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Absence of Late Gadolinium Enhancement on Cardiac Magnetic Resonance Imaging in Ventricular Fibrillation and Non-Ischemic Cardiomyopathy

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Running title: Fibrosis on cardiac MRI in VF

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Abstract

Introduction: CMR-identified late gadolinium enhancement (LGE), representing regional fibrosis, is often used to predict ventricular arrhythmia risk in non-ischemic cardiomyopathy (NICM). However, LGE is more closely correlated with sustained monomorphic ventricular tachycardia (SMVT) than ventricular fibrillation (VF). We characterised CMR findings of ventricular LGE in VF survivors.

Methods: We examined consecutively resuscitated VF survivors undergoing contrast-enhanced 1.5T CMR between 9/2007–7/2016. We excluded coronary artery disease, hypertrophic cardiomyopathy, amyloid, sarcoid, ARVC, channelopathy. Pre-existing ICD was a CMR contraindication. VF patients were divided into three groups: (i) NICM, (ii) LV dilatation with normal LVEF, (iii) Normal LV size and LVEF. Two groups of NICM patients with and without SMVT were examined for comparison.

Results: We analysed 87 VF patients, and found that LGE was seen in 8/22 (36%) with NICM (LVEF 38±11%, LVEDVI 134±68 mL/BSA), 11/40 (28%) with LV dilatation and normal LVEF (LVEDVI 103±17 mL/BSA), 4/25 (16%) with normal LV size and LVEF. Incidence of LGE in NICM patients without prior VT/VF (LVEF 36±12%, LVEDVI 141±46 mL/BSA) was 117/277 and was not lower than those with VF & NICM (42% vs 36%;p=0.59). By contrast, 22/37 NICM patients with SMVT (LVEF 42±11%, LVEDVI 123±48 mL/BSA) were LGE-positive (59% NICM-SMVT vs 36% NICM-VF;p=0.04).

Conclusion: Most VF survivors with a diagnosis of NICM did not have LGE on CMR and would not have met 'primary prevention ICD criteria' based on LVEF. Absence of LGE may

not portend a benign prognosis in NICM. Novel strategies for determining SCD risk in this cohort are required.

Key Words: Cardiac, Magnetic Resonance, Non-ischemic, Ventricular Fibrillation, Arrest

Abbreviations

VF – Ventricular fibrillation

SMVT – Sustained monomorphic ventricular tachycardia

NICM – Non-ischemic cardiomyopathy

LVEF – Left ventricular ejection fraction (%)

LGE – Late Gadolinium Enhancement

CMR – Cardiac Magnetic Resonance Imaging

LV – Left ventricle

LVEDVI – Left Ventricular End-Diastolic Volume Index (mL/BSA)

ICD – Implantable cardioverter defibrillator.

SCD – Sudden Cardiac Death

Introduction

In patients with non-ischemic cardiomyopathy (NICM), macroscopic scarring is often absent at autopsy[1] with replacement interstitial fibrosis more commonly seen. In the catheter

ablation literature, the vast majority of NICM patients presenting with sustained monomorphic ventricular tachycardia (SMVT) are found to have scar related re-entry as the arrhythmia mechanism[2]. In these cases electroanatomic mapping of the ventricles identifies low voltage areas representing regions of fibrosis[3]. Critical SMVT isthmuses are found within these low voltage areas which form the target for ablation. Low voltage areas may be found on the endocardium, epicardium or both[4]. Typically such areas are located in perivalvular locations, the interventricular septum or left ventricular free wall. Late gadolinium enhancement (LGE) on cardiac MRI correlates with regional fibrosis found histologically[5], and is predictive of either the inducibility of SMVT or the occurrence of SMVT during implantable cardioverter-defibrillator (ICD) follow-up[6-8]. Interestingly, patients with NICM and PVCs but not SMVT appear to have a low prevalence of LGE/scar[9]. However, in survivors of cardiac arrest with NICM where ventricular fibrillation (VF) is the clinical arrhythmia, there is less data on the role of myocardial scarring - either CMR-documented or identified by electroanatomic mapping.

The purpose of this study was to: 1) characterise the CMR findings of ventricular LGE in cardiac arrest survivors with documented VF; 2) compare and contrast CMR findings between three groups of patients presenting with resuscitated VF (normal LV size and systolic function, dilated LV with normal function, LV systolic dysfunction i.e. NICM); and 3) compare and contrast CMR findings between NICM patients with resuscitated VF and NICM patients without a prior history of sustained ventricular arrhythmias .

Methods

Patient selection

We retrospectively reviewed all cardiac MRIs performed at The Alfred Hospital between September 2007 and July 2016. VF was defined as resuscitated sudden cardiac death

(SCD) with documented VF. SMVT was defined as documented sustained monomorphic VT >100 bpm lasting > 30 seconds or requiring intervention for termination. All patients were screened and evaluated with echocardiography, coronary angiography, and daily 12-lead electrocardiogram analysis. The intensity of further evaluation was left to clinician discretion, including exercise stress testing for long QT syndrome or catecholaminergic polymorphic VT, flecainide or ajmaline challenge for Brugada syndrome (with leads V1 & V2 in the second intercostal space), provocative testing for coronary spasm and urinary toxicology screening for substance abuse.

Patients with an ultimate diagnosis of obstructive coronary artery disease/ischaemic cardiomyopathy, primary valvular cardiomyopathy, hypertrophic cardiomyopathy, sarcoid cardiomyopathy, cardiac amyloid, arrhythmogenic right ventricular cardiomyopathy and documented cardiac ion channelopathy (Long/short QT syndrome, Brugada syndrome, CPVT, WPW syndrome, Early repolarisation syndrome) were excluded. Patients felt to have potentially reversible causes of cardiomyopathy, including drug-related myocarditis, tachycardia-mediated, Takotsubo, and peripartum cardiomyopathy were excluded. Patients unable to receive Gadolinium contrast were not included in the final analysis. The presence of an ICD was a strict contraindication to CMR according to local institutional guidelines. The study was approved by Alfred Health Human Research Ethics Committee.

We included five groups in the analysis:

1. VF patients with NICM (LVEF < 50%)
2. VF patients with preserved LV systolic function, but with LV dilatation (indexed LV End-Diastolic Volume cut-offs: LVEDVI >80 mL/BSA women and >85 mL/BSA men)

3. VF patients with normal LV size and systolic function who otherwise satisfied the above inclusion and exclusion criteria.
4. SMVT patients with NICM
5. NICM patients with no prior history of VF or SMVT.

Patient demographics and follow-up

Medical records were reviewed to ensure exclusion criteria were not met and determine baseline NYHA functional class, medical therapy and QRS width on ECG. Where available, ICD interrogations and follow-up echocardiograms were reviewed in VF patients with either NICM or LV dilatation (but preserved LVEF). Appropriate therapy was defined as either anti-tachycardia pacing (ATP) for SMVT or a shock for VT or VF. Follow-up transthoracic echocardiograms were performed using commercially available equipment and standard techniques used in standard clinical practice. LVEF was assessed on transthoracic echocardiography using Simpson's disc method in the apical 4-chamber view, supplemented by visual inspection.

CMR Data Acquisition

All CMR scans were performed using a clinical 1.5 T CMR scanner (Signa HD 1.5 T, GE Healthcare, Waukesha, Wisconsin, USA). Sequences were acquired during a 10–15 s breath hold. LVEF was assessed using a contiguous short axis steady-state free precession (SSFP) stack extending from the mitral annulus to the LV apex. Late Gadolinium enhancement (LGE) was evaluated 10 min following a bolus of gadolinium–diethylene triamine penta-acteic acid (DTPA) (0.2 mmol/kg BW Magnevist®, Schering, Germany) to identify regional fibrosis using an inversion-recovery gradient echo technique (TR: 7.1 ms; TE: 3.1 ms; inversion time individually determined to null the myocardial signal, range: 180–

250 ms, slice thickness: 8 mm, matrix: 256 × 192, number of acquisitions = 2). LGE imaging was performed using both standard long-axis and short-axis views of the LV. The scanning protocol did not change during the study period.

CMR Analysis

Cine sequences were acquired in the four-chamber view (4CV), two-chamber view (2CV) and short-axis view. End-diastolic volume, end-systolic volume, and LVEF were analyzed on commercially available post processing software, and 4CV measurements were used where possible. Papillary muscles were regarded as part of the ventricular cavity.

Scar analysis for regional fibrosis (delayed enhancement imaging) was performed in both long-axis and short-axis views. Scar analysis was performed using semi-automated software developed at our institution as a plug in to the open-source DICOM viewer. Endocardial and epicardial LV myocardial borders were manually delineated on the short-axis LGE-CMR images. For each patient with scar (i.e. LGE), the maximum signal intensity (SI) within a scar region in each image of the LV stack was automatically determined, and scar was defined as myocardium with an SI 50% of the maximum SI. Regional fibrosis was identified by LGE within the myocardium, defined quantitatively by myocardial post-contrast signal intensity > 2 standard deviations above that within a reference region of healthy myocardium within the same slice. Scar was automatically segmented, and any areas identified as scar by the software but not deemed to be scar by the user were excluded manually. Myocardial LGE was defined as being present only if it was identified in both long-axis and short-axis views as determined by visual assessment of the reporting MRI cardiologist.

All scans were clinically-indicated and hence analyzed and reported within 24 hours. Measurements were performed by a CMR imaging fellow and verified by one of two experienced CMR cardiologists (CMR fellowship trained, > 1000 cases experience). Measurements for this research study were taken from the report issued at the time of the scan and no scans were re-analyzed.

Statistics

Summary statistics for continuous data are presented as mean ± standard deviation or median, as appropriate. Comparisons of the clinical characteristics between groups were performed using a chi-square or Fisher exact test. Mean values were compared using the student t-test for two independent groups and one-way ANOVA for more than two groups. Mann-Whitney U test was used for continuous variables where normal distribution was not present. Data analysis was performed using The Statistical Package for the Social Sciences for Windows (SPSS version 21, IBM). A p value < 0.05 was considered statistically significant.

Results

Clinical and demographic data

A total of 87 subjects with resuscitated VF arrest meeting the inclusion criteria underwent CMR. Median time from admission to CMR was 6.5 days. Of these, 22 (25%) had NICM with LVEF < 50%. Their LV dimensions and mean LVEF were similar to the NICM cohort without a hisotry of ventricular arrhythmias (LVEDVI 134±68 vs 141±46; p=0.51 and LVEF 38±11 vs 36±12; p=0.38). An additional 40 (46%) VF patients with LV dilatation but normal LVEF were included (LVEDVI 103±17), while 25 (29%) of VF patients had preserved LV size and function. An additional 37 NICM patients with SMVT and 277

patients with NICM and no prior SMVT or VF were included. Table 1 shows baseline characteristics of subjects in each group.

Compared with VF survivors, both the NICM group without prior arrhythmias and NICM-SMVT group were older and had a wider mean QRS duration. Only 6/22 (27%) VF survivors with NICM would have qualified for an ICD based on primary prevention criteria (LVEF < 35%), compared with 139/277 (50.1%) in the NICM group without prior ventricular arrhythmias. Similarly, 7/37 (19%) of NICM-SMVT patients had LVEF < 35%. Moreover, the majority of patients in both groups were asymptomatic (median NYHA class I).

CMR findings

The presence or absence of CMR LGE in 401 patients from all five groups is represented in Figure 1. Interestingly in all three groups presenting with VF, the majority 64/87 (74%) did not have LGE, including 14/22 (64%) with NICM. Incidence of LGE in NICM patients without prior VT/VF was 117/277 and was not lower than those with VF and NICM (42% vs 36%;p=0.59). As expected, the highest prevalence of LGE was seen in the SMVT group with NICM 22/37 (59%), followed by the NICM cohort without prior ventricular arrhythmias 117/277 (42%). In NICM patients referred for CMR following an arrhythmia, LGE was more likely to be seen following SMVT compared to VF (59% vs 36%; p=0.04). Of VF survivors with preserved systolic function, 15/65 (23%) were LGE positive, representing either old myocarditis or a precursor to NICM. When examining NICM patients presenting with either SMVT or VF (n=59), there was no significant difference in LVEF (LVEF 39±13% vs 42±8%; p=0.23) or LV size (LVEDVI 125±50 vs 131±67 mL/BSA;p=0.72) between those with and without LGE.

Patterns of regional fibrosis by group are shown in Table 2, with distributions summarized as a percentage of those with LGE in the patient group. Isolated mid-wall fibrosis, the 'hallmark' of NICM was seen in all groups, but was considerably more prevalent in the large NICM population without a prior history of ventricular arrhythmias (71% of those with LGE). By contrast, isolated subepicardial LGE was rarely seen in NICM without prior arrhythmias (3% of those with LGE), compared with NICM-SMVT (23%) and NICM-VF (13%). compared with the more common in NICM-SMVT patients (36%) while 11/22 (50%) in this group had some subepicardial LGE.

Follow-up

Over a mean follow-up 39±28 months, echocardiographic and ICD data were obtained for the 70/87 (80%) VF survivors, where available. Follow-up LVEF measurements in the NICM and LV dilation (but normal initial LVEF) groups were similar to the time of CMR scanning at 42±11% (p=0.41) and 56±8% (p=0.08) respectively. Proportion of patients receiving appropriate ICD therapy in the VF groups during follow-up were: 32% (NICM), 23% (dilated LV, normal LVEF), 15% (normal LV size/function), with timing of device therapy demonstrated in Figure 2 and no significant difference observed between the groups (Log Rank p = 0.17). In those with resuscitated VF with, presence of LGE did not predict appropriate ICD therapy at follow-up (p=0.09).

Discussion

Main findings

This study highlights several important findings:

1. The majority of patients presenting with resuscitated VF, including those with NICM, did not have LGE on CMR.
2. The presence of LGE in NICM was strongly associated with SMVT (as expected).
3. VF survivors with evidence of LV dilatation and preserved systolic function had a 28% incidence of LGE.
4. Isolated mid-wall fibrosis was highly prevalent in the NICM population without a prior history of ventricular arrhythmias but considerably less common in those with resuscitated VF.

Role of LGE in NICM

The presence of regional fibrosis as an arrhythmogenic substrate of VT in patients with NICM has been demonstrated in numerous studies and is a major cause of SCD. However, left ventricular ejection fraction (LVEF) remains the most widely used risk stratification tool in the primary prevention setting, owing to five large randomised trials demonstrating survival benefit from ICDs where severely reduced LVEF was a key trial inclusion criteria. While many patients may have significant improvements in LVEF over a short period often mitigating their SCD risk[10], others with milder systolic dysfunction but significant scar may be overlooked. In fact, the majority of NICM patients with VF or SMVT in our cohort would not have received an ICD by primary prevention criteria using LVEF alone.

CMR has emerged as an increasingly useful non-invasive modality to visualise and quantify scar burden. A recent large meta-analysis of NICM patients demonstrated that LGE was a powerful predictor of ventricular arrhythmias in those with severe systolic dysfunction, with the composite arrhythmic endpoint reached in 23.9% of patients with LGE, compared

with 4.9% of patients without LGE[11]. It also holds great promise in potentially identifying patients at higher risk of SCD who may benefit from ICD implantation even if they do not fulfil current primary prevention criteria based on LVEF[12]. As expected, the majority of NICM patients presenting with SMVT in our cohort had LGE and LVEF > 35%, supporting this notion. Moreover, the heightened VT risk associated with sub-epicardial scar described recently by Shin et al[13] is also supported by our findings, with 50% of our SMVT-NICM cohort demonstrating this finding.

Our study demonstrates that many NICM patients without LGE may still develop VF, suggesting that macroscopic scarring is not a prerequisite for this arrhythmia. This also appeared to be the case in patients with LV dilatation and preserved systolic function. Wu et al. observed in one of the few human studies looking specifically at the characteristics of wavefronts during VF in explanted hearts from transplant recipients with dilated cardiomyopathy that non-uniform anisotropic wave propagation with fractionated electrograms were present. They showed that the most common mode of initiation of new re-entrant wavefronts during VF was related to the conduction block caused by increased interstitial and replacement fibrosis leading to formation of the electrical substrate for VF and continuous development of re-entry[14].

VF in NICM

NICM as an entity comprised of numerous heterogeneous conditions (including myocarditis, substance-induced, tachycardia-mediated, familial, etc) that do not share a single pathophysiological and arrhythmia mechanism. While LGE identifies regional fibrosis, it often misses interstitial fibrosis[15] which may have been present in the majority of NICM patients presenting with VF in our cohort. Novel CMR techniques, such as T1 mapping for assessment of diffuse interstitial fibrosis as a potential substrate for malignant ventricular

arrhythmias in NICM may hold some promise, particularly in LGE-negative patients. Chen et al reported that native T1 time was predictive of appropriate ICD therapy and SMVT in 59 NICM patients[16]. In a prospective observational study of 637 NICM patients undergoing CMR, native T1 was the sole multivariate predictor of all-cause mortality and heart failure[17].

Clinical implications

While the DANISH trial did show a reduction in risk of SCD from primary prevention ICDs in NICM (LVEF < 35%, NYHA II-III), it also drew attention to the low event rates in this cohort and thus failed to demonstrate a mortality benefit over a median follow-up of 67.6 months[18]. While ejection fraction and NYHA class remain important predictors of SCD in NICM, our study reinforces the notion that additional tools are still required to refine risk stratification in NICM - the median LVEF and NYHA class in our NICM VF group were 38% and Class I respectively.

CMR is playing an increasingly important clinical role in identifying patients with ventricular fibrosis at risk of ventricular arrhythmias. However, the role for CMR in selecting NICM patients at highest risk of VF based on LGE is limited. While LGE is predictive of higher risk of ventricular tachyarrhythmias (particularly SMVT), its absence may not necessarily predict a 'low risk' patient. Improved risk stratification tools, such as T1 mapping for diffuse fibrosis, may be useful in the NICM cohort to better predict those at higher risk of SCD. Additional predictors of SCD in NICM identified in a meta-analysis of 45 studies include fragmented QRS (RR 5.16), T-wave alternans (RR 3.25), LV dilatation (RR 2.85), non-sustained VT (RR 2.45), inducible VT on electrophysiological study (RR 2.09), prolonged QRS duration (RR 1.43)[19].

Study limitations

As a non-randomized retrospective analysis, our study has several limitations. The exact underlying pathology in the VF group with abnormal LV size but normal LVEF is not entirely clear and subjects may have in fact previously experienced an early cardiomyopathy, previous myocarditis or been misclassified as idiopathic VF. Those with an underlying undiagnosed channelopathy or coronary spasm may also have been missed. We also cannot absolutely exclude the possibility that some patients classified as NICM with patchy or epicardial scar had undiagnosed cardiac sarcoidosis. Lack of histological correlation means we cannot absolutely exclude the possibility of artefact being called scar. The documentation of VF does not exclude VT (either monomorphic or polymorphic) as the triggering initial arrhythmia in some cases, as electrophysiological study data was not available due to the retrospective nature of the analysis. While this study compares NICM patients with and without arrhythmias, these are different patient populations by virtue of the CMR indication and there may be a difference in duration of NICM diagnosis. Presentation with SCD was often the first manifestation of a cardiac condition in the former, while the latter group were all referred for CMR by their treating cardiologist. Because this study looks at VF and VT survivors only, one cannot exclude that there may be a subgroup of LGE positive patients with shock-refractory arrhythmias. This does not negate our key finding that a considerable portion of patients with LV dilatation and/or systolic dysfunction develop VF despite absence of regional fibrosis on CMR. While it may be argued that myocardial stunning post-VF may contributed to systolic dysfunction in those classified as NICM, most patients in this group had significant LV dilatation comparable with the NICM cohort without a history of ventricular arrhythmias, indicating a degree of chronicity.

Conclusion

In this study, the majority of patients presenting with VF did not have LGE on CMR, including those with NICM and isolated LV dilatation. Most would not have met 'primary prevention ICD criteria' based on LVEF. Whilst the absolute risk of VF in this group (NICM and LGE negative) is unknown, the absence of LGE may not portend a benign prognosis. Novel strategies for determining SCD risk in this cohort are required.

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Figure Legend

Figure 1: CMR findings based on presence of LGE (% of cases)

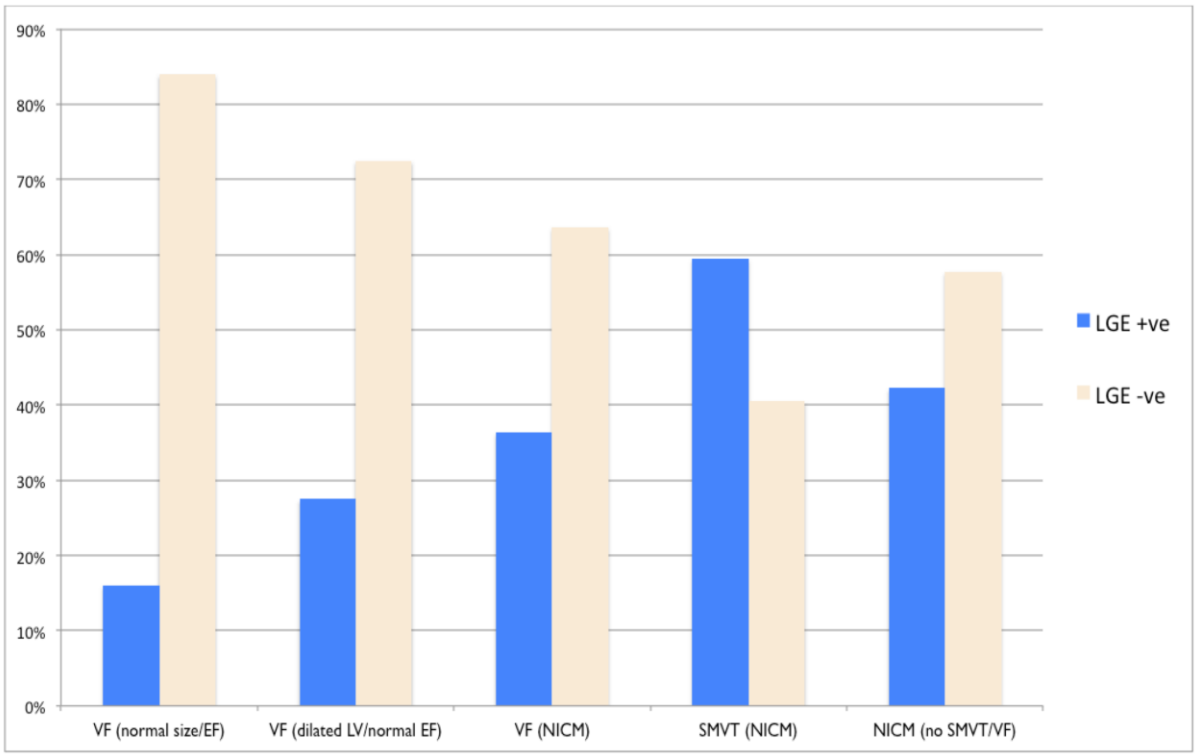

Figure 2: Appropriate Device Therapy for Ventricular Arrhythmias during follow-up

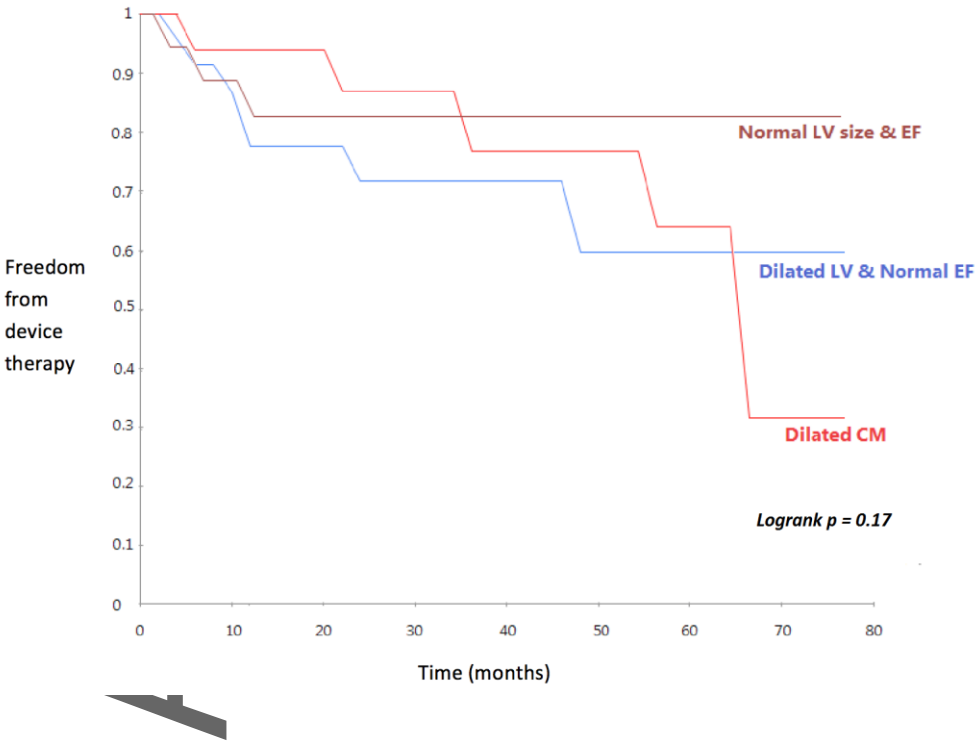

Table 1: Baseline Characteristics

Indication for CMR: Patient group:	**VF** Normal LV size + Normal LVEF (n=25)	**VF** Dilated LV + Normal LVEF (n=40)	**VF** NICM (n=22)	**SMVT** NICM (n=37)	**NICM** No previous VT/VF (n=277)	ANOVA p value
Age, yrs	43±14	41±13	40±13	55±14	51±16	<0.01
Male, %	64	58	45	68	69	-
QRS width, ms	91±7	97±14	105±26	115±21	121±33	<0.01
NYHA class,(median)	1	1	1	1	2	-
LVEF, %	62±5	61±6	38±11	42±11	36±12	<0.01
LVEDVI, mL/BSA	71±9	103±17	134±68	123±48	141±46	<0.01

Abbreviations: CMR: Cardiac MRI, NYHA: New York Heart Association, ACE: Angiotensin Converting Enzyme, LVEF: Left Ventricular Ejection Fraction, LVEDVI: Left Ventricular End-Diastolic Volume Index, NICM: Non-Ischemic Cardiomyopathy, VT: SMVT: Sustained Monomorphic Ventricular Tachycardia, VT: Ventricular Tachycardia, VF: Ventricular Fibrillation.

Table 2: Patterns of Late Gadolinium Enhancement (regional fibrosis)

Indication for CMR: Patient group:	VF Normal LV size + Normal LVEF (n=25)	VF Dilated LV + Normal LVEF (n=40)	VF NICM (n=22)	SMVT NICM (n=37)	NICM No previous VT/VF (n=277)
Presence of LGE (%)	4 (16%)	11 (28%)	8 (36%)	22 (59%)	117 (42%)
Distribution					

Mid-wall only	2/4 (50%)	4/11 (36%)	3/8 (38%)	8/22 (36%)	83/117 (71%)
Subepicardial only	1/4 (25%)	0	1/8 (13%)	5/22 (23%)	4/117 (3%)
Patchy/Other	1/4 (25%)	7/11 (64%)	4/8 (50%)	9/22 (41%)	30/117 (26%)

Abbreviations: CMR: Cardiac MRI, NYHA: LGE: Late Gadolinium Enhancement, LVEF: Left Ventricular Ejection Fraction, NICM: Non-Ischemic Cardiomyopathy, VT: SMVT: Sustained Monomorphic Ventricular Tachycardia, VT: Ventricular Tachycardia, VF: Ventricular Fibrillation.