

Prediction of Arrhythmic Events in Ischemic and Dilated Cardiomyopathy Patients Referred for Implantable Cardiac Defibrillator

Evaluation of Multiple Scar Quantification Measures for Late Gadolinium Enhancement Magnetic Resonance Imaging

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Background—Scar signal quantification using late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) identifies patients at higher risk of future events, both in ischemic cardiomyopathy (ICM) and nonischemic dilated cardiomyopathy (DCM). However, the ability of scar signal burden to predict events in such patient groups at the time of referral for implantable cardioverter-defibrillator (ICD) has not been well explored. This study evaluates the predictive use of multiple scar quantification measures in ICM and DCM patients being referred for ICD.

Methods and Results—One hundred twenty-four consecutive patients referred for ICD therapy (59 with ICM and 65 with DCM) underwent a standardized LGE-CMR protocol with blinded, multithreshold scar signal quantification and, for those with ICM, peri-infarct signal quantification. Patients were followed prospectively for the primary combined outcome of appropriate ICD therapy, survived cardiac arrest, or sudden cardiac death. At a mean follow-up of 632 ± 262 days, 18 patients (15%) had suffered the primary outcome. Total scar was significantly higher among those suffering a primary outcome, a relationship maintained within each cardiomyopathy cohort ($P < 0.01$ for all comparisons). Total scar was the strongest independent predictor of the primary outcome and demonstrated a negative predictive value of 86%. In the ICM subcohort, peri-infarct signal showed only a nonsignificant trend toward elevation among those having a primary end point.

Conclusions—Myocardial scar quantification by LGE-CMR predicts arrhythmic events in patients being evaluated for ICD eligibility irrespective of cardiomyopathy etiology. (*Circ Cardiovasc Imaging*. 2012;5:448-456.)

Key Words: ventricular arrhythmia ■ MRI ■ implantable cardioverter-defibrillator (ICD) ■ sudden cardiac death

Approximately two thirds of fatal cardiovascular events in patients with a left ventricular ejection fraction (LVEF) $\leq 35\%$ are caused by sudden cardiac death (SCD).¹ Implantable cardiac-defibrillators (ICD) offer significant reductions in SCD in patients with both ischemic cardiomyopathy (ICM)^{2,3} and nonischemic dilated cardiomyopathy (DCM).⁴⁻⁶ These devices currently are recommended for patients with symptomatic heart failure and an LVEF $\leq 35\%$, and for asymptomatic ICM patients with an LVEF $\leq 30\%$.⁴⁻⁶ However, post hoc analysis of the MADIT II study identified that only 35% of patients receiving ICDs subsequently received appropriate therapy at 3 years.⁷ Furthermore, many patients

with resuscitated SCD are found to have an LVEF above current ICD implantation guidelines thresholds.⁸ Therefore, current selection criteria for primary prevention ICD are suboptimal and emphasize a need for supplementary or alternate risk stratification tools.⁹

Clinical Perspective on p 456

Myocardial scar is a recognized substrate for the development of malignant arrhythmias in patients with systolic dysfunction.¹⁰ While the mechanisms contributing to arrhythmia generation in this population remain complex, relatively simple markers of scar burden from late gadolinium

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enhancement-cardiovascular magnetic resonance (LGE-CMR) imaging appear to hold prognostic value.^{11–16} In patients with DCM, the presence of myocardial hyper-enhancement (HE) on LGE-CMR has been associated with future arrhythmic events.^{11,12} Similarly, HE extent has been associated with future cardiac death¹³ and appropriate ICD therapy^{14–16} in patients with ischemic cardiomyopathy. Collectively, these studies suggest HE signal quantification to be potentially useful as a risk stratification tool in both ICM and DCM patients being referred for ICD. The aim of this study was to assess the predictive use of HE signal quantification for the prediction of appropriate ICD therapy, survived cardiac arrest (SCA), or SCD in patients with ICM or DCM being referred for ICD therapy.

Methods

Study Population

This prospective cohort study was conducted at a large, tertiary care referral center (London Health Sciences Centre, London, Ontario, Canada). The study population consisted of 124 consecutive patients referred to the electrophysiology service for consideration of ICD.

Patients were eligible for the study if they had a LVEF $\leq 35\%$ estimated by echocardiography and were on maximal tolerated heart failure therapy for ≥ 3 months. Prior to enrollment all patients underwent coronary angiography or computed tomography angiography (CTA) to determine cardiomyopathy etiology. ICM was defined as those with obstructive coronary artery disease in ≥ 1 major epicardial vessel (stenosis $\geq 70\%$), all other patients being classified as DCM. CMR imaging was performed in all consenting patients, with the LVEF provided to assist in clinical decision making. Patients were excluded if standard contraindications to LGE-CMR existed, inclusive of a glomerular filtration rate of ≤ 30 mL/min/1.73 m².

All patients agreed to participation by giving both verbal and written informed consent. The study was approved by the Health Sciences Research Ethics Board at the University of Western Ontario.

Cardiovascular Magnetic Resonance Imaging Protocol

Cardiovascular magnetic resonance imaging was performed using a 3T magnetic resonance imaging (MRI) scanner (TIM Trio or Verio, Siemens) equipped with a 32-channel cardiac coil. Cardiac function was assessed in sequential short axis views at 10 mm intervals from the atrioventricular annulus to apex using a standard steady state free precession (SSFP)-based “cine” pulse sequence. Typical imaging parameters were slice thickness 6 mm, gap 4 mm, TE 1.3 ms, flip angle 10 degrees, matrix 256 \times 205, iPAT 2, and temporal resolution 28 to 38 ms. Ten to 15 minutes following intravenous administration of Gadolinium contrast (0.15–0.2 mmol/kg, Gadovist, Bayer Inc; Toronto, Canada) LGE imaging was performed using a standard, segmented inversion recovery gradient echo pulse sequence in identical imaging planes. Typical imaging parameters were slice thickness 6 mm, gap 4 mm, TR 800 ms, TE 3.9 ms, flip angle 20 degrees, matrix 256 \times 205, segments 13 to 21, and iPAT 2. The inversion time was optimized to null normal myocardium, as previously described.¹⁷

Cardiovascular Magnetic Resonance Image Analysis

Quantitative image analysis was performed using commercially available software (CMR42; Circle Cardiovascular Imaging Inc, Calgary, Canada). Cine images were examined to determine the LV end systolic volume, LV end diastolic volume, and LV mass by semiautomated endocardial and epicardial contour tracing. An experienced CMR interpreter (J.A.W.), blinded to all baseline and clinical outcome variables, performed HE signal quantification on de-identified and randomly ordered short axis LGE datasets.

The presence or absence of any myocardial HE was visually determined and the most dominant pattern scored, as follows: (1) subendocardial based, (2) midwall, or (3) subepicardial. HE signal quantification then was performed using manual endocardial and epicardial contour tracing, with the manual exclusion of any visible artifacts. Employing the signal threshold versus reference myocardium (STRM) technique, as previously described,¹⁸ 3 different signal thresholds for the definition of total HE were evaluated: $\geq 2SD$, $\geq 3SD$, and $\geq 5SD$ above the mean signal of reference myocardium. This was performed to identify the optimal threshold for the prediction of clinical events using this signal analysis technique. The reference myocardium was identified manually as the largest contiguous region of homogeneously nulled myocardium, as shown in Figure 1. In those with ICM, peri-infarct signal also was calculated as described by Yan et al¹³ as the difference between total HE measured by $\geq 2SD$ and $\geq 3SD$ thresholds. In this cohort HE signal analysis also was performed using the full width half max (FWHM) technique, as previously validated and described,^{14,18} similarly used to quantify both the total HE and peri-infarct zone signal. All HE measures were expressed in grams by multiplying HE area by slice thickness, and then converting to mass by multiplying by a specific gravity of 1.05.

Interobserver and Intraobserver Variability

Inter- and intraobserver variability was evaluated for HE signal quantification. Two experienced and blinded interpreters independently performed and described signal analysis on 2 separate occasions. This was performed for 10 randomly selected ICM cases and 10 randomly selected DCM cases.

Device Implantation and Programming

Implantable cardiac-defibrillator implantations were performed in a standard fashion at a median of 27 days (interquartile range 8–45) following CMR. ICD devices were programmed to detect ventricular fibrillation (VF) if 18 of 24 R-R intervals were ≤ 240 ms. “Fast ventricular tachyarrhythmias (VT)” was defined as 18 of 24 consecutive R-R intervals ≤ 320 ms and “slow VT” as 16 consecutive R-R intervals ≤ 400 ms. For primary prevention patients’ devices routinely were programmed to deliver antitachycardia pacing (ATP) or shock therapy for VF or fast VT, and to monitor (ie, not deliver therapy) for slow VT. In patients receiving secondary prevention ICD this programming was altered to treat slow VT using both ATP and shock therapies.

Follow-Up and Clinical Events

Clinical follow-up was initiated from the time of CMR imaging. The primary composite clinical outcome was defined as the occurrence of appropriate ICD therapy, SCA, or SCD. Occurrence of the primary outcome or nonsudden cardiac death served as a secondary composite clinical outcome. In patients having ≥ 2 clinical events registered during follow-up, the time to first clinical event was used for analysis of event-free survival.

All patients receiving ICDs underwent interrogations at 1, 3, and 6 months, and every 6 months thereafter. At study closure all interrogations were de-identified and adjudicated by 2 electrophysiologists blinded to CMR analysis. Appropriate ICD therapy was defined as ATP or shock for fast VT (R-R < 320 ms) or VF. ICD therapy was classified as inappropriate when delivered for non-target arrhythmias, such as sinus or supraventricular tachycardia, T-wave oversensing, or for any device system malfunction, such as lead conductor wire fracture. All study patients, irrespective of ICD implantation status, were evaluated for the clinical occurrence of SCA or SCD. SCD was defined as death occurring within 1 hour of symptom onset. This was performed at 12 month intervals and at study closure by telephone interview and a review of all medical records.

Statistical Analysis

Continuous data are expressed as mean \pm SD and categorical data in frequencies and percentages. Respective baseline differences between

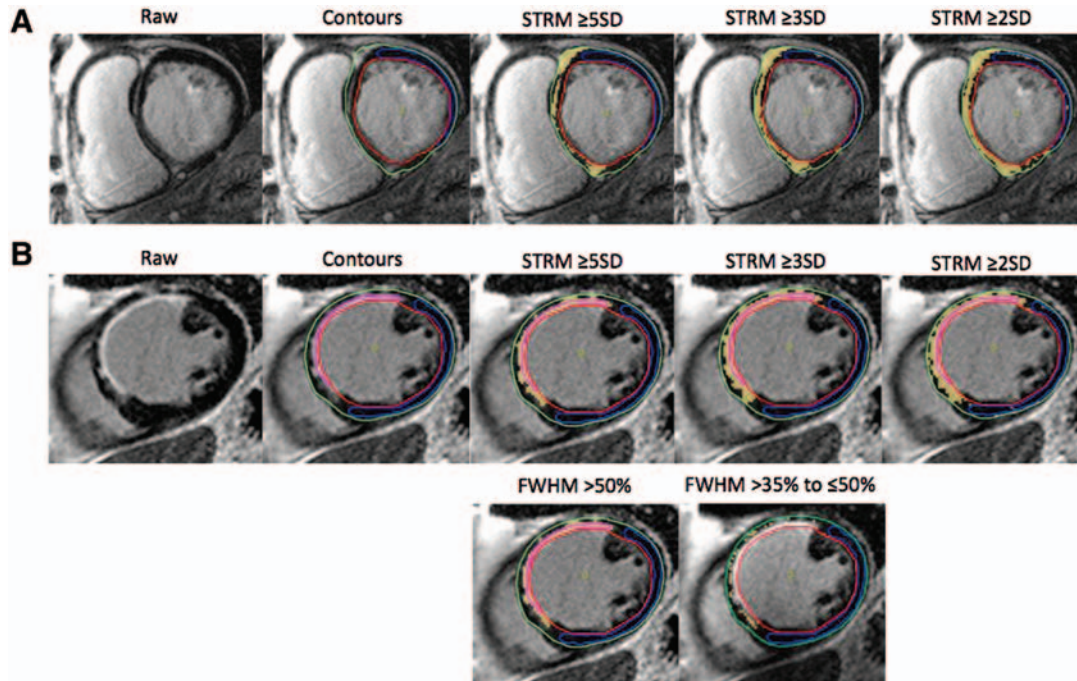


Figure 1. Example of contour tracing performed on late gadolinium enhancement imaging in a patient with **A)** dilated cardiomyopathy, and **B)** ischemic cardiomyopathy. Endocardial border shown in red, epicardial border shown in green, normal reference myocardium shown in blue. A scar reference contour (purple) is shown incrementally in the patient with ischemic cardiomyopathy. Hyper-enhancement volume analysis is shown by predefined signal thresholds using each of the signal threshold versus reference myocardium (STRM) and full width half width (FWHM) approaches.

patients with and without the primary outcome were compared by the independent sample *t* test, and Chi-square (χ^2) test. ANOVA was used for comparison of means from multiple groups. Survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test. Univariable and multivariable analyses of event free survival were performed according to the Cox regression model. We constructed a multivariable model to assess the incremental association of total HE and all baseline clinical variables (Table 1) to the primary outcome using backward stepwise selection ($P < 0.10$ for entry and $P > 0.05$ for removal). Only a single variable (“primary prevention ICD”) was found to be eligible and therefore was used to provide an adjusted hazards ratio (HR) for total HE. Due to the limited number of events ($N=18$), no other covariates were forced into the model to comply with the general rule that 10 events should be available for each variable tested.^{19,20} Unadjusted and adjusted HRs with corresponding 95% CIs then were described. Receiver operating characteristic curve analysis with logistic regression and discriminant predicted probabilities was performed to test associations between HE measure and the primary outcome.

Interobserver and intraobserver variability was assessed using Bland-Altman analysis and interclass correlation coefficient (ICC) with 95% CI. ICC was used rather than the correlation coefficient as it incrementally provides assessment of systematic error between observers.²¹ All tests were 2-sided with a level of statistical significance set at $P \leq 0.05$. All analyses were performed using the SPSS software package 19.0 (SPSS, Inc.).

Results

Baseline Patient Characteristics

A total of 124 patients were enrolled, 59 with ICM and 65 with DCM. Of the latter group, a definite etiology was established in 18 patients by combined consideration of patient history, clinical records, and CMR imaging findings. These were viral cardiomyopathy ($N=8$, defined by a clear history of viral

illness plus midwall or subepicardial HE), cardiac sarcoid ($N=6$), chemotherapy-induced cardiomyopathy ($N=3$), and arrhythmogenic right ventricular cardiomyopathy (ARVC) with LV involvement ($N=1$). All other baseline clinical characteristics are presented in Table 1.

Of all patients enrolled, 79 (64%) underwent ICD implantation, 41 with ICM, and 38 with DCM. Of these, 69 devices (87%) were inserted for the primary prevention of SCD, while 10 patients (13%) had a prior history of sustained VT ($N=8$) or VF ($N=2$). No differences were observed in ICD insertion rates between those with ICM or DCM ($P=0.37$). Forty-five patients (57%) received cardiac resynchronization therapy (19 with ICM and 26 with DCM). Of patients that did not receive an ICD, 21 failed to verify LVEF criterion by CMR imaging, all having an LVEF between 36% and 40%. All other patients met LVEF criteria but either refused to proceed with device implantation ($N=14$) or were declined on the basis of comorbidity ($N=10$). Of the latter group 5 had severe heart failure, 3 had severe pulmonary disease, and 2 had a cancer detected by screening investigations.

Clinical Follow-Up: Primary and Secondary Events

All patients prospectively were followed for the occurrence of survived SCA, SCD, or, in those receiving devices, appropriate ICD therapy. During a mean follow-up of 632 ± 262 days, 18 patients (15%) suffered a primary outcome, 10 patients with ICM and 8 patients with DCM. Of these patients 15 had an appropriate ICD therapy (ATP in 13, shock in 11), 2 had SCD, and 1 patient had SCA. In addition, 6 patients suffered a non-sudden cardiac death

Table 1. Non-Magnetic Resonance Imaging Baseline Patient Characteristics, Presented for the Total Population and for Those With and Without the Primary Outcome

Variable	Total Population (N=124)	Without Primary Outcome (N=106)	With Primary Outcome (N=18)	P Value
Age, y	61±11	61±11	60±11	0.518
Male sex	100 (81%)	85 (80%)	15 (83%)	0.522
Race (Caucasian)	103 (83%)	89 (84%)	14 (79%)	0.522
Cardiomyopathy etiology				
ICM	59 (48%)	49 (46%)	10 (55%)	0.468
DCM	65 (52%)	57 (53%)	8 (44%)	0.468
Hypertension	64 (52%)	54 (51%)	10 (56%)	0.720
Diabetes mellitus	30 (24%)	26 (24%)	4 (22%)	0.834
Hyperlipidemia	72 (58%)	61 (58%)	11 (61%)	0.779
Smoking	53 (43%)	44 (42%)	9 (50%)	0.505
Any prior revascularization	42 (34%)	36 (34%)	6 (33%)	0.959
History of MI	57 (46%)	46 (43%)	11 (61%)	0.166
Systolic BP (mm Hg)	119±18	118±18	116±21	0.515
Diastolic BP (mm Hg)	72±9	72±9	69±8	0.186
GFR (mL/min/1.73 m ²)	76±19	75±19	72±19	0.478
LBBB	55 (44%)	46 (43%)	9 (50%)	0.606
QRS duration (msec)	136±29.8	136±30	136±22	0.963
NYHA functional class	2.5±0.9	2.5±0.9	2.2±1.0	0.196
ICD implantation	79 (64%)	64 (60%)	15 (83%)	0.062
Primary prevention	69 (56%)	58 (55%)	11 (61%)	0.023*
Secondary prevention	10 (8%)	6 (6%)	4 (22%)	0.093*
CRT Implantation	45 (36%)	39 (37%)	6 (33%)	0.780
Medications				
ACE inhibitor	88 (71%)	75 (71%)	13 (72%)	0.946
Amiodarone	9 (7%)	8 (8%)	1 (6%)	0.758
ARB	31 (25%)	29 (27%)	3 (17%)	0.332
ASA	84 (68%)	72 (68%)	12 (67%)	0.874
Beta blocker	99 (80%)	86 (81%)	13 (72%)	0.342
Digoxin	29 (23%)	25 (24%)	4 (22%)	0.885
Diuretic	73 (59%)	62 (58%)	11 (61%)	0.871
Plavix	14 (11%)	13 (12%)	1 (6%)	0.404
Statin	66 (53%)	55 (52%)	11 (61%)	0.497

*Considered eligible for multivariable analysis.

Continuous data are expressed as mean±SD, categorical data as n (%). ICM indicates ischemic cardiomyopathy; DCM, dilated cardiomyopathy; MI, myocardial infarction; BP, blood pressure; GFR, glomerular filtration rate; LBBB, left bundle-branch block; NYHA, New York Heart Association; CRT, cardiac resynchronization therapy; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid.

due to progressive heart failure (4 with ICM and 2 with DCM), contributing to a total of 24 secondary outcomes.

Non-Hyper-Enhancement Cardiovascular Magnetic Resonance Measures

Baseline CMR imaging findings are presented in Table 2 for the total population, ICM subcohort, and DCM subcohort. The mean LVEF of the population was 26±7%. No significant differences were observed among any non-HE variables between those with and without a primary outcome, irrespective of cardiomyopathy etiology (Table 2).

Prevalence and Pattern of Hyper-Enhancement by Visual Interpretation

Overall, 105 patients (85%) had any HE scored by visual assessment, 59/59 ICM patients (100%) and 46/65 DCM patients (71%; Table 2). Eleven patients with ICM (19%) demonstrated a secondary pattern of nonischemic HE, and 8 DCM patients demonstrated incidental subendocardial ischemic injury. Of the 46 DCM patients showing nonischemic HE, 31 patients (67%) had a predominantly midwall pattern, while 17 patients (37%) had a predominantly subepicardial pattern. Neither the presence of HE nor any of these patterns of HE showed significant

Table 2. Baseline Magnetic Resonance Imaging Characteristics of Study Population in Those With and Without the Primary Outcome Stratified According to Cardiomyopathy Etiology

Variable	Total Population (N=124)			ICM (N=59)			DCM (N=65)		
	PO- (N=106)	PO+ (N=18)	P Value	PO- (N=49)	PO+ (N=10)	P Value	PO- (N=57)	PO+ (N=8)	P Value
Non-HE variables									
LVEF (%)	26±7	25±7	0.471	27±8	23±8	0.072	26±7	28±7	0.350
LV EDV (mL)	251±68	261±73	0.557	244±65	283±66	0.087	257±71	234±76	0.394
LV ESV (mL)	186±61	195±56	0.554	180±61	216±32	0.075	192±62	170±69	0.356
LV mass (g)	184±45	186±60	0.862	179±40	199±58	0.208	188±48	171±64	0.388
HE, visual									
Any HE	88 (83%)	17 (94%)	0.166	49 (100%)	10 (100%)	0.524	39 (68%)	7 (87%)	0.274
Sub-endocardial HE	57 (54%)	10 (56%)	0.775	49 (100%)	10 (100%)	0.524	8 (14%)	0 (0%)	0.265
Mid-wall HE	35 (33%)	7 (39%)	0.630	9 (18%)	2 (20%)	0.906	26 (46%)	5 (62%)	0.378
Sub-epicardial HE	14 (13%)	4 (22%)	0.319	1 (2%)	0 (0%)	0.655	13 (23%)	4 (50%)	0.104
HE, total HE (g)									
STRM									
≥2SD	32±19	59±30	0.001	42±19	69±17	0.001	23±15	46±38	0.003
≥3SD	22±18	48±31	0.001	33±18	59±19	0.001	13±12	34±38	0.001
≥5SD	13±15	35±29	0.001	23±15	44±22	0.001	5±7	23±34	0.001
FWHM									
>50%				25±14	37±10	0.01			
HE, peri-infarct (g)									
STRM									
2–3 SD				9±5	11±6	0.270			
2–5 SD				19±10	25±11	0.107			
FWHM									
35%–50%				17±11	25±16	0.075			

Data expressed as mean±SD. ICM indicates ischemic cardiomyopathy; DCM, dilated cardiomyopathy; PO, primary outcome; HE, hyper-enhancement; LVEF, left ventricular ejection fraction; LV, left ventricular; EDV, end diastolic volume; ESV, end systolic volume; STRM, signal threshold versus reference myocardium; FWHM, full width half max

association with the primary outcome (Table 3). The number of HE patterns (ie, combined patterns) similarly was not predictive.

Total Hyper-Enhancement by Quantitative Analysis

Table 2 summarizes the results of quantitative HE signal analysis. STRM-based analysis, previously validated for use in both cohorts, showed total HE to be significantly higher in those with ICM versus those with DCM ($P<0.001$). Within each subcohort the burden of total HE did not differ between those receiving versus not receiving an ICD ($P=0.4$ for both comparisons).

Total Hyper-Enhancement Versus the Primary Outcome

Among the entire population, STRM-based analysis showed total HE to be significantly higher among those suffering a primary outcome, irrespective of the signal threshold used (Table 2). Using a $\geq 2SD$ threshold, the mean total HE mass among those with versus without a primary outcome was $59\pm 30g$ versus $32\pm 19g$ ($P=0.001$). This difference was maintained when analysis was constrained to those receiving an ICD ($P<0.001$). In the group not receiving an ICD, clinical events occurred in 3 patients (2 SCD and 1 survived SCA).

Total HE mass $\geq 2SD$ still was significantly higher among those suffering events (41 ± 19 versus $22\pm 16g$, $P=0.05$).

Total Hyper-Enhancement Versus the Secondary Outcome

Among the total population total HE was higher among those with versus those without a secondary outcome. However, in contrast to the primary outcome, this only reached statistical significance for the $\geq 2SD$ STRM-based signal threshold (47 ± 26 versus $33\pm 24g$, $P=0.04$).

All Baseline and Magnetic Resonance Imaging Variables Versus the Primary Outcome

Univariable analysis of all baseline clinical and MRI variables revealed only “primary prevention ICD” and total HE mass (all signal thresholds) to be associated with the primary outcome. The HR obtained for total HE mass $\geq 2SD$ was 1.40/10g (95% CI, 1.21–1.62, $P=0.001$), with similar hazards identified for $\geq 3SD$ and $\geq 5SD$ thresholds (HR 1.40 and 1.43, respectively). Multivariable analysis, performed separately for each total HE threshold definition, reliably revealed total HE to be the strongest independent predictor of the primary outcome. Following adjustment for “primary prevention ICD”, the adjusted HR for total HE $\geq 2SD$ was 1.38/10g (95% CI, 1.18–1.62, $P<0.001$).

Table 3. Univariate Analysis of Magnetic Resonance Imaging Variables for the Prediction of the Primary Outcome Stratified According to Cardiomyopathy Etiology

Variable	Total Population (N=124)				ICM (N=59)				DCM (N=65)			
	HR	95% CI	χ^2	PValue	HR	95% CI	χ^2	PValue	HR	95% CI	χ^2	PValue
Non-HE variables												
LVEF (%)	0.75	0.40–1.42	0.8	0.380	0.92	0.80–1.00	2.9	0.049	1.74	0.62–4.87	1.1	0.292
LV EDV (per 10 mL)	1.02	0.95–1.09	0.3	0.609	1.06	0.98–1.15	2.1	0.117	0.94	0.84–1.05	1.3	0.258
LV ESV (per 10 mL)	1.02	0.95–1.10	0.3	0.568	1.07	0.99–1.16	2.4	0.087	0.93	0.81–1.05	1.5	0.233
LV mass (per 10 g)	1.00	0.90–1.11	0.0	0.957	1.08	0.95–1.23	1.3	0.225	0.92	0.80–1.06	1.3	0.245
HE, visual												
Any HE	3.65	0.49–27.4	2.3	0.209	21.3	0.00–4.48	0.7	0.681	3.04	0.37–24.7	1.4	0.299
Sub-endocardial HE	1.14	0.45–2.88	0.1	0.787	21.3	0.00–4.48	0.7	0.681	0.04	0.00–208.8	2.4	0.459
Mid-wall HE	1.32	0.51–3.42	0.3	0.565	1.07	0.23–5.04	0.0	0.935	2.12	0.51–8.89	1.1	0.304
Sub-epicardial HE	1.64	0.54–4.97	0.7	0.386	0.48	0.00–3.76	0.3	0.772	2.87	0.72–11.5	2.1	0.136
HE, total HE mass (per 10 g)												
STRM												
$\geq 2SD$	1.40	1.21–1.62	16.3	0.001	1.70	1.26–2.30	12.9	0.001	1.31	1.08–1.60	5.3	0.007
$\geq 3SD$	1.40	1.21–1.63	15.9	0.001	1.67	1.25–2.24	11.9	0.001	1.34	1.10–1.63	5.5	0.004
$\geq 5SD$	1.43	1.21–1.68	14.2	0.001	1.58	1.19–2.10	9.2	0.001	1.39	1.11–1.74	5.3	0.004
FWHM												
$>50\%$					1.81	1.09–3.02	5.6	0.023				
HE, gray-zone HE mass (per 10 g)												
STRM												
2–3 SD					2.04	0.60–6.88	1.2	0.251				
2–5 SD					1.54	0.91–2.60	2.4	0.108				
FWHM												
35%–50%					1.47	0.96–2.26	2.7	0.074				

ICM indicates ischemic cardiomyopathy; DCM, dilated cardiomyopathy; HR, hazards ratio; HE, hyper-enhancement; LVEF, left ventricular ejection fraction; LV, left ventricular; EDV, end diastolic volume; ESV, end systolic volume; STRM, signal threshold versus reference myocardium; FWHM, full width half max

Sub-Cohort Analysis: Ischemic Cardiomyopathy and Dilated Cardiomyopathy

Within each of the ICM and DCM subcohorts, total HE mass was significantly higher among those with a primary outcome versus those without, irrespective of the signal threshold used. The mean total HE mass $\geq 2SD$ in those with and without a primary outcome was 69 ± 17 versus $42 \pm 19g$ ($P=0.001$) for those with ICM, and 46 ± 38 versus $23 \pm 15g$ ($P=0.003$) for those with DCM (Figure 2). Univariable analysis revealed that, while all signal thresholds were predictive, a $\geq 2SD$ threshold produced the highest HR in the ICM subcohort, while a $\geq 5SD$ threshold produced the highest in the DCM cohort (Table 3). A nonsignificant trend toward elevation in total HE mass was seen among those having a secondary outcome in each subcohort.

Event-Free Survival

Kaplan-Meier analyses were performed individually for the ICM and DCM subcohorts using their respective median values for total HE $\geq 2SD$ (38.7 g for ICM, and 20.8 g for DCM). These showed a higher cumulative risk of the primary outcome for those with high total HE burden in both cohorts. This finding reached significance for those with ICM (HR 3.7, 95%

CI, 1.1–12.1, $P=0.03$), but did not reach significance for those with DCM (HR 1.8, 95% CI, 0.4–7.6, $P=0.4$).

Event-free survival among the total population was estimated using respective median values for ICM and DCM patients as a cut-off, and is summarized in Figure 3. Those patients with a total HE mass above their respective median value demonstrated a higher cumulative risk for the primary outcome (HR 3.17, 95% CI, 1.3–8.0, $P=0.01$). Over a

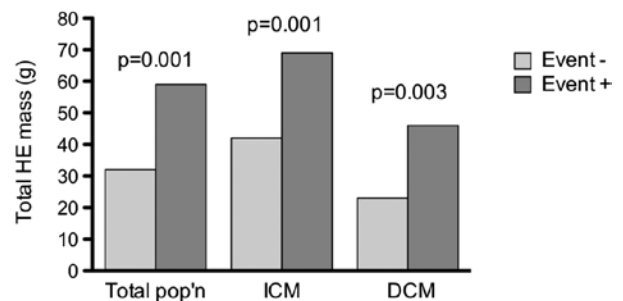


Figure 2. Graph showing mean total hyper-enhancement (HE) mass (signal threshold versus reference myocardium [STRM] $\geq 2SD$ threshold) in those with and without a primary outcome. Values are shown for the total population, ischemic cardiomyopathy (ICM) subcohort, and dilated cardiomyopathy (DCM) subcohort.

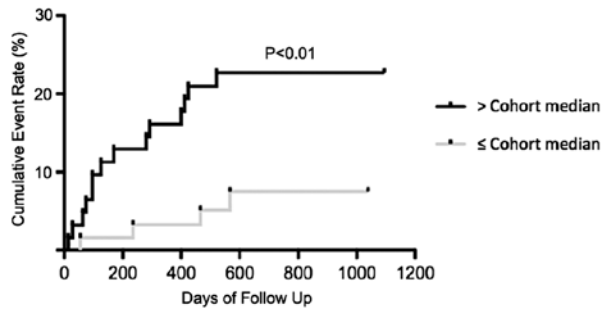


Figure 3. Kaplan-Meier analysis demonstrating the cumulative occurrence of the primary end point (appropriate implantable cardiac-defibrillator therapy, survived cardiac arrest, or sudden cardiac death) among the total population. Results shown according to a high versus low total hyper-enhancement burden (signal threshold versus reference myocardium ≥ 2 SD definition), using respective median cut off values for those with ischemic cardiomyopathy and dilated cardiomyopathy.

median follow-up of 632 ± 262 days, 14 patients (22%) in the high burden group versus only 4 patients (6%) in the low burden group experienced a primary outcome. The negative predictive value of total HE for the occurrence of the primary outcome was 86%.

Ischemic Cardiomyopathy Subcohort: Full Width Half Max-Based Analysis and Quantification of the Peri-Infarct Zone

To compare the use of STRM-based versus FWHM-based HE measures in those with ICM, individual receiver operating characteristic analyses were performed. This revealed only minor differences in predictive accuracy for total HE mass obtained using these techniques. For example, area under the curve (AUC) values for the STRM-based thresholds of ≥ 2 SD, ≥ 3 SD, and ≥ 5 SD were 0.78, 0.76, and 0.76, while the FWHM-based total HE achieved an AUC of 0.75.

Peri-infarct signal was calculated using the previously published STRM-based method (2SD minus 3SD)¹³ and the FWHM-based method.¹⁴ These measures, summarized in Table 2, showed only nonsignificant trends toward being higher in those with a primary outcome.

Interobserver and Intraobserver Reproducibility

Interobserver and intraobserver observer variability testing demonstrated excellent agreement for all HE measures. The ICC for intraobserver reliability for total HE measure was 0.96 (95% CI, 0.89–0.98), with ICC for interobserver reliability being 0.90 (95% CI, 0.78–0.96). Bland-Altman analyses of all HE measures are shown in Figure 4. Overall, the STRM-based ≥ 5 SD measure demonstrated the best reproducibility. Within the ICM cohort, the FWHM approach showed marginally better reproducibility compared with STRM-based techniques.

Discussion

This study identifies predictive utility for the quantification of HE by LGE-CMR in patients being referred for ICD therapy, irrespective of cardiomyopathy etiology. Total HE mass was found to be significantly higher among ICM and DCM patients suffering from appropriate ICD therapy, SCA, or SCD.

The extent of irreversible myocardial injury has been recognized as a marker of arrhythmia risk in ICM for some time. Bolick et al²² demonstrated in 1986 that the extent of myocardial scar on autopsy correlated with a prior history of VT in patients with ICM. Supporting this, Van der Burg et al²³ subsequently demonstrated that the extent of fixed perfusion defects on single photon emission computed tomography imaging predicted future arrhythmic events and death in patients with a history of survived SCA. Following these observations, Bello et al²⁴ performed a sentinel study demonstrating the direct measurement of myocardial scar extent by LGE-CMR and its correlation with the rate of VT inducibility at electrophysiological testing.

While clinical outcome-based studies evaluating the prognostic utility of LGE imaging have emerged,^{13,25,26} only 3 have evaluated arrhythmic events in an ICD referral population, each being limited to ICM.^{14,15,27} In the first study, published by Roes et al,¹⁴ 91 patients with ICM referred for primary or secondary prevention ICD were followed for the occurrence of appropriate ICD therapy (20%) over a median of 8.5 months. Using FWHM-based HE analysis, total infarct mass and the peri-infarct gray zone were found to be significantly higher in those with a primary outcome. In a second study, published by Scott et al,¹⁵ the FWHM technique was used again to measure total percent scar in 64 patients with ICM referred for ICD, and showed a strong association with the occurrence of appropriate ICD therapy (HR 1.75/10%). Finally, a recent study by de Haan et al²⁷ evaluated 55 patients with ICM referred for ICD, measuring total scar, core scar, and the peri-infarct zone. In this study total scar was predictive of arrhythmic events but, as seen in the current study, no incremental predictive value was provided by the measurement of the peri-infarct zone. This latter study also compared STRM-based and FWHM-based approaches for HE quantification, and found them to be similar for the estimation of total scar size, similar to the current study.

Our study provides further support for the predictive utility of HE quantification in patients with ICM referred for ICD, but incrementally suggests that HE quantification may be of value in those referred with DCM. Similar to their ICM counterparts, patients with DCM suffering from arrhythmic events demonstrated a significantly higher burden of total HE.

Study Limitations

Similar to published studies to date, ours was performed within a single center, was limited by a small sample size, and accrued a modest number of events. This underscores the need for larger, multicenter clinical studies aimed at evaluating the use of LGE imaging for the prediction of arrhythmic events in patients referred for ICD. Accordingly, our findings require confirmation within such a setting prior to their clinical application.

The study population consisted of patients being referred for ICD therapy with their MRI findings (LVEF) being accessible for clinical decision making. Accordingly, a number of patients were declined for ICD therapy due to a failure to confirm guideline-based LVEF criteria, all such patients having an LVEF between 36% and 40%. In addition, several patients were declined for ICD therapy due to comorbidity or to patient refusal to proceed. All enrolled patients were included in the final

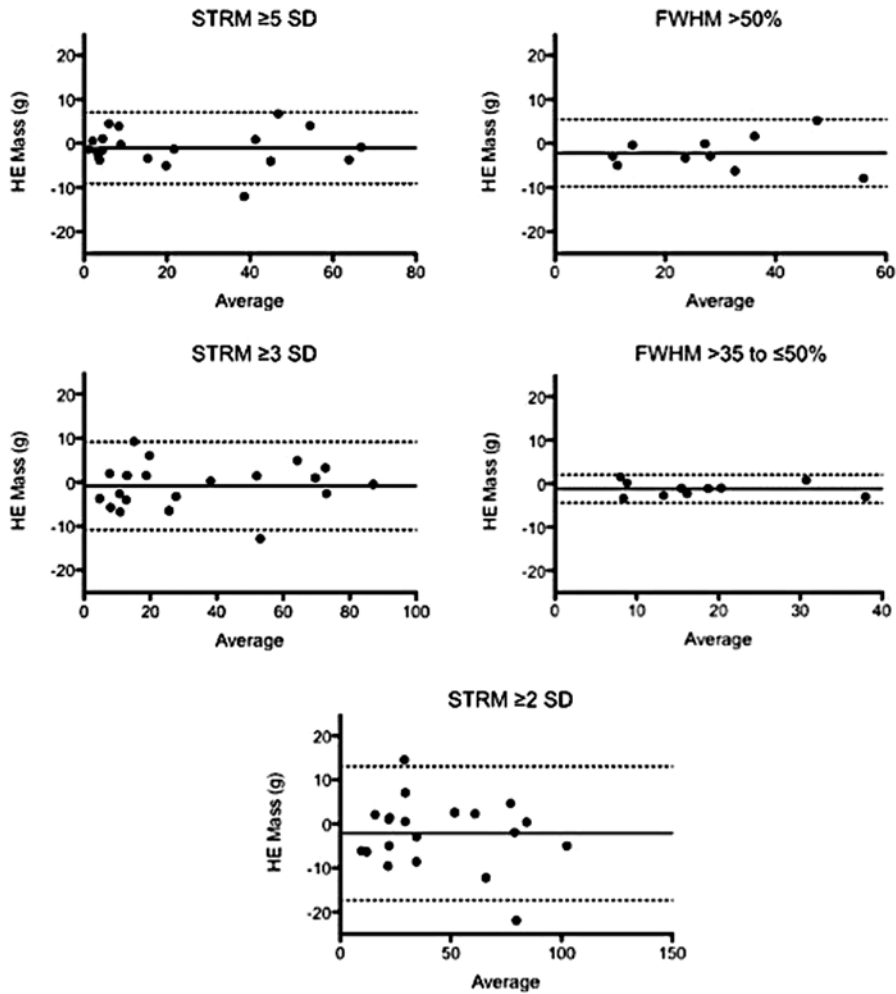


Figure 4. Interobserver variability testing results shown using Bland and Altman analysis for the signal threshold versus reference myocardium (STRM) technique (3 signal thresholds tested) and the full width half max (FWHM) technique.

analysis as it was the intent of this study to evaluate the role of LGE-CMR to predict future events when performed at time of ICD referral. In those patients not receiving ICD, a more robust clinical outcome (SCD or SCA) was mandated. All analyses were repeated with adjustment for ICD implantation status and demonstrated no significant differences.

The composite primary end point included appropriate ICD therapy, an outcome inherently dependent on programmed device settings. Ventricular tachyarrhythmias with cycle lengths slower than 320 ms (ie, “slow VT”) were monitored only by the device and not included within the composite primary end point. Progression of any such rhythm to life-threatening events (ICD therapy, SCD, or SCA) was captured routinely.

The FWHM-based HE quantification approach was employed only in the ICM cohort as it has not been validated for use in patients with DCM. From our center’s experience, the FWHM approach is not well-suited to HE quantification in DCM, as the peak HE signal is frequently modest and inherently leads to regions of normally nulled myocardium being labeled as “enhanced” relative to the modest HE reference signal. We do not consider this to be a limitation of the study, rather an inherent limitation of the described quantification technique for this patient cohort.

Conclusions

Total HE mass, measured by LGE-CMR imaging, is a strong predictor of appropriate ICD therapy, resuscitated SCA, or SCD among patients with ICM or DCM referred for ICD.

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CLINICAL PERSPECTIVE

Scar signal quantification on late gadolinium enhancement cardiac magnetic resonance has been proposed to have use for the prediction of arrhythmic events in patients with ischemic cardiomyopathy eligible for implantable cardiac defibrillators (ICD). For this noninvasive tool to have widespread clinical value it would ideally be applicable to ischemic and nonischemic referral populations, predict highly relevant clinical outcomes (such as appropriate ICD therapy, resuscitated cardiac arrest, and sudden cardiac death), and demonstrate associations independent of other validated risk markers, such as ejection fraction. In the current study of 124 consecutively referred patients, we demonstrate that total scar burden by signal quantification is a reproducible imaging biomarker that appears to meet these desired criteria. While being sensitive to distinct thresholds for ischemic and nonischemic subcohorts, the quantification of total scar burden identifies patients at an elevated risk of future arrhythmic events. These findings support a need for the expanded investigation of this imaging modality to identify patients most likely to benefit from ICD implantation.