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ORIGINAL RESEARCH

Entropy as a Measure of Myocardial Tissue Heterogeneity in Patients With Ventricular Arrhythmias

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ABSTRACT

OBJECTIVES The authors investigated the incremental prognostic value of entropy, a novel measure of myocardial tissue heterogeneity by cardiac magnetic resonance (CMR) imaging in patients presenting with ventricular arrhythmias (VAs).

BACKGROUND CMR can characterize myocardial areas serving as arrhythmogenic substrate.

METHODS Consecutive patients undergoing CMR imaging for VAs were followed for major adverse cardiac events (MACEs) defined by all-cause death, incident VAs requiring therapy, or heart failure hospitalization. Entropy was derived from the probability distribution of pixel signal intensities of the left ventricular (LV) myocardium.

RESULTS A total of 583 patients (age 54 ± 15 years, female 39%, left ventricular ejection fraction [LVEF] 54 ± 13%) were followed for a median of 4.4 years and experienced 141 MACEs. Entropy showed strong unadjusted association with MACE (HR: 1.88; 95% CI: 1.63-2.17; $P < 0.001$). In a multivariable model including LVEF, QRS duration, late gadolinium enhancement, and presenting arrhythmia, entropy maintained independent association with MACE (HR: 1.61; 95% CI: 1.32-1.96; $P < 0.001$). Entropy was further significantly associated with MACE in patients without myocardial scar (HR: 2.43; 95% CI: 1.55-3.82; $P < 0.001$) and in those presenting with nonsustained VAs (HR: 2.16; 95% CI: 1.43-3.25; $P < 0.001$). Addition of LV entropy to the baseline multivariable model significantly improved model performance (C-statistic improvement: 0.725 to 0.754; $P = 0.003$) and risk reclassification.

CONCLUSIONS In patients with VAs, CMR-assessed LV entropy was independently associated with MACE and provided incremental prognostic value, on top of LVEF and late gadolinium enhancement. LV entropy assessment may help risk stratification in patients with absence of myocardial scar or with nonsustained VAs.
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ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CMR = cardiac magnetic resonance
LGE = late gadolinium enhancement
LV = left ventricular
LVEDVI = left ventricular end-diastolic volume index
LVEF = left ventricular ejection fraction
LVESVI = left ventricular end-systolic volume index
NSVT = nonsustained ventricular tachycardia
PCI = percutaneous coronary intervention
RV = right ventricular
VAs = ventricular arrhythmias
WMA = wall motion abnormality

Sudden cardiac death (SCD) by ventricular arrhythmias (VAs) occurs on average in 350,000 individuals in the United States annually. Patients presenting with VAs pose unique diagnostic and prognostication challenges. Although one can identify patients at the highest risk of recurrent arrhythmias and SCD, those patients account for a minority of all events; the complex pathophysiology of the myocardial arrhythmic substrate makes it difficult to identify the majority of patients at risk.[1]

Cardiac magnetic resonance (CMR) imaging has the ability to broadly characterize myocardial tissue and provides detail about myocardial structural abnormalities that potentially form the substrate for VAs. Myocardial fibrosis detected by CMR using late gadolinium enhancement (LGE) is the most extensively studied technique to noninvasively characterize the underlying scar architecture and inform toward risk of scar-related re-entry tachyarrhythmias and SCD.[2] However, most signal intensity-based methods of LGE quantitation, focus on measuring scar presence, pattern, and extent and have limitations in assessing non-enhanced regions of the myocardium.[3]

Left ventricular (LV) entropy is a metric of image complexity, directly derived from the distribution of pixel signal intensities of the LV myocardium, using the CMR images generated by LGE imaging. Compared to LGE, entropy assessment aims to capture tissue heterogeneity of the entire left ventricle beyond visual and signal-intensity threshold based assessment of myocardial scar. In earlier studies, LV entropy showed excellent reproducibility and independent prognostic value for arrhythmic events in patients with severe systolic dysfunction.[4,5] In the current study, we investigated whether LV entropy has independent prognostic association with major adverse cardiac events (MACEs) incremental to established clinical and imaging risk markers in patients presenting with VAs.

TABLE 1 Baseline Clinical and CMR Characteristics According to Major Adverse Cardiac Events

	Overall (N = 583)	No MACE (n = 442)	MACE (n = 141)	*P* Value
Clinical data				
Age, y	54 ± 15	53 ± 15	57 ± 15	0.007
Female	225 (38.6)	182 (41.2)	43 (30.5)	0.023
BMI, kg/m^2	28 ± 6	28 ± 6	30 ± 7	0.012
Hypertension	210 (36.0)	149 (33.7)	61 (43.3)	0.040
Diabetes mellitus	65 (11.2)	40 (9.1)	25 (17.7)	0.004
Smoking	80 (13.7)	46 (10.4)	34 (24.1)	<0.001
Hypercholesterolemia	175 (30.0)	113 (25.6)	62 (44.0)	<0.001
Family history of CAD	68 (11.7)	48 (10.9)	20 (14.2)	0.284
History of PCI	40 (6.9)	27 (6.1)	13 (9.2)	0.203
History of MI	42 (7.2)	16 (3.6)	26 (18.4)	<0.001
History of heart failure	66 (11.3)	34 (7.7)	32 (22.7)	<0.001
NSVT	314 (53.9)	267 (60.4)	47 (33.3)	<0.001
VT/SCD	269 (46.1)	175 (39.6)	94 (66.7)	
Medications				
Aspirin	216 (37.1)	150 (33.9)	66 (46.8)	0.006
Statin	187 (32.1)	125 (28.3)	62 (44.0)	0.001
ACEi or ARB	171 (29.3)	119 (26.9)	52 (36.9)	0.024
Beta blockers	312 (53.5)	225 (50.9)	87 (61.7)	0.025
Calcium channel blockers	66 (11.3)	51 (11.5)	15 (10.6)	0.769
Class III antiarrhythmics	84 (14.4)	55 (12.4)	29 (20.6)	0.017
ECG parameters				
Heart rate, beats/min	70 ± 15	69 ± 14	71 ± 17	0.205
Sinus rhythm	504 (89.5)	382 (90.1)	122 (87.8)	0.154
Atrial fibrillation	28 (5.0)	17 (4.0)	11 (7.9)	
Other	31 (5.5)	25 (5.9)	6 (4.3)	
Right bundle branch block	60 (10.7)	39 (9.2)	21 (15.1)	0.050
Left bundle branch block	35 (6.0)	19 (4.3)	16 (11.4)	0.002
PR duration, ms	166 ± 34	162 ± 30	178 ± 44	<0.001
QRS duration, ms	98 ± 23	95 ± 20	106 ± 27	<0.001
QTc duration, ms	440 ± 36	435 ± 32	457 ± 44	<0.001
Significant Q-wave	59 (10.5)	34 (8.0)	25 (18.0)	0.001
ST-segment abnormalities	126 (22.4)	86 (20.3)	40 (28.8)	0.037
T-wave inversion	187 (33.2)	130 (30.7)	57 (41.0)	0.025

Continued on the next page

METHODS

PATIENT POPULATION. The study included consecutive patients referred to undergo clinical CMR for primary assessment of nonsustained ventricular tachycardia (NSVT), sustained ventricular tachycardia (VT), or aborted sudden cardiac arrest (SCD), between December 2003 and December 2018 at the Brigham and Women's Hospital, Boston, Massachusetts, USA. NSVT was defined as 3 or more consecutive ventricular beats at a rate ≥100 beats/min terminating spontaneously in <30 seconds. Sustained VT was defined as VT lasting ≥30 seconds or requiring termination in <30 seconds due to hemodynamic compromise.[6] We excluded patients who: 1) developed VAs within 72 hours after an acute coronary syndrome; 2) had contraindications to a contrast-enhanced CMR, such as presence of magnetic resonance-incompatible implants or chronic kidney disease with a glomerular filtration rate <30 mL/min/1.73 m^2; or 3) had congenital VT (including catecholaminergic VT, Brugada syndrome, idiopathic QT syndromes or other, diagnosed on the basis of the family history, electrocardiogram [ECG], and genetic testing).

CMR PROTOCOL. All studies were performed with either a 3.0-T or a 1.5-T system (Tim Trio and Aera, Siemens). Assessment for LV and right ventricular (RV) function and LV mass was performed using steady-state free precession imaging with typical

parameters as follows: repetition time (TR), 3.4 ms; echo time (TE), 1.2 ms; in-plane spatial resolution 1.6 × 2 mm. Cine imaging was obtained in the short axis with slice thickness of 8 mm and no gap. For detection of LGE, patients underwent injection of a weight-based gadolinium agent (cumulative 0.15 mmol/kg), either gadolinium diethylenetriamine pentaacetic acid (Magnevist, Bayer HealthCare Pharmaceuticals) or gadoterate meglumine (Dotarem, Guerbet). Fifteen minutes after contrast injection, fast-gradient echo LGE imaging (TR, 4.8 ms; TE, 1.3 ms; inversion time, 200-300 ms) was performed using a segmented inversion-recovery pulse sequence.

Post-processing of CMR images was blinded to all clinical data and performed using specialized software (Medis Suite v3.1, Medis). Epicardial and endocardial contours were manually traced on steady-state free precession images to quantify left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF), and LV mass. The presence of wall motion abnormalities was assessed according to the 17-segment American Heart Association model. LGE was assessed according to presence/absence, pattern (subendocardial, midwall, epicardial, patchy, and other), and location (anterior, septal, inferior, and lateral). In patients with visual presence of LGE, LGE mass was quantified using the full-width at half maximum technique and expressed as a percentage of total LV mass.[7]

LV ENTROPY ASSESSMENT. To calculate LV entropy, epicardial and endocardial contours were manually traced on the stack of LGE short-axis images with careful exclusion of any blood pool signal. LV entropy values were directly derived from the distribution of pixel signal intensities of the LV myocardium on LGE images and automatically generated using ResearchMass (Leiden University Medical Center, Leiden, the Netherlands) according to the following formula[4,5]:

$$\text{Entropy} = -\sum_{i=1}^{n} P(x_i)\log_b P(x_i)$$

where $P(x_i)$ is the probability distribution of signal intensity x_i, and b is any chosen logarithm base ($b = 2$ by default in ResearchMass). Signal intensity was normalized according to a predefined range between 0 and 1,024 for each patient, such that the generated entropy values would range between 0 and 10.

FOLLOW-UP AND MACE. Electronic medical records across teaching hospitals of Mass General Brigham were blindly reviewed to assess for MACE. In cases where hospital records were insufficient, direct patient contact was further sought by a standardized checklist questionnaire by postal mail, a scripted telephone interview, or both. Mortality status was also verified using the Social Security Death Index. Two cardiologists (Y.G., P.A.) blinded to CMR results performed all standardized follow-up procedures and adjudication of all events. Ascertainment of MACE was performed until June 30, 2020, after which the data set was locked.

TABLE 1 Continued

	Overall (N = 583)	No MACE (n = 442)	MACE (n = 141)	*P* Value
CMR parameters				
LVEF, %	54 ± 13	57 ± 11	47 ± 16	<0.001
LVEDVi, mL/m^2	89 ± 28	85 ± 23	101 ± 38	<0.001
LVESVi, mL/m^2	43 ± 27	38 ± 21	57 ± 38	<0.001
LV mass index, g/m^2	58 ± 17	56 ± 16	66 ± 18	<0.001
RVEF, %	52 ± 9	53 ± 8	48 ± 10	<0.001
RVEDVi, mL/m^2	78 ± 20	78 ± 19	80 ± 21	0.134
RVESVi, mL/m^2	38 ± 15	37 ± 13	43 ± 18	<0.001
Presence of LGE	227 (38.9)	138 (31.2)	89 (63.1)	<0.001
Extent of LGE[a]				
1-2 segments	90 (39.7)	56 (40.6)	34 (38.2)	0.201
3-5 segments	82 (36.1)	54 (39.1)	28 (31.5)	
>5 segments	55 (24.2)	28 (20.3)	27 (30.3)	
Extent of LGE, % of LV mass	3.7 ± 6.8	2.8 ± 5.7	6.5 ± 8.7	<0.001
Pattern of LGE[a]				
Subendocardial	109 (48.0)	62 (14.0)	47 (33.3)	<0.001
Midwall	47 (20.7)	33 (7.5)	14 (9.9)	
Subepicardial	24 (10.6)	14 (3.2)	10 (7.1)	
Patchy	26 (11.5)	16 (3.6)	10 (7.1)	
Other	21 (9.2)	13 (2.9)	8 (5.7)	
Location of LGE				
Anterior	46 (7.9)	24 (5.4)	22 (15.6)	<0.001
Septum	138 (23.7)	85 (19.2)	53 (37.6)	<0.001
Inferior	110 (18.9)	66 (14.9)	44 (31.2)	<0.001
Lateral	129 (22.1)	79 (17.9)	50 (35.5)	<0.001
Resting WMA	187 (32.3)	112 (25.5)	75 (54.0)	<0.001
Anterior	117 (20.2)	65 (14.8)	52 (37.4)	<0.001
Septum	138 (23.8)	81 (18.4)	57 (41.0)	<0.001
Inferior	146 (25.2)	87 (19.8)	59 (42.5)	<0.001
Lateral	152 (26.3)	90 (20.5)	62 (44.6)	<0.001
LV wall entropy				
1.5-T (n = 124)	3.6 ± 0.6	3.5 ± 0.5	3.8 ± 0.7	0.014
3.0-T (n = 459)	4.8 ± 0.7	4.6 ± 0.6	5.3 ± 0.7	<0.001
LV wall entropy, z-score	0 ± 1.0	-0.2 ± 0.9	0.6 ± 1.1	<0.001
1.5-T (n = 124)	0 ± 1.0	-0.1 ± 0.9	0.3 ± 1.2	0.014
3.0-T (n = 459)	0 ± 1.0	-0.2 ± 0.9	0.7 ± 1.0	<0.001

Values are mean ± SD or n (%), unless otherwise stated. [a]In patients with LGE.

ACEi = angiotensin conversion enzyme inhibitors; ARB = angiotensin II receptor blockers; BMI = body mass index; CAD = coronary artery disease; CMR = cardiac magnetic resonance; ECG = electrocardiogram; LGE = late gadolinium enhancement; LV = left ventricular; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVi = left ventricular end-systolic volume index; MACE = major adverse cardiac events; MI, myocardial infarction; NSVT = nonsustained ventricular tachycardia; PCI = percutaneous coronary intervention; RVEDVi = right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi = right ventricular end-systolic volume index; SCD = sudden cardiac death; VT = sustained ventricular tachycardia; WMA = wall motion abnormality.

TABLE 2 Univariate Association of Clinical and CMR Characteristics With Major Adverse Cardiac Events

	HR (95% CI)	Chi Square	*P* Value
Age, per 10 y	1.19 (1.05-1.34)	7.7	0.006
Male	1.53 (1.07-2.18)	5.6	0.021
BMI, per kg/m^2	1.03 (1.01-1.05)	5.9	0.009
Hypertension	1.47 (1.05-2.05)	5.0	0.024
Diabetes mellitus	1.97 (1.28-3.03)	8.1	0.002
Smoking	2.21 (1.50-3.25)	14.0	<0.001
Hypercholesterolemia	1.95 (1.40-2.72)	14.8	<0.001
Family history of CAD	1.06 (0.66-1.70)	0.1	0.815
History of PCI	1.64 (0.93-2.90)	2.5	0.090
History of MI	4.00 (2.61-6.13)	29.9	<0.001
History of heart failure	2.72 (1.83-4.03)	20.3	<0.001
VT/SCD vs NSVT	2.80 (1.97-3.97)	35.5	<0.001
Right bundle branch block	1.65 (1.04-2.63)	4.0	0.034
Left bundle branch block	2.79 (1.66-4.71)	11.5	<0.001
PR duration, per 10 ms	1.09 (1.05-1.13)	18.5	<0.001
QRS duration, per 10 ms	1.16 (1.10-1.23)	21.5	<0.001
QTc duration, per 10 ms	1.14 (1.10-1.18)	38.5	<0.001
Significant Q-wave	2.30 (1.49-3.55)	11.8	<0.001
ST-segment abnormalities	1.60 (1.11-2.31)	5.9	0.012
T-wave inversion	1.61 (1.15-2.25)	7.3	0.006
LVEF, per 5%	0.79 (0.75-0.83)	68.0	<0.001
LVEDVi, per 10 mL/m^2	1.14 (1.10-1.19)	30.7	<0.001
LVESVi, per 10 mL/m^2	1.15 (1.11-1.19)	40.9	<0.001
LV mass index, per 10 g/m^2	1.24 (1.16-1.32)	29.6	<0.001
RVEF, per 5%	0.77 (0.71-0.83)	36.8	<0.001
RVEDVi, per 10 mL/m^2	1.10 (1.01-1.19)	4.3	0.035
RVESVi, per 10 mL/m^2	1.25 (1.14-1.37)	18.6	<0.001
Resting WMA	3.05 (2.18-4.27)	41.7	<0.001
Presence of LGE	3.35 (2.38-4.74)	39.2	<0.001
Extent of LGE (vs no LGE)		49.6	
1-2 segments	2.92 (1.89-4.50)		<0.001
3-5 segments	2.94 (1.85-4.67)		<0.001
>5 segments	5.07 (3.17-8.10)		<0.001
Extent of LGE, per 10% of LV mass	1.91 (1.61-2.28)	54.8	<0.001
LV Wall Entropy, per 1 SD[a]	1.88 (1.63-2.17)	66.8	<0.001

[a]After standardization of LV wall entropy values by field strength (1.5T or 3.0T) and calculation of an overall LV wall entropy Z-score (mean of 0, SD of 1).
Abbreviations as in Table 1.

MACEs were defined as a composite of: 1) all-cause death; 2) any new sustained VT requiring therapy; or 3) heart failure hospitalization, as per standardized clinical trial definitions.[8] The definition of MACE was prespecified before the start of the study. When multiple events occurred in the same patient, only the first event was counted. All study procedures were approved by the Institutional Review Board at Brigham and Women's Hospital and written informed consent was waived for this study. All patients had the option of refusing follow-up contact throughout the study duration.

STATISTICAL ANALYSIS. Continuous variables were expressed as mean ± SD or as median with IQR and compared using a 2-sample Student *t*-test or Wilcoxon rank-sum test, depending on the distribution. Categorical variables were presented as frequencies with percentages and compared using the chi square test. Because the magnetic field strength may affect the signal intensity distribution and measured entropy values, we accordingly standardized LV wall entropy values by calculating a corresponding LV wall entropy Z-score (mean of 0, SD of 1), by field strength (1.5-T or 3.0-T).[4] Annualized event rates were calculated by dividing the number of patients who experienced MACE by total patient-years of follow-up. Univariable associations of each covariate with MACE were determined by Cox proportional hazards regression. The proportional hazards assumption was evaluated using visual inspection of the log-log survival curves and the Schoenfeld residuals test. Cumulative incidence curves were displayed using Kaplan-Meier and compared with the log-rank test. To test the independent association of LV entropy with MACE, we constructed a multivariable baseline clinical model by including variables that: 1) showed robust association ($P < 0.001$) with MACE in univariate analysis; and 2) reflected clinical decision-making according to current guidelines and practice.[6,9] The baseline multivariable model included age, sex, presenting arrhythmia (VT/SCD vs NSVT), QRS duration >120 ms, CMR-assessed LVEF, and extent of LGE. Standardized LV entropy was then added to the multivariable model to assess its incremental prognostic value. We further calculated the change in model discrimination by the Harrell's C-statistic, before and after addition of LV entropy. Given that treatment-related clinical risk categories have not been determined in patients with VAs, we finally assessed the category-free, continuous net reclassification improvement (cNRI) and integrated discrimination index (IDI), before and after addition of LV entropy.[10,11] SAS was used for all statistical analysis version 9.4 (SAS Institute Inc). A 2-sided *P* value of <0.05 was deemed significant.

RESULTS

BASELINE CLINICAL AND CMR CHARACTERISTICS OF THE STUDY POPULATION. Six hundred forty-two patients met initial inclusion and exclusion criteria. After further exclusion of 14 patients who lacked LGE sequences and 45 patients with uninterpretable LGE images and, hence, missing LV entropy values, a total of 583 patients formed the cohort for this analysis. Table 1 shows baseline clinical and CMR characteristics according to MACE. Mean age at presentation was 54 ± 15 years of age, with 39% female and a 1:1 ratio of

NSVT:VT/SCD as the presenting arrhythmia. Patients who experienced MACE were older, more likely to be male, with a higher prevalence of cardiovascular risk factors—including hypertension, diabetes, smoking, hypercholesterolemia, history of myocardial infarction (MI), history of heart failure—and higher rates of cardiovascular medications ($P < 0.05$ for all). They were also more likely to clinically present with VT/SCD instead of NSVT and had significantly higher rates of left bundle branch block, wide QRSs, significant Q waves, and ST/T abnormalities ($P < 0.05$ for all) on ECG.

With regards to CMR parameters, mean LV and RV systolic function were within the normal range (LVEF: 54 ± 13%; RVEF: 52 ± 9%). Thirty-nine percent of subjects had evidence of myocardial fibrosis by LGE, the majority of them showing a subendocardial (48%) or midwall (21%) pattern. Subjects with MACE had significantly lower LVEF, lower RVEF, higher LV mass, and a higher prevalence and extent of wall motion abnormalities (WMAs) and LGE ($P < 0.001$ for all). They also presented with significantly higher LV entropy values (**Table 1**).

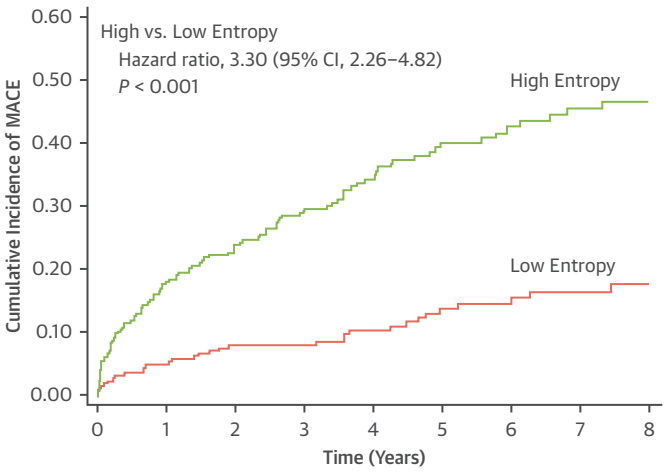
Finally, associations of LV entropy with clinical and CMR characteristics are presented in Supplemental Table 1. LV entropy was significantly positively associated with history of MI ($P < 0.001$), presence and extent of LGE ($P < 0.001$), LV mass index ($P = 0.002$), and negatively correlated with LVEF and RVEF ($P < 0.001$ for both).

ASSOCIATIONS OF CLINICAL AND CMR PARAMETERS WITH MACE. Median follow-up was 4.4 years (IQR: 2.0-7.7 years). We observed 141 MACE events, consisting of a total of 96 sustained VAs, 33 heart failure hospitalizations, and 51 deaths.

Univariate associations of clinical and CMR parameters with MACE are presented in **Table 2**. Age, male sex, hypertension, diabetes, smoking, and hypercholesterolemia had significant associations with MACE ($P < 0.05$ for all), and so had history of MI ($P < 0.001$) or history of heart failure ($P < 0.001$). Subjects presenting with VT/SCD had an HR of 2.8 (95% CI: 1.97-3.97; $P < 0.001$) for MACE compared to those presenting with NSVT. Among ECG parameters, right bundle branch block, left bundle branch block, increasing PR, QRS, or QTc durations, significant Q waves and ST/T abnormalities also showed significant associations with MACE.

CMR-assessed biventricular function (per 5% LVEF HR: 0.79, 95% CI: 0.75-0.83; per 5% RVEF HR: 0.77, 95% CI: 0.71-0.83; $P < 0.001$ for both) and LV mass (HR: 1.24; 95% CI: 1.16-1.32; $P < 0.001$) were strong predictors for MACE as were presence of WMA, and presence (HR: 3.35; 95% CI: 2.38-4.74; $P < 0.001$) and extent of LGE (per 10% LV mass HR: 1.91; 95% CI: 1.61-2.28; $P < 0.001$).

FIGURE 1 Time-To-Event Curves for MACE Stratified by "High" Vs "Low" LV Wall Entropy Values

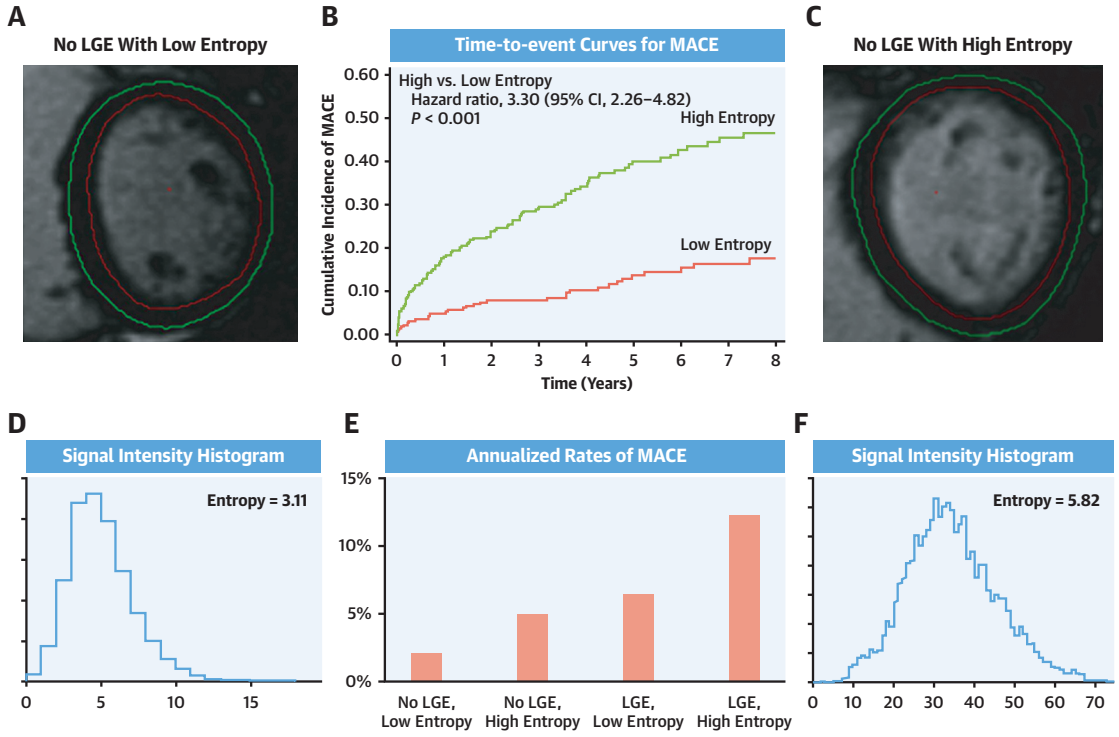


Time-to-event curves for MACE. Event-free survival for patients with "above median" (high) versus "below median" (low) LV entropy are shown in **green,** and **red,** respectively. Statistical analysis using log-rank test for high vs low LV entropy. LV = left ventricular; MACE = major adverse cardiac event.

LV entropy was a strong univariate predictor for MACE (per 1 SD HR: 1.88; 95% CI: 1.63-2.17; $P < 0.001$) as well as individual components of MACE (Supplemental Table 2): VA (per 1 SD HR: 1.80; 95% CI: 1.52-2.14; $P < 0.001$), heart failure hospitalization (per 1 SD HR: 2.50; 95% CI: 1.93-3.24; $P < 0.001$), and all-cause mortality (per 1 SD HR: 1.83; 95% CI: 1.46-2.30; $P < 0.001$). In Kaplan-Meier analysis, patients with "high" (above median) vs "low" (above median) LV entropy had significantly higher cumulative incidence of MACE (HR: 3.3; 95% CI: 2.26-4.82; $P < 0.001$) (**Figure 1, Central Illustration**). Similar results were obtained in patients with absence of LGE on CMR as well as in the subgroup of patients presenting with NSVT (Supplemental Figure 1).

Annualized rates for MACE stratified by absence/presence of LGE and low/high entropy are shown in **Figure 2** and the **Central Illustration**. In subjects with absence of LGE, those with low LV entropy had a 2.1% annual rate for MACE, compared to 5.0% for those with high LV entropy. In subjects with presence of LGE, those with low LV entropy had a 6.5% annual rate for MACE, compared to 12.4% for those with high LV entropy. Annualized rates for MACE stratified by presenting arrhythmia (NSVT vs VT/SCD) and low/high entropy are presented in **Figure 3**. For NSVT, low LV entropy portended a 1.4% per year rate for MACE,

CENTRAL ILLUSTRATION Left Ventricular Wall Signal Intensity Histograms, MACE Rates and Survival Curves Stratified by Entropy Values



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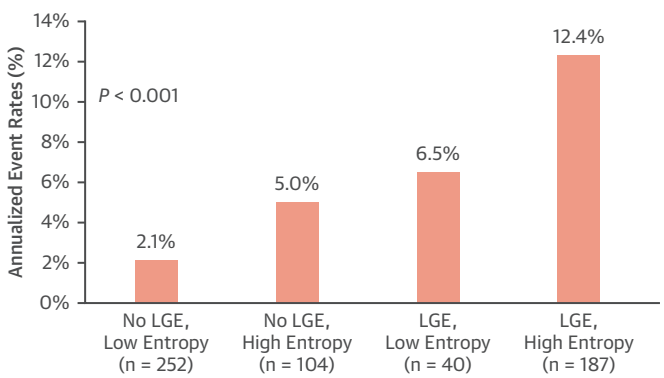
(A, C) Short-axis LV wall images with the epicardial border in **green** and the endocardial border in **red,** from 2 patients with absence of LGE, but markedly different LV entropy values. **(B)** Time-to-event curves for MACE stratified by "high" **(green)** vs "low" **(red)** LV wall entropy values. **(D, F)** Histograms of signal intensity in LV wall among the aforementioned patients. The high frequency of pixels within a narrow range of signal intensities for patient 1 suggest little heterogeneity of the myocardial tissue (LV entropy = 3.11) **(D)**. Significantly more dispersed distribution of signal intensities for patient 2 suggest marked heterogeneity of the myocardial tissue, despite the absence of scar (LV entropy = 5.82) **(F)**. Both patients were scanned using 3.0-T scanners. **(E)** Annualized event rates stratified by absence vs presence of LGE and/or "low" vs "high" entropy.

FIGURE 2 Annualized Event Rates Stratified by Absence Vs Presence of LGE and "Low" Vs "High" Entropy



"Low"/"high" entropy values defined as "below median"/"above median," respectively. LGE = late gadolinium enhancement.

compared to 5.6% for high entropy. For VT/SCD, low LV entropy carried a 5.0% per year rate for MACE, compared to 13.2% for high entropy.

MULTIVARIABLE MODEL AND SUBGROUP ANALYSIS. We constructed a multivariable baseline clinical model by including variables that showed an association at $P < 0.001$ with MACE in univariate analysis and reflect clinical practice based on current guidelines. The baseline multivariable model included age, sex, presenting arrhythmia (VT/SCD vs NSVT), QRS duration >120 ms, CMR-assessed LVEF, and extent of LGE. When LV entropy was added to this baseline model, it maintained its independent association with MACE (per 1 SD HR: 1.61; 95% CI: 1.32-1.96; $P < 0.001$) (Table 3). LV entropy further maintained a significant adjusted association with the arrhythmic endpoint of new sustained VT alone (per 1 SD HR:

1.55; 95% CI: 1.22-1.97; $P < 0.001$) (Supplemental Table 3).

The association of LV entropy with MACE remained robust in the subgroup of patients with absence of LGE, where LV entropy was the strongest predictor of MACE (per 1 SD HR: 2.43; 95% CI: 1.55-3.82; $P < 0.001$) (**Table 4**). LV entropy was also significantly associated with MACE in those with presence of LGE (per 1 SD: HR: 1.29; 95% CI: 1.04-1.60; $P = 0.021$) (**Table 4**). Comparable results were obtained with regards to the arrhythmic endpoint of new sustained VT alone (Supplemental Table 4). Finally, LV entropy maintained a significant association with MACE in the subgroup of patients presenting with NSVT (per 1 SD HR: 2.16; 95% CI: 1.43-3.25; $P < 0.001$) (**Table 5**). In those patients, the adjusted association of LV entropy with new sustained VT alone was further maintained (per 1 SD HR: 2.43; 95% CI: 1.47-4.04; $P = 0.001$) (Supplemental Table 5). Similar results were obtained in patients presenting with VT/SCD, where LV entropy was the only significant predictor of MACE (per 1 SD HR: 1.43; 95% CI: 1.13-1.81; $P < 0.003$) (**Table 5,** Supplemental Table 5).

MODEL DISCRIMINATION AND RECLASSIFICATION IMPROVEMENT. Adding LV entropy on top of the multivariable baseline model significantly improved the C-statistic (0.725 [95% CI: 0.684-0.766] to 0.754 [95% CI: 0.715-0.792]; $P = 0.003$), as well as reclassification indices (IDI: 0.060 [95% CI: 0.036-0.083]; $P < 0.001$; cNRI: 0.555 [95% CI: 0.341-0.754]; $P < 0.001$) (**Table 6**) for MACE. For the arrhythmic endpoint of new sustained VT alone, we obtained comparable results (C-statistic improvement from 0.714 to 0.749; $P = 0.007$) (Supplemental Table 6).

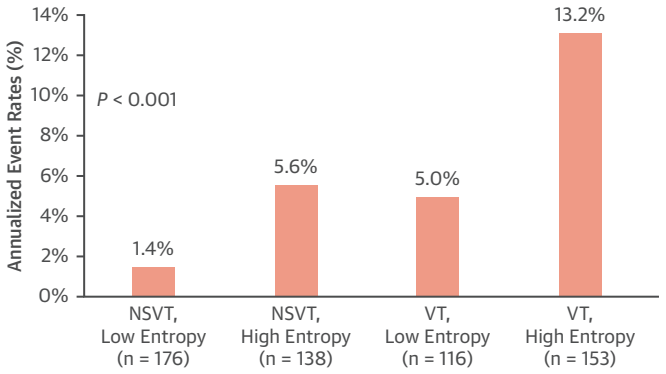
Further, in subjects with absence of LGE, addition of LV entropy to the baseline clinical model also yielded a significant improvement in C-statistic (0.723 [95% CI: 0.682-0.765] to 0.749 [95% CI: 0.711-0.788]; $P = 0.041$) and reclassification metrics (IDI: 0.058 [95% CI: 0.032-0.085]; $P < 0.001$; cNRI: 0.578 [95% CI: 0.299-0.971]; $P < 0.001$) (Supplemental Table 7). Results were similar in the subgroup of patients presenting with NSVT (C-statistic improvement: 0.748 [95% CI: 0.667-0.828] to 0.788 [95% CI: 0.712-0.864]; $P = 0.026$) (Supplemental Table 8).

DISCUSSION

We observed that in patients presenting with ventricular arrhythmias, LV entropy—a novel measure of myocardial heterogeneity—demonstrated a strong prognostic association with MACE beyond guideline-based, clinical risk markers including LVEF, QRS duration, presence and size of LGE, or presenting arrhythmia (NSVT or VT/SCD). Furthermore, in patients with absence of myocardial scar, LV entropy emerged as the strongest multivariable predictor of MACE. LV entropy can be rapidly derived from routine LGE images with minimal postprocessing and involves the entire LV myocardium, holding promise as a reliable marker of global myocardial tissue inhomogeneity with prognostic value.

LV ENTROPY AS AN EMERGING RISK STRATIFICATION TOOL FOR MACE. Several small-scale observational studies have examined the prognostic association of LV entropy in selected patients with LV dysfunction referred for implantable cardioverter-defibrillator (ICD) placement. In 130 patients with dilated cardiomyopathy (DCM) referred for primary prevention ICD, Muthalaly et al[4] reported that LV entropy was predictive of arrhythmic events beyond clinical

FIGURE 3 Annualized Event Rates Stratified by Presenting Arrhythmia (NSVT vs VT) and "Low" Vs "High" Entropy



"Low"/"high" entropy values defined as "below median"/"above median," respectively. NSVT = nonsustained ventricular tachycardia; VT = ventricular tachycardia.

TABLE 3 Multivariable Association of Clinical and CMR Characteristics With MACE

	HR (95% CI)	*P* Value
Age, per 10 y	1.11 (0.98-1.25)	0.110
Male	1.25 (0.85-1.84)	0.265
VT/SCD vs NSVT	2.02 (1.40-2.92)	<0.001
QRS >120 ms	0.92 (0.58-1.45)	0.714
LVEF, per 5%	0.86 (0.80-0.92)	<0.001
Extent of LGE, per % of LV mass	0.98 (0.95-1.01)	0.229
LV wall entropy, per 1 SD[a]	1.61 (1.32-1.96)	<0.001

[a]After standardization of LV wall entropy values by field strength (1.5T or 3.0T) and calculation of an overall LV wall entropy Z-score (mean of 0, SD of 1).
Abbreviations as in Table 1.

TABLE 4 Multivariable Association of Clinical and CMR Characteristics With MACE, Stratified by the Presence of LGE

	Patients Without LGE (n = 356)		Patients With LGE (n = 227)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, per 10 y	1.15 (0.96-1.39)	0.138	1.06 (0.90-1.25)	0.506
Male	1.80 (0.99-3.26)	0.054	0.81 (0.49-1.33)	0.404
VT/SCD vs NSVT	2.16 (1.20-3.89)	0.011	1.74 (1.08-2.79)	0.023
QRS >120 ms	1.55 (0.68-3.55)	0.296	0.89 (0.52-1.53)	0.684
LVEF, per 5%	0.82 (0.72-0.93)	0.002	0.88 (0.81-0.95)	0.001
LV wall entropy, per 1 SD[a]	2.43 (1.55-3.82)	<0.001	1.29 (1.04-1.60)	0.021

[a]After standardization of LV wall entropy values by field strength (1.5T or 3.0T) and calculation of an overall LV wall entropy Z-score (mean of 0, SD of 1)

Abbreviations as in Table 1.

variables and LGE extent. In patients with ischemic cardiomyopathy and LV dysfunction, Androulakis et al[5] showed that LV entropy was associated with mortality, whereas entropy of the myocardial scar was associated with arrhythmic events. Gould et al[12] studied a mix of ischemic and nonischemic cardiomyopathies and used filtered LGE images before entropy calculation. Higher entropy (heterogeneity) of the myocardial scar was associated with more aggressive VAs requiring cardioversion.

Our study expands on the existing literature in significant ways. First, our cohort represents the largest experience using LV entropy to improve the prognosis of patients at risk of VAs. Second, whereas previous studies included patients referred with low LVEF, our study focused on the potential value of LV entropy in a population with largely preserved ventricular function—a heterogeneous group that accounts for the majority of SCDs, and for whom risk stratification is particularly challenging. Therefore, we were able to assess the prognostic value of LV entropy beyond the presence of underlying structural heart disease and myocardial scar across both primary and secondary prevention of MACE.

TABLE 5 Multivariable Association of Clinical and CMR Characteristics With MACE, Stratified by the Presenting Arrhythmia

	Patients With NSVT (n = 314)		Patients With VT/SCD (n = 269)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, per 10 y	1.27 (0.99-1.63)	0.056	1.07 (0.93-1.24)	0.355
Male	1.82 (0.95-3.52)	0.073	0.95 (0.58-1.54)	0.827
QRS >120 ms	0.84 (0.29-2.50)	0.759	1.21 (0.72-2.02)	0.472
LVEF, per 5%	0.75 (0.68-0.83)	<0.001	0.93 (0.85-1.01)	0.093
Extent of LGE, per % of LV mass	0.89 (0.81-0.97)	0.007	1.01 (0.98-1.05)	0.527
LV wall entropy, per 1 SD[a]	2.16 (1.43-3.25)	<0.001	1.43 (1.13-1.81)	0.003

[a]After standardization of LV wall entropy values by field strength (1.5T or 3.0T) and calculation of an overall LV wall entropy Z-score (mean of 0, SD of 1)

Abbreviations as in Table 1.

IMPLICATIONS FOR PRIMARY PREVENTION OF MACE. NSVT is associated with a wide range of clinical conditions from asymptomatic, healthy, young individuals to patients with significant underlying heart disease and annual mortality rates exceeding 50%.[13] Apart from few disease-specific indications, current guidelines for identifying candidates for ICD therapy in primary prevention mainly rely on using LVEF <35% as the principal criterion for selection.[6,9] However, LVEF does not have the ability to capture the underlying arrhythmogenic substrate and has a limited predictive ability for events.[14] In our study, of the 47 patients in the NSVT group who experienced MACE, 36 (77%) had an LVEF >35%, 24 (51%) had a normal LVEF (>52%), and 14 (30%) had both a normal LVEF and absence of LGE on CMR. Those observations underscore the current limitations of prognostication based solely on LVEF assessment and suggest a potential role of LV entropy in refining risk prediction in patients presenting with NSVT, as part of a multiparametric assessment of myocardial tissue by CMR.

LV ENTROPY FOR ASSESSMENT OF MYOCARDIAL HETEROGENEITY. The presence of fibrosis causing electric instability in the LV myocardium through reentrant arrhythmias is a well-recognized mechanism for SCD. In electrophysiological studies, a key aim is to identify areas of fibrosis as a focus for ablation, and LGE by CMR has been shown to have important prognostic value in patients presenting with VT/SCD, as well as NSVT.[15-17] The prognostic association of LGE presence with MACE has already been established both for ischemic and nonischemic cardiomyopathies.[14,18] However, most of these studies followed patients who already qualified for an ICD and therefore had severely depressed LVEF compared to our cohort where more than two-thirds had preserved LVEF (>52%). Furthermore, more than one-half of patients with nonischemic cardiomyopathy do not show LGE in part caused by its limitation in delineating diffuse myocardial fibrosis.[3]

For patients with absence of myocardial scar, LV entropy emerged as the strongest predictor of MACE above LVEF, QRS duration, and mode of presentation (NSVT vs VT/SCD). Of the 52 patients with absence of LGE who experienced MACE, 22 (42%) presented with NSVT, 46 (88%) had an LVEF >35%, and a considerable 38% presented both with NSVT and LVEF >35%. In this specific population of patients, where risk stratification tools are scarce, LV entropy

TABLE 6 Model Discrimination and Reclassification Improvement for MACE After Addition of LV Entropy to the Multivariable Baseline Model

	Statistic (95% CI)	*P* Value
C-statistic		
Baseline model	0.725 (0.684-0.766)	—
Baseline model + LV wall entropy	0.754 (0.715-0.792)	0.003
IDI	0.060 (0.036-0.083)	<0.001
cNRI	0.555 (0.341-0.754)	<0.001

Baseline model adjusted for age, sex, presenting arrhythmia (NSVT vs VT/SCD), QRS duration, LVEF, and extent of LGE.

cNRI = continuous net reclassification improvement; IDI = integrated discrimination index; other abbreviations as in Table 1.

may represent a valuable marker of prognostic importance.

Both in patients with and without macroscopic scar, LV entropy captures the heterogeneity of the totality of myocardial tissue. Therefore, LV entropy assessment in patients with myocardial scar indirectly includes characterization the peri-infarct zone. Heterogeneity in this area—referred to as "gray zone" in contrast to "core scar"—has been shown to represent myocardial tissue that is arrhythmogenic.[19,20] Nevertheless, the definitions of core scar and gray zone require setting signal intensity thresholds that often vary between studies.[21] Derived from the entirety of the signal intensity distribution, LV entropy is threshold-free and possibly allows detection of more gradual differences in myocardial texture. In patients without myocardial scar, those subtle differences in tissue heterogeneity may correspond to early myocardial fibrosis.

STUDY LIMITATIONS. First, our study was unable to assess the prognostic value of LV entropy across various specific causes of structural heart disease. Second, because T1 mapping was not performed in the majority of this retrospective cohort, we could not directly compare LV entropy to imaging markers of fibrosis, such as native T1 and extracellular volume, in order to gain mechanistic insights of the current findings. However, the significant associations of LV entropy with history of MI, presence and extent of LGE, and LV mass index imply an underlying link with markers of myocardial fibrosis. Third, despite being the largest study so far on the role of LV entropy in risk stratification, this was an observational, single-center experience. With regards to the NSVT subgroup, the absolute numbers of various components of adverse events were too small to draw any definite conclusions toward guidance of specific management. Further clinical studies are needed to fully evaluate and standardize any impact from different scanner field strengths and types of LGE pulse sequences onto measured LV entropy values, determine the potential value of entropy in different patient populations, and validate it prospectively.

CONCLUSIONS

In patients presenting with VAs, LV entropy by CMR provides incremental prognostic value for MACE, independently of LVEF, presence or extent of LGE, and QRS duration both in patients presenting with NSVT and VT/SCD. Further studies are required to understand biologic and imaging factors that affect LV entropy and test its prognostic significance in different patient populations.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In patients with VAs, LV entropy, a novel measure of myocardial tissue heterogeneity by CMR, improved prediction of MACEs beyond conventional clinical and imaging markers of risk. This prognostic association was maintained for patients without myocardial scar, or in those presenting with NSVT, 2 compelling groups for risk stratification for SCD.

TRANSLATIONAL OUTLOOK: Future prospective studies should assess biologic and imaging factors affecting LV entropy, examine its correlation with imaging, laboratory, and histological markers of myocardial fibrosis, and establish its prognostic significance prospectively, in different patient populations at risk of arrhythmic events.

REFERENCES

1. Travin Mark I, Feng D, Taub Cynthia C. Novel imaging approaches for predicting arrhythmic risk. *Circ Cardiovasc Imaging*. 2015;8:e003019.

2. Hennig A, Salel M, Sacher F, et al. High-resolution 3-dimensional late gadolinium-enhanced cardiac magnetic resonance imaging to identify the underlying substrate of ventricular arrhythmia. *Europace*. 2018;20:f179–f191.

3. Di Marco A, Anguera I, Schmitt M, et al. Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. *J Am Coll Cardiol HF*. 2017;5:28–38.

4. Muthalaly RG, Kwong RY, John RM, et al. Left ventricular entropy is a novel predictor of arrhythmic events in patients with dilated cardiomyopathy receiving defibrillators for primary prevention. *J Am Coll Cardiol Img*. 2019;12:1177–1184.

5. Androulakis AFA, Zeppenfeld K, Paiman EHM, et al. Entropy as a novel measure of myocardial tissue heterogeneity for prediction of ventricular arrhythmias and mortality in post-infarct patients. *J Am Coll Cardiol EP*. 2019;5:480–489.

6. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2018;72:e91–e220.

7. Flett AS, Hasleton J, Cook C, et al. Evaluation of techniques for the quantification of myocardial scar of differing etiology using cardiac magnetic resonance. *J Am Coll Cardiol Img*. 2011;4:150–156.

8. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and stroke endpoint definitions for clinical trials. *J Am Coll Cardiol*. 2018;71:1021–1034.

9. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J*. 2015;36:2793–2867.

10. Pencina MJ, D'Agostino RB Sr, D'Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008;27:157–172. discussion 207–212.

11. Pencina MJ, D'Agostino RB Sr, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med*. 2011;30:11–21.

12. Gould J, Porter B, Claridge S, et al. Mean entropy predicts implantable cardioverter-defibrillator therapy using cardiac magnetic resonance texture analysis of scar heterogeneity. *Heart Rhythm*. 2019;16:1242–1250.

13. Katritsis DG, Camm AJ. Nonsustained ventricular tachycardia: where do we stand? *Eur Heart J*. 2004;25:1093–1099.

14. Wu Katherine C. Sudden cardiac death substrate imaged by magnetic resonance imaging. *Circ Cardiovasc Imaging*. 2017;10:e005461.

15. Neilan TG, Farhad H, Mayrhofer T, et al. Late gadolinium enhancement among survivors of sudden cardiac arrest. *J Am Coll Cardiol Img*. 2015;8:414–423.

16. Rodrigues P, Joshi A, Williams H, et al. Diagnosis and prognosis in sudden cardiac arrest survivors without coronary artery disease: utility of a clinical approach using cardiac magnetic resonance imaging. *Circ Cardiovasc Imaging*. 2017;10:e006709.

17. Dawson DK, Hawlisch K, Prescott G, et al. Prognostic role of CMR in patients presenting with ventricular arrhythmias. *J Am Coll Cardiol Img*. 2013;6:335–344.

18. Aljaroudi WA, Flamm SD, Saliba W, Wilkoff BL, Kwon D. Role of CMR imaging in risk stratification for sudden cardiac death. *J Am Coll Cardiol Img*. 2013;6:392–406.

19. Yan AT, Shayne AJ, Brown KA, et al. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. *Circulation*. 2006;114:32–39.

20. Schmidt A, Azevedo CF, Cheng A, et al. Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. *Circulation*. 2007;115:2006–2014.

21. Haghbayan H, Lougheed N, Deva DP, Chan KKW, Lima JAC, Yan AT. Peri-infarct quantification by cardiac magnetic resonance to predict outcomes in ischemic cardiomyopathy: prognostic systematic review and meta-analysis. *Circ Cardiovasc Imaging*. 2019;12:e009156.

KEY WORDS cardiovascular magnetic resonance, entropy, myocardial tissue heterogeneity, prognosis, ventricular arrhythmia

APPENDIX For supplemental tables and a figure, please see the online version of this paper.