- LV- Left ventricle; LVZ- low voltage zone; No.- Number; pts.- patients

Table 4-3: List of clinical variables and electrogram characteristics with significant differences between patients with and without ventricular tachycardia

Variables	Patients with VT (n=20)	Patients without VT (n=23)	P Value
Diabetes mellitus	9 (45)	2 (9)	0.01*
Mean Creatinine (mg/dl)	0.91±0.17	0.78±0.19	0.04*
Mean LVEF (%)	38±10	49±9	<0.001*
Mean LVEF (%) at 6 months (n=17)	39±9	49±4	0.007*
Mean LVEF (%) at 1 year (n=14)	43±5	55±8	0.02*
HFrEF	11 (55)	4 (17)	0.009*
HFpEF	1 (5)	14 (61)	<0.001*
Mean Bipolar voltage (mV)	2.6±1.4	3.1±1.6	0.02*
Mean Unipolar voltage (mV)	8.3±2.8	11.5±3.5	<0.001*
Mean Unipolar peak negative voltage (mV)	-5.2±1.9	-7.2±2.3	<0.001*
Mean Unipolar peak positive voltage (mV)	3.1±1.4	4.3±1.4	<0.001*
% Area of Bipolar LVZ	33.5±21	21±13	0.02*
% Area of Unipolar LVZ	56±20	30±18	<0.001*
Extent of Unipolar LVZ	8±4	3.1±1.6	0.02*

- P values <0.05 have been denoted as * for the significant differences between the 2 groups
- Categorical variables are presented as frequencies (proportions in % within parenthesis), Continuous variables are presented as mean ± standard deviation with 95% confidence intervals
- LVEF- Left Ventricular Ejection Fraction; HFrEF- heart failure with reduced ejection fraction; HFmrEF- Heart Failure with mid-range ejection fraction; HFpEF- heart failure with preserved ejection fraction; EGM- electrogram; LVZ- low voltage zone
- Variables not listed: Age; Males; Females; Hypertension; Mean Hemoglobin; AF ablation; HFmrEF; Patients with Bipolar LVZ; Mean EGM duration; Mean Impedance; Mean Unipolar dv/dt; Percentage Bipolar scar; Percentage EGM duration>40ms; Percentage EGM duration>60ms; Extent of Bipolar LVZ

Table 4-4: Logistic regression analysis for the predictors of ventricular tachycardia in patients with non-ischemic cardiomyopathy

Model 1*		
Covariates	**P value**	**Hazards ratio**
MAGGIC score[$]	0.03	1.2 (1.02-1.3)
Percentage area Unipolar low voltage zone	0.009	1.1 (1.02-1.2)
Model 2		
MAGGIC score	0.02	1.2 (1.02-1.4)
Extent of Unipolar low voltage zone	0.006	1.6 (1.1-2.3)
Model 3		
MAGGIC score	0.03	1.2 (1.01-1.3)
Mean Unipolar voltage	0.008	0.4 (0.2-0.8)
Model 4		
MAGGIC score	0.03	1.1 (1.01-1.3)
Presence of Unipolar low voltage zone	0.9	-

*Regression analysis was performed for unipolar electrogram variables and MAGGIC score
$ MAGGIC score based on age, gender, creatinine, body mass index, left ventricular ejection fraction, NYHA symptom class, systolic blood pressure, smoking status, diabetes, chronic lung diseases, betablockers, use of ACE inhibitors and duration of heart failure symptoms; Lower and upper 95% confidence intervals of the hazards ratio are mentioned in the paranthesis

Figure 4-1: Panel A shows the distribution of heart failure patients according to categories of ejection fraction in patients of non-ischemic cardiomyopathy with and without ventricular tachycardia, HFrEF- heart failure with reduced ejection fraction; HFmrEF- Heart Failure with mid-range ejection fraction; HFpEF- heart failure with preserved ejection fraction. Panel B is the Receiver-Operating-Characteristic (ROC) curve for extent of bipolar and unipolar low voltage zones (LVZ) for prediction of ventricular tachycardia, the area-under-curve (AUC) and the best diagnostic accuracies for the curves are shown in the inset

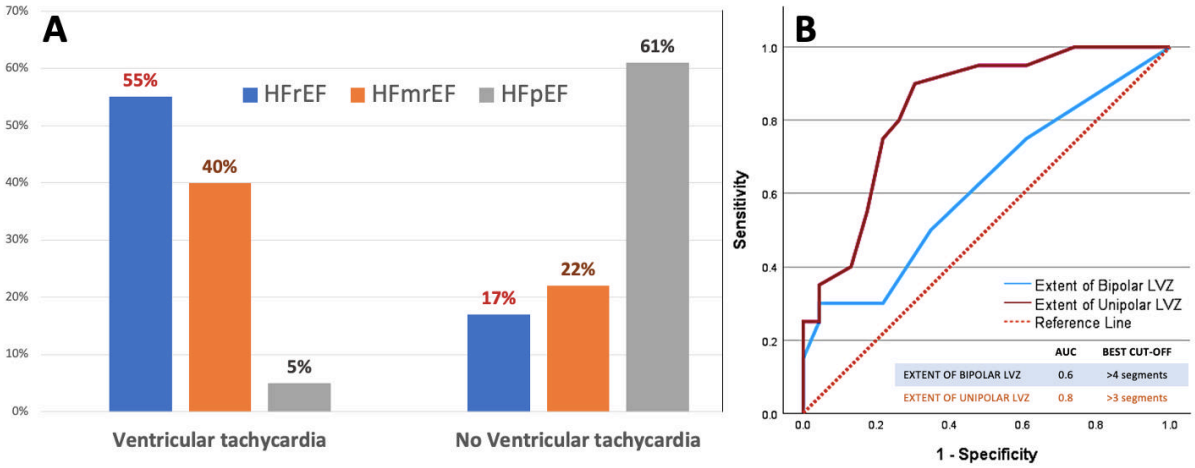
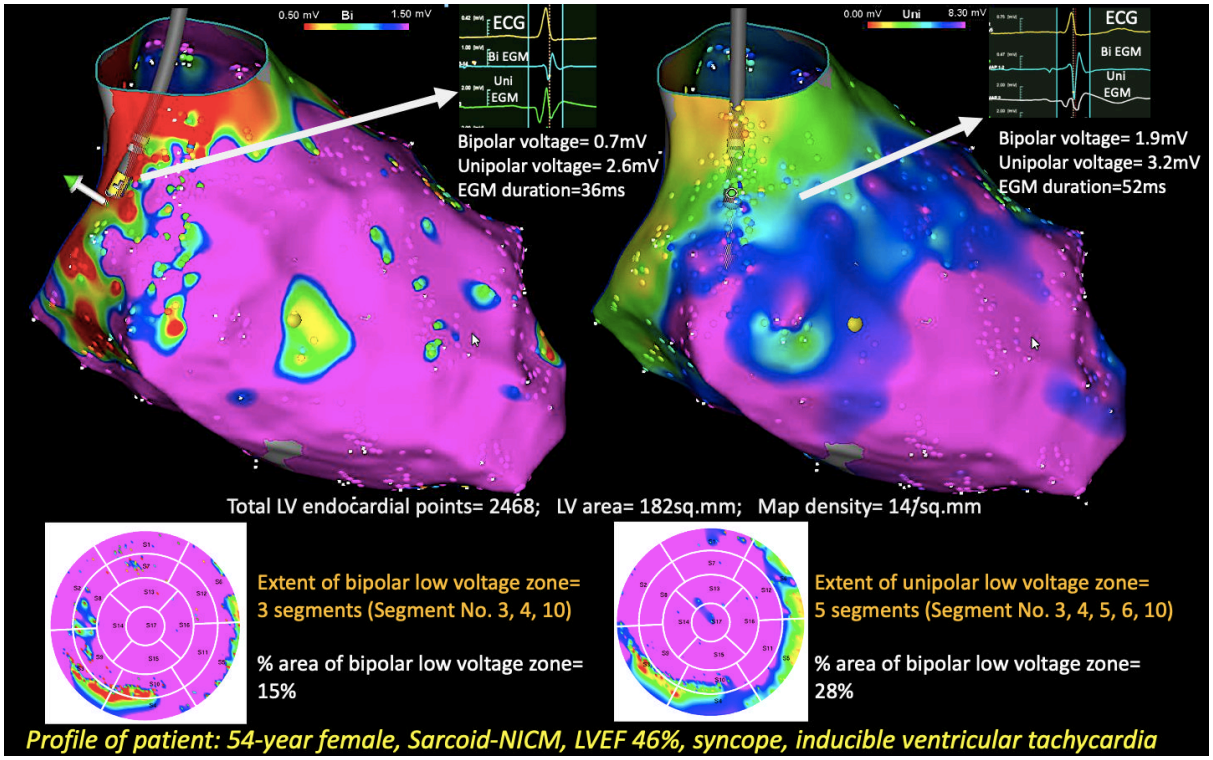


Figure 4-2: Electro-anatomical maps of a 54-year female with sarcoid-related non-ischemic cardiomyopathy, mid-range ejection fraction and presentation with ventricular tachycardia. Bipolar voltage map is shown on the left and unipolar voltage map on the right, respective polar plot maps of the 17-segment left ventricular model are shown in the bottom row, sample points with bipolar and unipolar electrograms (EGM) and respective voltages are shown with white arrows, extent and percentage area of LVZ is mentioned next to the polar plots.



Supplementary material

Figure 4-3: Supplementary figure 1: Flowchart showing the selection of the final cohort of 43 patients of Nonischemic cardiomyopathy.

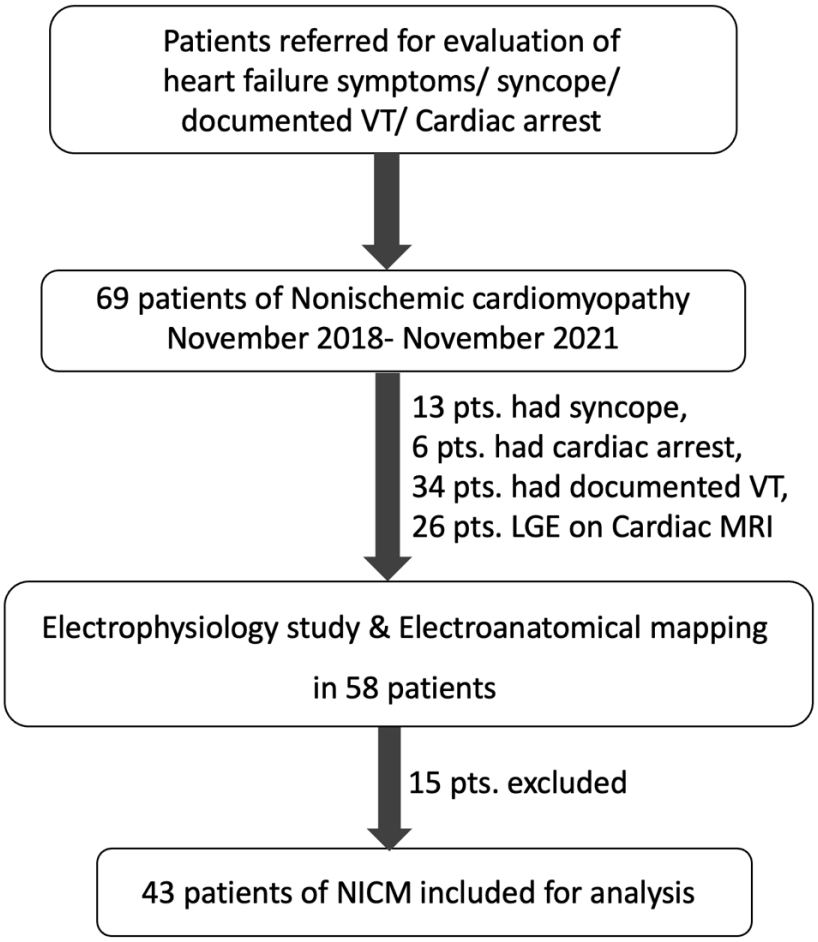


Figure 4-4: Supplementary figure 2: Receiver-Operating-Characteristic (ROC) curve for percentage areas of unipolar LVZ and the extent of bipolar and unipolar low voltage zones (LVZ) for prediction of ventricular tachycardia, the area-under-curve (AUC) and the best diagnostic accuracies for the curves are shown in the inset.

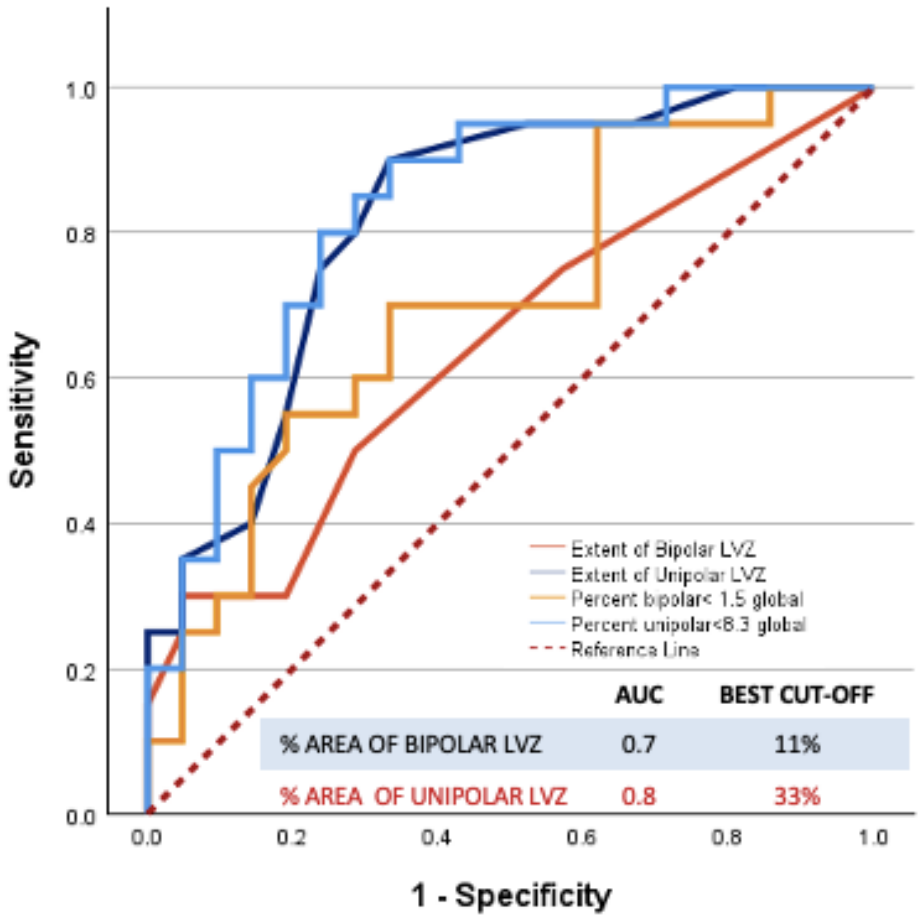


Figure 4-5: Supplementary figure 3:Electro-anatomical maps of a 47-year male with idiopathic non-ischemic cardiomyopathy, reduced ejection fraction and presentation with ventricular tachycardia. Bipolar voltage map is shown on the left and unipolar voltage map on the right, sample points with bipolar and unipolar electrograms (EGM) and respective voltages are shown with white arrows, extent and percentage area of LVZ is mentioned in the bottom-row.

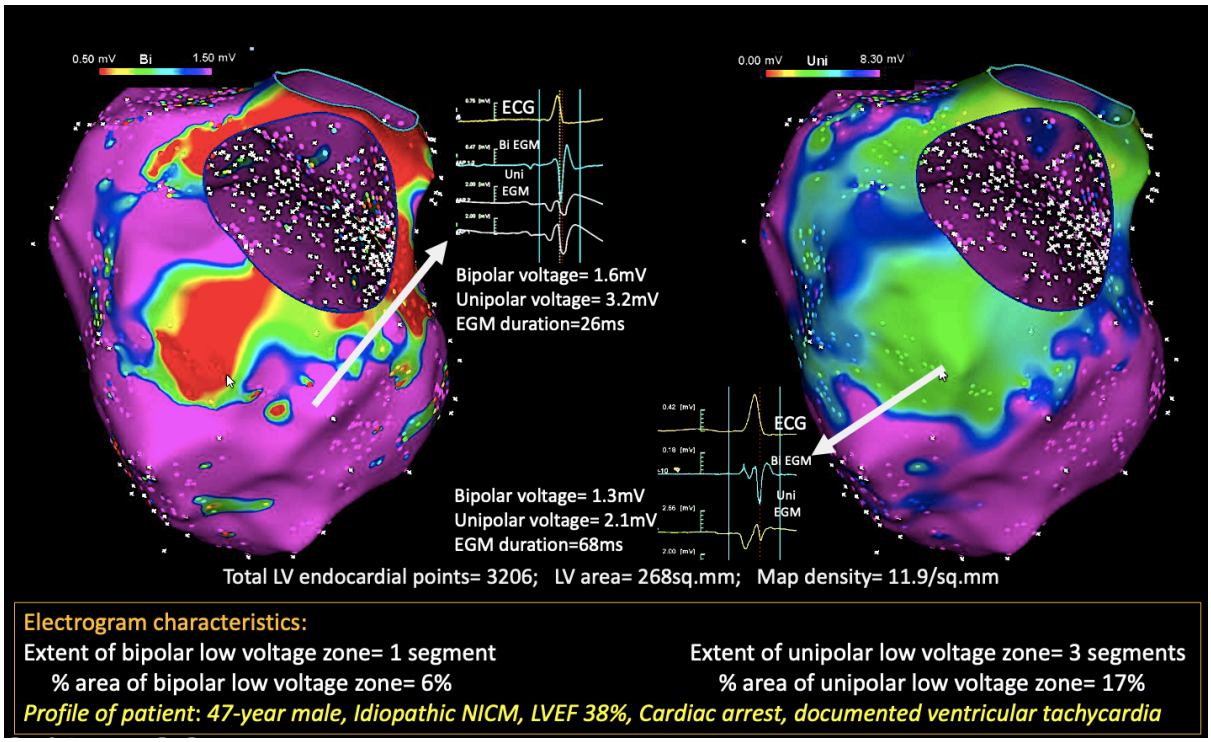


Table 4-5 Supplementary table 1: Correlation of Bipolar and Unipolar electrogram characteristics with left ventricular ejection fraction

	LVEF	Bipolar voltage	EGM duration	Impedance	Unipolar dv/dt	Peak Negative Unipolar voltage	Peak Positive Unipolar voltage	Unipolar voltage
LVEF		+0.13	+0.24	-0.01	-0.23	**-0.42***	**+0.38***	**+0.36***
Bipolar voltage	+0.13		-0.33	+0.39*	-0.72*	-0.48*	+0.53*	+0.51*
EGM duration	+0.24	-0.33		-0.04	+0.21	-0.14	+0.23	+0.24
Impedance	-0.01	+0.39*	-0.04		+0.15	-0.06	+0.3	+0.2
Unipolar dv/dt	-0.23	-0.72*	+0.21	+0.15		+0.58*	-0.42*	-0.53*
Peak negative Unipolar voltage	**-0.42***	-0.48*	-0.14	-0.07	+0.58*		-0.89*	-0.91*
Peak positive Unipolar voltage	**+0.38***	+0.53*	+0.23	+0.3	-0.42*	-0.89*		+0.93*
Unipolar voltage	**+0.36***	+0.51*	+0.24	+0.2	-0.53*	-0.91*	+0.93*	

- Significant correlation with P values <0.05 have been denoted as *
- LVEF- left ventricle ejection fraction, EGM- electrogram

Table 4-6 Supplementary table 2: Correlation of Extended Bipolar and Unipolar electrogram characteristics with left ventricular ejection fraction

Variables	LVEF	% Area Bipolar LVZ	% Area Bipolar Scar	% Area Bipolar LVA	% Area Unipolar LVZ	% Area EGM duration >40ms	% Area EGM duration >60ms
LVEF		+0.03	+0.13	-0.03	-0.41*	+0.19	+0.01
% Area of Bipolar LVZ	+0.03		+0.78*	+0.91*	+0.48*	+0.32	+0.41*
% Area of Bipolar Scar	+0.13	+0.78*		+0.73*	+0.32	+0.22	+0.41*
% Area of Bipolar LVA	-0.03	+0.91	+0.73*		+0.58*	+0.13	+0.44*
% Area of Unipolar LVZ	-0.41*	+0.48*	+0.32	+0.58*		+0.02	+0.21
% Area of EGM duration >40ms	+0.19	+0.32	+0.22	+0.13	+0.02		+0.51*
% Area of EGM duration >60ms	+0.01	+0.41*	+0.41*	+0.44*	+0.21	+0.51*	

- Significant correlation with P values <0.05 have been denoted as *
- LVEF- left ventricle ejection fraction, LVZ- Low voltage zone; LVA- Low voltage area

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Table 4-7 Supplementary table 3: Comparison of clinical variables and electrogram characteristics between patients with and without ventricular tachycardia

Variables	Patients with VT (n=20)	Patients without VT (n=23)	P Value
Age (years)	64±12	60±11	0.3
Males	12 (66)	12 (52)	0.7
Females	8 (40)	11 (47)	0.7
Diabetes mellitus	9 (45)	2 (9)	0.01*
Hypertension	4 (20)	6 (26)	0.7
Coronary artery disease	2 (10)	2 (9)	1
Chronic kidney disease	1 (5)	1 (4)	1
Smoking	3 (15)	2 (9)	0.6
Alcohol	1 (5)	1 (4)	1
Familial cardiomyopathy	2 (10)	3 (13)	1
Mean Hemoglobin g/dl	13.7±1.4	14.0±1.7	0.7
Mean Creatinine mg/dl	0.91±0.17	0.78±0.19	0.04*
AF ablation	2 (10)	3 (13)	1
Mean LVEF (%)	38±10	49±9	<0.001*
Mean LVEF (%) at 6 months (n=17)	39±9	49±4	0.007*
Mean LVEF (%) at 1 year (n=14)	43±5	55±8	0.02*
HFrEF	11 (55)	4 (17)	0.009*
HFmrEF	8 (40)	5 (22)	0.2
HFpEF	1 (5)	14 (61)	<0.001*
Patients with Bipolar LVZ	15 (75)	14 (60)	0.3
Patients with Unipolar LVZ	17 (85)	20 (86)	0.4
Mean Bipolar voltage (mV)	2.6±1.4	3.1±1.6	0.02*
Mean EGM duration (ms)	43±4.2	44±4.5	0.4
Mean Impedance (ohms)	145±14	151±13	0.5
Mean Unipolar voltage (mV)	8.3±2.8	11.5±3.5	<0.001*
Mean Unipolar peak negative voltage (mV)	-5.2±1.9	-7.2±2.3	<0.001*
Mean Unipolar peak positive voltage (mV)	3.1±1.4	4.3±1.4	<0.001*
Mean Unipolar dv/dt	-1.1±0.5	-1.2±0.6	0.1
% Area of Bipolar LVZ	33.5±21	21±13	0.02*
% Area of Bipolar scar	8.7±6.7	5.2±4.3	0.2
% Area of Unipolar LVZ	56±20	30±18	<0.001*
% Area of EGM duration>40ms	55±42	67±40	0.3
% Area of EGM duration>60ms	1.4±0.8	1.2±0.8	0.9
Extent of Bipolar LVZ	4±3	3±3	0.08
Extent of Unipolar LVZ	8±4	3.1±1.6	0.02*

- P values <0.05 have been denoted as * for the significant differences between the 2 groups
- Categorical variables are presented as frequencies (proportions in % within parenthesis), Continuous variables are presented as mean ± standard deviation with 95% confidence intervals
- LVEF- Left Ventricular Ejection Fraction; HFrEF- heart failure with reduced ejection fraction; HFmrEF- Heart Failure with mid-range ejection fraction; HFpEF- heart failure with preserved ejection fraction; EGM- electrogram; LVZ- low voltage zone

Table 4-8 Supplementary table 4: Significance of Area-under-curves for the EGM variables

EGM variable	AUC (95% C.I)	p value	Paired p value *
Percentage area of Unipolar LVZ	0.83 (0.71-0.96)	0.01	0.03
Extent of Unipolar LVZ	0.82 (0.69-0.95)	<0.001	0.04
Percentage area of Bipolar LVZ	0.70 (0.54-0.86)	0.01	0.37
Extent of Bipolar LVZ	0.64 (0.47-0.81)	0.09	-
EGM- electrogram; LVZ- low voltage zone: * comparison against extent of bipolar LVZ			

4.8 Appendix- Data collection:

1. Name, age, gender, treating physician, history of diabetes, hypertension, chronic kidney disease (CKD), lung disease, malignancy, alcohol/ drug abuse.
2. Kidney functions namely serum creatinine and estimated glomerular filtration rate (eGFR) and echocardiographic findings including type and severity of valve pathologies.
3. LVEF was calculated based on biplane Simpson's method by an experienced echocardiographer. LVEF was studied at 6 months and 1 year follow-up.
4. Left ventricular ejection fraction (LVEF) at time of inclusion were recorded. LVEF at 6 months and 1-year follow-up was also recorded.
5. History of coronary artery disease (CAD)/ myocardial infarction (MI)/ type of MI- ST elevation (STEMI) and non-ST elevation (NSTEMI)/ percutaneous coronary intervention (PCI)/ history of bypass surgery/ valve replacement/ major non-vascular surgeries
6. Documented arrhythmias- supraventricular (inclusive of atrial flutter and fibrillation) and ventricular (shockable rhythms like ventricular fibrillation, monomorphic and polymorphic ventricular tachycardias)
7. List of anti-arrhythmic and heart failure medications
8. Symptoms of syncope or sudden cardiac arrest (SCA) or documented VT
9. History of radiofrequency ablation (RFA) for supraventricular tachycardia and VT
10. Type of device implant: Defibrillator (ICD) or cardiac resynchronisation therapy (CRT)

Study definitions:

The major study definitions are detailed in the main manuscript. Additional definitions are following:

1. Syncope was defined as a witnessed episode of loss of consciousness associated with loss of postural tone with spontaneous recovery.
2. Sudden cardiac arrest (SCA) was defined as out-of-hospital events of successful cardio-pulmonary resuscitation with or without direct current shocks delivered by an external cardioverter-defibrillator.
3. Non-sustained ventricular tachycardia (NSVT) was defined as ≥ 3 consecutive ventricular premature beats with a rate >100 beats/min, lasting < 30 s and without hemodynamic instability. NSVT should have been documented during exercise testing, loop monitoring or 24-h Holter monitoring.
4. Diabetes mellitus and hypertension were considered if the patient was on long standing medications for treatment of these conditions.
5. Chronic kidney disease was diagnosed if the patients were already categorised so by the treating physician based on evidence of kidney damage like elevated serum creatinine or reduced estimated glomerular filtration rate (<60ml/mt/1.73sq.mt) with or without ongoing haemodialysis.
6. Chronic lung disease was diagnosed if the patients were already categorised so by the treating physician based on evidence of suggestive clinical symptoms requiring treatment for the same.
7. Malignancy was diagnosed if the patients were already categorised so by the treating physician based on evidence of clinical symptoms, biochemical markers or imaging evidence requiring one or more of chemotherapy or radiation therapy or surgical removal. The organ involved was also noted.

8. The categories of NICM were as follows: post-myocarditis sequelae, sarcoidosis, infiltrative cardiomyopathy (amyloidosis, hemochromatosis), valvular heart disease (severe valvular stenosis/ regurgitation leading to dilatation of heart and low LVEF), alcohol-related (documented alcohol abuse or dependence leading to deterioration in LVEF), and chemotherapy-related cardiomyopathy. Patients with no known aetiology other than those stated above, but with LVEF ≤35%, were classified as idiopathic dilated cardiomyopathy (DCM).
9. Coronary artery disease (CAD) was defined by the presence of stenosis ≥50% on coronary angiography (CAG) in at least one of three major epicardial vessels or ≥30% in the left main vessel. Lesions were graded visually by two cardiologists on the following ordinal scale: 0% to <50%, ≥ 50% to <75%, ≥ 75% and 100%. Patients with severe CAD (≥ 75%) were excluded from the study.

Electro-anatomical mapping and catheter ablation:

All antiarrhythmic drugs were discontinued routinely at least 5 days before the procedure. VT induction was attempted in all patients with programmed ventricular stimulation with triple extra-stimuli from at least two right ventricular (RV) or left ventricular (LV) sites with at least two drive cycle lengths. Induced VTs were identified as clinical if they matched the 12-lead ECG or the cycle length and morphology of the stored electrograms from the ICD when available. Contact force sensing catheters were also used for ablation. The primary endpoint for ablation was elimination of the clinical VT and all mappable nonclinical VT.

Electro-anatomical map of the endocardial LV was performed using the CARTO 3 Version 7 mapping system (Biosense Webster) using a multi-electrode mapping catheter (PENATRAY™, Biosense Webster). Three-dimensional (3D) LV geometry was reconstructed by intracardiac echocardiography (ICE; 64-element, 5.5 to 10Hz; SOUNDSTAR™, CARTOSOUND™ module Biosense Webster, La Jolla, California, USA). The geometry created whilst using ICE was registered to an endocardial 3D shell of LV acquired by the mapping catheter. High density mapping of the LV was performed at all the segments of the LV. The low voltage zones were verified further by a point-by-point mapping using a deflectable 3.5-mm irrigated-tip mapping catheter with contact force (THERMOCOOL SMARTTOUCH-SF™, Biosense Webster) during sinus rhythm. Geometry, bipolar and unipolar EGMs were simultaneously recorded, and all segments of the ventricle were sampled. The mitral and aortic annuli were defined by ICE. In addition, the mitral annulus was verified as that with a 1:1 ratio between atrial and ventricular EGMs. Low voltage points acquired with <3g contact force, <10mm from the endocardial shell, points with unstable cycle length, points within 1 cm of the aortic and mitral valve annulus were all excluded from analysis. Bipolar signals were filtered at 30 to 400 Hz. Unipolar signals were measured between the tip electrode and Wilson-central terminal and were filtered at 1 to 240 Hz. The fill threshold was set to 10 mm.

Analysis of Electrogram characteristics:

The raw electro-anatomical datasets were exported from the CARTO system and imported into the open-source platform, 'EPLab Research Works' application (www.eplabworks.com). Automatic annotation of all EGMs and automatic segmentation of the LV into 17-segments was performed.[13] Stable baseline QRS was set as the reference. The annotations were manually checked for accuracy and the landmarks for LV segmentation were verified by an experienced electrophysiologist. All pacing artifacts and catheter-

induced PVCs were excluded from the EGM annotations. Discrepancy in adjacent points within the same segment was resolved by deleting points with low voltage or artifacts. Onset and offset of bipolar EGM duration was calculated on the software with a set SD-window of 40ms and SD-threshold of 10%.[14] Detailed segmental and global analysis of all electrogram characteristics was performed in each segment.

Chapter 6: Future directions

6.1 Current Sudden Cardiac Death Risk-prediction Models in DCM

While SCD risk-prediction models have been developed for hypertrophic cardiomyopathy, there is still a search for a model with good predictive accuracies in DCM.

The Seattle Heart Failure Model incorporated age, gender, NYHA class, ischemic heart disease, diuretic dose, LVEF, systolic blood pressure, serum sodium, serum hemoglobin, percent lymphocytes, serum uric acid, and serum cholesterol.[126] This model showed good prediction of mortality with a receiver-operating-characteristic area-under-curve of 0.72 (95% CI 0.71 to 0.74). The predicted versus actual 1-year survival rates was 73.4% versus 74.3% in the derivation cohort and 90.5% versus 88.5% in the validation cohorts. An interactive algorithm was developed which allowed estimation of the benefit of adding medications or devices to the patient. However, this model was derived from studies prior to 2005, and did not incorporate biomarkers like BNP or IL-6, ECG parameters and imaging characteristics.

6.2 The Meta-analysis Global Group in Chronic Heart Failure

(MAGGIC) risk-model included age, gender, lower EF, NYHA class, serum creatinine, diabetes, beta-blocker, ACE-inhibitor or angiotensin-receptor blockers, systolic blood pressure, body mass index, time since diagnosis, smoking, chronic obstructive pulmonary disease.[127] The predicted and observed mortality matched each other when the model was applied to the general population. In the preserved EF group, the receiver-operating-characteristic area-under-curve was 0.74 (95% CI 0.68 to 0.80) and similar to the Seattle HF model. However, this model does not consider biomarkers like BNP or IL-6, ECG parameters, echo and CMR findings.

The Barcelona Bio Heart Failure risk calculator included biomarkers (hs-cTnT, ST2, and NT-proBNP) in addition to the variables in the Seattle HF model.[128] The c-statistic analysis using this model was 0.82 and better than the earlier models, emphasizing the utility of adding biomarkers to the risk-stratification tools. Improving upon the previous models, ***the Krakow DCM Risk Score*** incorporated sex, age, symptoms duration and severity, comorbidities (diabetes mellitus, stroke, liver and kidney diseases, dyslipidaemia, anaemia), biomarker namely NT-proBNP, ECG parameter namely LBBB, echocardiography parameters namely LV

size and LVEF, HF medicines and CRT.[129] The model had good discriminatory power with an AUC ranging from 0.71 to 0.77 for 1-, 2-, 3-, 4- and 5-year mortality.

A SCD prediction model has been derived and validated in a combined analysis of 2 large US-based cohorts (ARIC and CHS) with more than 17,000 subjects. The model included 12 independent risk factors namely age, male gender, black race, smoking, diabetes mellitus, systolic blood pressure, use of antihypertensive medication, high-density lipoprotein, serum potassium, serum albumin, estimated glomerular filtration rate, and QTc interval. This model showed good to excellent discrimination for SCD risk (c-statistic 0.820 in ARIC cohort and 0.745 in CHS cohort).[11]

6.3 Challenges in using Machine Learning (Artificial Intelligence, AI) for SCD risk prediction

ML goes by the adage garbage-in and garbage-out. Though most ML models show good discriminative value in internal validation, the results may not the generalisable, as the outcomes applies to the derivation data used in ML. This lack of external validation is a major drawback. To achieve a good model, a large and diverse dataset is desirable for training. However, given the low incidence rates of SCD in the general population, it is difficult to obtain such a large dataset. This would result in 'overfitting' outcomes and poor generalisability. In choosing datasets, identifying patients at a high risk of SCD after accounting for the competing modes of death is important for accurate prediction and prevention.[130]

Nevertheless, ECG-AI and CMR-based ML models have been introduced to predict SCD in cardiomyopathies. A recently introduced ECG-AI index had significant independent association with SCD (adjusted HR 1.25; 95% CI, 1.04–1.4) and had better discriminatory power when added to conventional parameters like LVEF and symptom class, in both ischemic and nonischemic subgroups.[131] A CMR-based ML model had reasonable AUC of 0.72 to predict appropriate ICD chocks and SCD at 5 years in 122 patients with ischaemic cardiomyopathy and EF <35%.[132]

6.4 Need for a Composite SCD Risk-stratification model in NICM (Table 6-1)

None of the risk-prediction models described earlier seem to incorporate clinical, biomarker levels, genetic risk markers, ECG characteristics along with imaging-derived risk

stratification tools, echocardiography and CMR features. Such an inclusive composite model can result in higher diagnostic accuracies. Based on our key analyses derived from our studies, we propose to include a a wide range of variables, as listed in the table, in an effort develop a comprehensive and composite SCD-risk prediction model in NICM. This model needs to be prospectively validated and compared with the existing sudden cardiac death risk scores in NICM.

6.5 Future directions

1. The phenotype of Heart failure with mid-range ejection fraction (HFmrEF) is largely unexplored. Risk of cardiovascular deaths in this category and the needed risk-stratification tools needs to be studied. Adoption of a standard reporting guideline on long-term outcomes with respect to the clinically relevant confounders could reduce the level of heterogeneity between studies. Transition in LVEF needs to be considered while analysing the outcomes in chronic heart failure. Additional risk-stratification tools should be aggressively sought to understand better the similarities and differences between HFmrEF and HFpEF.
2. The phenotype of 'mixed cardiomyopathy' is relatively new and waiting to be analysed in great depths. The influence of concomitant coronary artery disease in patients with NICM cannot be underestimated. This phenotype of mixed cardiomyopathy seems to have a poor prognosis, as explored in our study. Large-scale studies focusing on this phenotype need to assess the mediators of poorer prognosis due to underlying pathophysiological substrate and the associated coexisting illnesses. The influence of CAD in patients with heart failure can be better studied with novel tools like nuclear myocardial perfusion studies. The association of such perfusion abnormalities with outcomes in this subset of patients can give better insights.
3. The cut-offs that we have defined for the extent of distribution of endocardial unipolar voltage abnormalities and its association with VT need to be prospectively validated in NICM cohorts.
4. A composite tool of cardiac MRI parameters incorporating LGE, strain, and T1 indices needs to be analysed for prediction of SCD in NICM, irrespective of LVEF.

5. A composite risk-stratification score as detailed in chapter 6, must be validated internally in our ICD recipients. Then the risk-model will be used prospectively on NICM patients to study the risk of SCD.
6. Conduction system pacing (CSP) is rapidly evolving. His bundle pacing is effective, albeit lead implantation has significant technical challenges. Hence, it failed to become mainstream. Left bundle branch pacing (LBBP) has been shown to be safe and effective alternative to BiV-CRT. However, comprehensive evidence with respect to outcomes of CSP in NICM patients is lacking.

Table 6-1: Variables proposed to be included in SCD Risk-stratification model for NICM*

Demographic Factors	Age	**Ambulatory ECG**	PVC burden
	Gender		NSVT
Clinical Variables	Body mass index		Heart rate variability
	Systolic blood pressure	**Echocardiography**	EDVi
Symptoms	Syncope		LVEF<40%
	NYHA class II/III		LVEF 40-49%
	Duration of symptoms		LVEF≥50%
Comorbidities	Diabetes mellitus		Global longitudinal strain
	Hypertension		Mechanical dispersion
	Chronic lung disease	**Cardiac MRI**	LGE
	Chronic kidney disease		Distribution of LGE
	Malignancy		T1/ ECV abnormalities
	Smoking		Myocardial strain abnormalities
Blood parameters	Hemoglobin	**Coronary artery disease (50-75% epicardial stenosis) / Myocardial perfusion defect**	
	Creatinine/ eGFR	**Invasive electrophysiology study**	Inducible VT
	NT BNP		Endocardial unipolar low voltage zones>3 segments or >33% LV area
	CRP/ IL-6	**Genetic markers**	LAMIN A/C
ECG characteristics	QRS duration		Desmosomal mutations
	QTc		Phospholomban
	SAECG abnormality		Filamin

*NICM excludes hypertrophic cardiomyopathy, tachycardiomyopathy, right ventricular cardiomyopathy, valvular heart diseases, LV noncompaction, congenital heart disease, pulmonary heart diseases

SCD- sudden cardiac death; NICM- nonischemic cardiomyopathy; GFR-glomerular filtration rate; NT-BNP- NT brain natriuretic peptide; CRP- c-reactive protein; IL-6- Interleukin 6; SAECG- signal average ECG; PVC-premature ventricular complex; NSVT- nonsustained Ventricular tachycardia; EDV- end-diastolic volume; LVEF- left ventricular ejection fraction; LGE- late gadolinium enhancement