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Park, J.; Desjardins, B.; Liang, J.J.; Zghaib, T.; Xie, S.L.; Lucena-Padros, I.; ... ; Nazarian, S.

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Association of scar distribution with epicardial electrograms and surface ventricular tachycardia QRS duration in nonischemic cardiomyopathy

Jaeseok Park MD[1,2] | Benoit Desjardins MD, PhD[3] | Jackson J. Liang DO[1] | Tarek Zghaib MD[1] | Shuanglun Xie MD[1] | Irene Lucena-Padros MD[1] | Erica Zado PAC[1] | Pasquale Santangeli MD, PhD[1] | David S. Frankel MD[1] | David J. Callans MD[1] | Rob J. van der Geest PhD[4] | Francis E. Marchlinski MD[1] | Saman Nazarian MD, PhD[1]

[1]Section of Cardiac Electrophysiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[2]Division of Cardiology, Department of Internal Medicine, Mediplex Sejong Hospital, Incheon, South Korea

[3]Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[4]Department of Radiology, Leiden University Medical Centre, Leiden, The Netherlands

Correspondence
Saman Nazarian, MD, PhD, Section of Cardiac Electrophysiology, Perelman School of Medicine, University of Pennsylvania, 3400 Spruce St, Founders 9, Philadelphia, PA 19104, USA.
Email: Saman.Nazarian@uphs.upenn.edu

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Abstract

Introduction: The association of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) with epicardial and surface ventricular tachycardia (VT) electrogram features, in nonischemic cardiomyopathy (NICM), is unknown. We sought to define the association of LGE and viable wall thickness with epicardial electrogram features and exit site paced QRS duration in patients with NICM.

Methods: A total of 19 patients (age 53.5 ± 11.5 years) with NICM (ejection fraction 40.2 ± 13.2%) underwent CMR before VT ablation. LGE transmurality was quantified on CMR and coregistered with 2294 endocardial and 2724 epicardial map points.

Results: Both bipolar and unipolar voltage were associated with transmural signal intensity on CMR. Longer electrogram duration and fractionated potentials were associated with increased LGE transmurality, but late potentials or local abnormal ventricular activity were more prevalent in nontransmural versus transmural LGE regions ($p < .05$). Of all critical VT sites, 19% were located adjacent to regions with LGE but normal bipolar and unipolar voltage. Exit site QRS duration was affected by LGE transmurality and intramural scar location, but not by wall thickness, at the impulse origin.

Conclusions: In patients with NICM and VT, LGE is associated with epicardial electrogram features and may predict critical VT sites. Additionally, exit site QRS duration is affected by LGE transmurality and intramural location at the impulse origin or exit.

KEYWORDS
CMR, electrogram voltage, LGE, QRS duration

[Correction added on 06 July 2020, after first online publication: ORCID ID has been added for Jaeseok Park]

1 | INTRODUCTION

In patients with nonischemic cardiomyopathy (NICM) presenting with recurrent ventricular tachycardia (VT), catheter ablation is an effective treatment to eliminate or reduce VT burden and implantable cardioverter-defibrillator (ICD) shocks. Late gadolinium-enhanced (LGE) cardiovascular magnetic resonance (CMR) can identify the extent and intramural location of scar as the underlying substrate for VT in patients with NICM, with demonstrated prognostic value for VT inducibility, major adverse cardiac events and all-cause mortality.[1-3] Additionally, electroanatomic map (EAM) image integration techniques have uncovered associations between LGE extent and electrogram characteristics, as well as critical VT sites in NICM.[4,5] However, data on the association of epicardial EAM with LGE distribution is limited and the effect of LGE characteristics and wall thickness on exit site QRS duration has not been studied. The purpose of this study was to (a) extend the reported associations between LGE and electrogram characteristics to epicardial electrograms using a population that underwent extensive epicardial mapping, and (b) define the association of exit site QRS duration with LGE distribution in NICM patients undergoing VT ablation.

2 | METHODS

2.1 | Patient population

The study cohort consisted of patients with NICM and drug-refractory VT that underwent epicardial ablation at the Hospital of the University of Pennsylvania, between January 2013 and December 2017. Patients with idiopathic VT > 75% stenosis in at least one coronary artery or revascularization, congenital heart disease, and arrhythmogenic right ventricular cardiomyopathy were excluded. Of 167 NICM patients who met the inclusion criteria, 19 remained for analysis after exclusion of patients that did not undergo pre-ablation CMR ($n = 104$) and patients with suboptimal or no LGE sequences on CMR ($n = 44$). All 19 patients had idiopathic non-ischemic cardiomyopathy. No patients with known genetic cardiomyopathy, viral cardiomyopathy, or positron emission tomography or biopsy evidence of sarcoidosis were included. The study was approved by our institutional review board, and all patients provided written informed consent for their anonymized medical information to be included in research studies.

2.2 | Cardiac magnetic resonance acquisition

ECG-gated images were acquired using a 1.5-T scanner (Siemens Magnetom Avanto, Erlangen, Germany). A standardized protocol was followed including cine steady-state free precession images in long-axis and short-axes covering the LV. In addition, the proximal aorta was imaged using a black-blood turbo spin-echo sequence. Within 10–15 minutes after administration of 0.14 mmol/kg of IV Gadobenate Demeglumine (Multihance, Bracco Diagnostics, Princeton, NJ, USA) free breathing navigator gated inversion recovery 3-dimentional (3-D) LGE sequence (in-plane resolution 1.4 × 1.4 mm, slice thickness 2 mm) was performed. Inversion time was optimized to null normal myocardium. Additional sequences utilizing the modified 2-D wideband LGE sequence in the same planes to decrease image artifact were used as necessary.[6]

2.3 | EAM, electrophysiologic study, and catheter ablation

Antiarrhythmic drugs were discontinued at least five half-lives before ablation. An 8-Fr deflectable ablation catheter (ThermoCool or SmartTouch; Biosense Webster Inc., Diamond Bar, CA, USA) was advanced to the right ventricle (RV), left ventricle (LV) (retrograde aortic or transseptal approach), or epicardial space and 3-D EAM was created during sinus ($n = 16$) or paced rhythm ($n = 3$) (CARTO-3; Biosense Webster, Inc.). Electrograms were filtered at 16–500 Hz (bipolar) and 2–240 Hz (unipolar). Local electrogram was considered to have "fractionated potential" in the presence of two of following three characteristics: (1) electrogram voltage < 0.5 mV; (2) electrogram duration > 133 ms; (3) amplitude/duration ratio < 0.005.[7] An electrogram was categorized as exhibiting a late potential or local abnormal ventricular activity (LAVA) if any component was recorded after the end of the QRS, or if a high-frequency component was present > 20 ms away from a far-field ventricular electrogram.[8] Electrogram duration was measured manually from the earliest electrical activity to the onset of the amplification signal decay artifact. Paced QRS duration was measured from the beginning of the Q wave to the end of the S wave as a surrogate of site dependent QRS duration for focal VT or PVCs (i.e., impulse origin) or site dependent QRS duration for reentrant VT (i.e., exit).

Clinical VTs induced by programmed ventricular stimulation and reproducibly induced nonclinical VTs with cycle length of > 250 ms were targeted. Critical VT sites were defined as EAM points with entrainment showing concealed QRS fusion and difference between post-pacing interval and VT cycle length ≤ 30 ms, or as sites with 12/12 paced morphology match to VT in the setting of hemodynamically unstable VT. Radiofrequency energy was delivered at these sites using power ≤ 50 W targeting a 12–15 Ω impedance drop. For hemodynamically unstable VTs, VT substrate was delineated by identifying late potentials and LAVAs and pace-mapping within low voltage regions. An epicardial approach was used when (1) 12-lead ECG of clinical VT suggested a subepicardial origin, (2) there was evidence of subepicardial substrate based on low unipolar voltage area on endocardial EAM, and (3) the endocardial ablation approach did not achieve VT quiescence. Upon reversal of the activated clotting time with protamine, percutaneous access to the pericardial space was obtained using a Tuohy needle (subxiphoid approach) and the ablation catheter was advanced through a sheath.

2.4 | Reconstruction of CMR-derived mesh and registration with EAM

Figure 1 summarizes the process of LGE-CMR analysis and coregistration with EAM. MASS research software (Medis, Leiden, the Netherlands) was used to measure LGE distribution, transmurality, and regional wall thickness on LGE-CMR short-axis planes. Signal intensities (SI) of all myocardial voxels on short-axis planes were measured by MASS software. LGE was defined as SI > 6 *SD* above the mean (μ) SI of remote normal myocardial regions.[1,9] The LV myocardium on each short-axis plane was divided into 100 radial segments and the LGE transmurality of each segment was computed as the average proportion of transmural radial lines (from the endocardium to the epicardium) intersecting LGE region. 3-D CMR meshes converted from 2-D contours by MASS software were imported into CARTO system and coregistered with EAMs utilizing incorporated CARTO merge software by matching the His bundle electrogram region of EAM to the area 5 mm beneath the right coronary and non-coronary cusp commissure of CMR mesh followed by surface registration.

2.5 | Reverse registration of EAM points to CMR short-axis planes

After registration, coordinates and electrogram data of EAM points were exported from the CARTO system and imported back into MASS software. The voltage data of all EAM points were superimposed on CMR short-axis planes by using reverse registration matrix and point coordinates incorporated in the Carto system. After excluding EAM points in regions of CMR artifact, electrogram data of each EAM point and structural data of the corresponding CMR segment were exported as panel data for point-by-point analysis. The *z* score of a radial segment on CMR was calculated using the μ and *SD* of the SI distribution for all segments for each patient, using the following formula:

$$\text{Segmental } z \text{ score} = \frac{\text{Segmental SI} - (\mu \text{ of SI for patient})}{(SD \text{ of SI for patient})}.$$

The locations of points registered on CMR short-axis planes were annotated visually according to the 17-segment AHA model.[10] Each CMR short-axis plane was also divided into three intramural locations of subendocardium (inner, 5–35%), midmyocardium (mid, 35–65%), and subepicardium (outer, 65–95%). Relative LGE area was calculated as total LGE area divided by total myocardial area (%). The LGE volume was calculated as LGE area multiplied by slice thickness and indexed to the total myocardial volume (%).

2.6 | Statistical analysis

Continuous variables are expressed as mean ± *SD* and categorical variables as number with percentage. Continuous variables were compared using Student *t* test or one-way analysis of variance, and

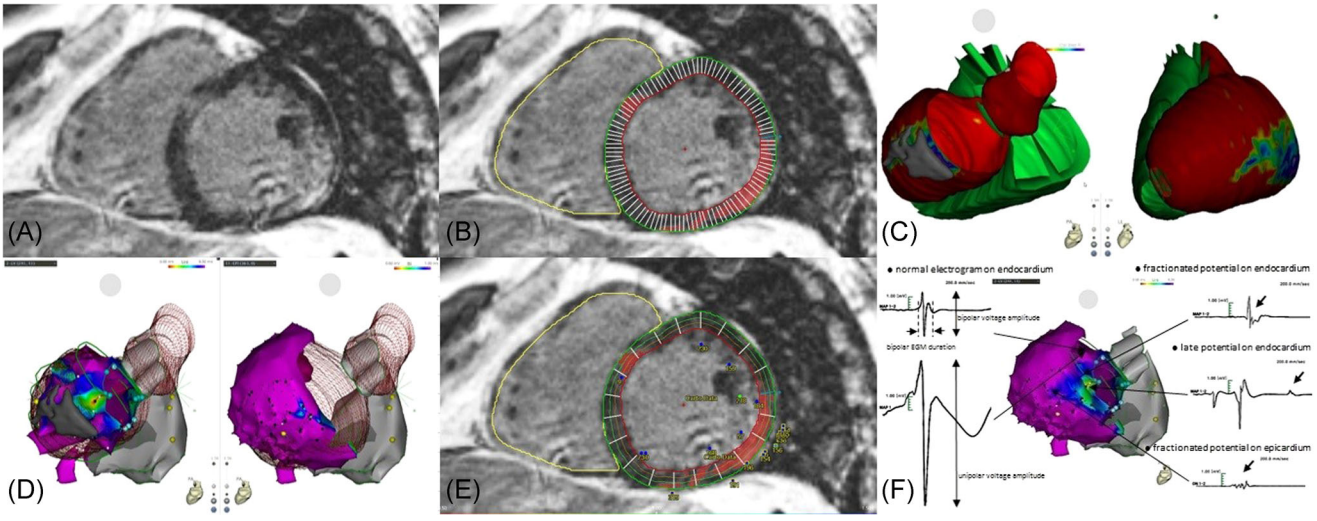

FIGURE 1 Process of LGE-CMR analysis and coregistration with EAM. A, CMR short-axis plane shows LGE in the LV basal inferolateral and septal segments. B, After drawing endocardium and epicardium contours, LGE regions (6 *SD*s above mean of normal myocardium) are represented in red. C, LGE transmurality is projected on LV endocardial (left panel) and epicardial mesh (right panel). Normal myocardium without LGE is represented in red and abnormal myocardium with various degree of LGE transmurality represented gradually in yellow-green-blue-purple. CMR mesh of LGE is shown in gray. D, Coregistration of EAM with CMR mesh. In posterior–anterior views of LV endocardial (left panel) and epicardial (right panel) EAMs, purple-colored region represents normal myocardium with normal voltage and the region with color gradient between blue and red represents scar region with low voltage. E, With reverse registration, endocardial and epicardial EAM points were co-registered on CMR short-axis planes. F, Example of normal electrogram, fractionated potential and late potentials or LAVA.
CMR, cardiac magnetic resonance; EAM, electroanatomic map; LAVA, local abnormal ventricular activity; LGE, late gadolinium enhancement; LV, left ventricular

comparisons between groups were done by Turkey's *b* posthoc method. Log transformation was performed to allow analysis of the skewed unipolar and bipolar voltage measurements in a linear framework. The frequencies of categorical variables were compared using χ^2 test or Fisher's exact test. Linear mixed-effects regression models, clustered by patients were used to examine the association of paced QRS duration as the dependent variable with LV wall thickness and LGE characteristics on CMR as independent variables after adjusting for electrogram features, pacing and clinical factors. Variables with significant or borderline significant association from univariable models and clinical variables proved to be associated in previous studies were included in multivariable models. A level of $p < .05$ was considered to indicate statistical significance. Statistical analysis was performed using SPSS for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).

3 | RESULTS

3.1 | Patient characteristics and procedural data

Patient characteristics are summarized in Table 1. Of 19 patients, 7 had LVEF < 35%, 14 had failed treatment with at least one antiarrhythmic drug, and 8 had undergone prior catheter ablation (2 prior ablations in 1 patient). A total of 58 distinct sustained VTs and 2 nonsustained VTs were induced (3.2 ± 2.0 VTs/patient). Entrainment mapping was possible only in 9 patients with hemodynamically tolerated VT. Of 39 defined critical VT sites, 20 were identified by entrainment mapping and 19 by pace mapping. After ablation, noninducibility of clinical VTs was achieved in 16 of 19 (84.2%) patients and noninducibility of both clinical and nonclinical VTs in 9 of 19 (47.4%) patients.

3.2 | Analyzed CMR and EAM points

Of 1941 LV wall segments, 1737 LV wall segments were suitable for quantitative analysis after excluding segments with image artifacts. LGE was identified in 392 (22.6%) segments. LGE intramural location was subendocardial, midmyocardial, subepicardial, and transmural in 12.0%, 16.8%, 44.6%, and 26.5%, respectively. The LV wall location of LGE was septal, anterior, lateral, inferior, and apical in 19.6%, 4.8%, 56.1%, 17.1%, and 2.3% of segments, respectively. Of 19 patients, 4 patients had LGE mainly in septum or anterior wall and 13 patients had LGE in lateral wall. All of four patients with septal wall LGE had mid-myocardial LGE location. Among 13 patients with lateral wall LGE, 5 had subepicardial, 4 had transmural LGE and no one had only midmyocardial LGE. After excluding EAM points registered to regions with CMR image artifact, 5018 EAM points (264.1 ± 105.3 /patient) consisting of 2294 endocardial (120.7 ± 43.7 /patient) and 2724 in epicardial (143.4 ± 80.2 /patient) points were analyzed. Of these points, pacing morphology data were available in 459 points (24.2 ± 11.1 /patient) with 235 in endocardium (12.4 ± 9.7 /patient) and 224 in epicardium (11.8 ± 6.6 /patient). The surface registration errors between CMR LV mesh and EAM were 4.4 ± 2.3 and 5.2 ± 4.1 mm for endocardium and epicardium, respectively.

3.3 | Association of LGE and electrogram characteristics

Of all EAM points, 19.6% had fractionated and 4.9% had late potentials or LAVA. Both electrogram types were more prevalent on epicardial versus endocardial EAM (26.0% vs. 12.4% for fractionated potential and 7.7% vs. 1.6% for late potential or LAVA). Figure 2 shows electrogram characteristics in 5 categories of EAM points based on LGE transmurality quartiles on CMR. Endocardial bipolar and unipolar voltage decreased as LGE transmurality increased. Epicardial bipolar and unipolar voltage were lower in all four categories with LGE compared with the no LGE category. Electrogram duration in both endocardial and epicardial EAMs was prolonged in categories with more than 50% LGE transmurality. The prevalence of fractionated potentials increased with LGE transmurality. In contrast, late potentials or LAVA were more prevalent in nontransmural LGE categories compared with no LGE but was not more prevalent in the transmural LGE category.

Table 2 shows electrogram characteristics in five categories of EAM points based on LGE intramural location. Endocardial bipolar and unipolar voltage were lower in categories with subendocardial and transmural LGE, and endocardial unipolar voltage was also lower in the category with midmyocardial LGE compared with no LGE.

TABLE 1 Characteristics of patients with NICM and VT

	***n* = 19**
Age (years)	53.5 ± 11.5
Sex (male/female)	16 /3
Previous ablation	8
ICD /S-ICD /CRT-D implanted	11 /1 /3
Baseline QRS duration, ms	121.3 ± 31.1
Echocardiography	
LV ejection fraction, %	40.2 ± 13.2
LV diastolic diameter, mm	58.4 ± 6.5
Cardiac magnetic resonance	
LV ejection fraction, %	37.8 ± 10.1
LV end-diastolic volume, ml	236.7 ± 68.6
Total LGE volume of LV, %	9.6 ± 3.8
LGE distribution as VT substrate (S/A/A-L/I-L/I)	3 /1 /2 /11 /2
LGE intramural location (Endo/Mid/Epi/Trans)	3 /4 /8 /4

Abbreviations: CRT-D, cardiac resynchronization therapy with defibrillator; Endo/Mid/Epi/Trans, subendocardial/midmyocardial/subepicardial/transmural; ICD, implantable cardioverter defibrillator; LV, left ventricle; NICM, nonischemic cardiomyopathy; S/A/A-L/I-L/I, septal/anterior/anterolateral/inferolateral/inferior wall; S-ICD, subcutaneous ICD; VF, ventricular fibrillation; VT, ventricular tachycardia.

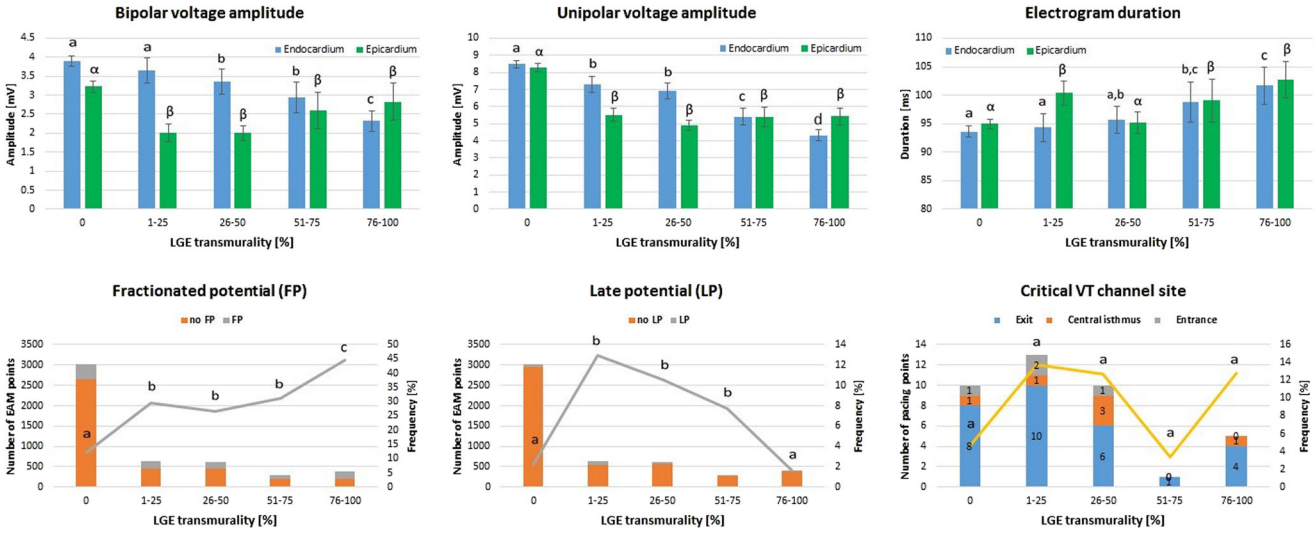

FIGURE 2 Association between LGE quartile transmurality on CMR and electrogram features. Same subscript letters indicate no statistical difference between categories. Critical VT sites were quantified both as total number and the percentage of pacing points. CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; VT, ventricular tachycardia

However, endocardial unipolar voltage was less diminished in the setting of remote subepicardial LGE. Epicardial bipolar and unipolar voltage were lowest in categories with subepicardial and transmural LGE, and epicardial unipolar voltage also identified remote mid-myocardial and endocardial LGE. Electrogram duration was prolonged only in the setting of transmural LGE. Fractionated potentials were more prevalent in categories with subendocardial and transmural LGE on endocardial EAM, while these potentials were more prevalent in all four LGE locations on epicardial EAM. Late potentials or LAVA on both endocardial and epicardial EAMs

TABLE 2 Association between LGE intramural location on CMR and electrogram features

LGE location	None	Subendocardial	Midmyocardial	Subepicardial	Transmural	*p* value
Endocardium						
Number of points	1405 (61.2%)	258 (11.2%)	85 (3.7%)	352 (15.3%)	190 (8.3%)	
Bipolar voltage, mV	3.89 ± 2.61^{a}	2.13 ± 1.71^{b}	3.47 ± 2.56^{a}	4.27 ± 2.88^{a}	2.33 ± 1.88^{b}	<.001
Unipolar voltage, mV	8.49 ± 4.23^{a}	4.64 ± 2.59^{c}	6.72 ± 3.01^{b}	8.30 ± 3.87^{a}	4.31 ± 2.28^{c}	<.001
lectrogram duration, ms	93.6 ± 18.6^{a}	$97.4 \pm 18.9^{a,b}$	95.2 ± 20.3^{a}	94.7 ± 20.5^{a}	101.7 ± 22.8^{b}	<.001
Fractionated potential	117 /1396 (8.4%)^{a}	63 /243 (25.9%)^{b}	11 /85 (12.9%)^{a,b}	35 /344 (10.2%)^{a}	54 /190 (28.4%)^{b}	<.001
Late potential or LAVA	5 /1396 (0.4%)^{a}	4 /243 (1.6%)^{a,b}	4 /85 (4.7%)^{b}	21 /344 (6.1%)^{b}	2 /190 (1.1%)^{a,b}	<.001
Critical VT site	2 /99 (2.0%)^{a}	11 /62 (17.7%)^{b}	0 /14 (0%)^{a,b}	2 /34 (5.9%)^{a,b}	1 /22 (4.5%)^{a,b}	.005
Exit	2	6	0	2	1	
Central isthmus	0	4	0	0	0	
Entrance	0	1	0	0	0	
Epicardium						
Number of points	1641 (60.2%)	305 (11.2%)	94 (3.5%)	492 (18.1%)	192 (7.0%)	
Bipolar voltage, mV	3.22 ± 2.83^{a}	2.54 ± 2.61^{b}	2.55 ± 2.41^{b}	1.77 ± 2.05^{c}	2.82 ± 3.41^{c}	<.001
Unipolar voltage, mV	8.27 ± 4.87^{a}	$5.55 \pm 3.35^{b,c}$	6.04 ± 4.14^{b}	4.90 ± 3.10^{c}	$5.42 \pm 3.42^{b,c}$	<.001
Electrogram duration, ms	95.0 ± 16.5^{a}	$98.2 \pm 21.6^{a,b}$	$99.3 \pm 16.9^{a,b}$	$97.6 \pm 20.2^{a,b}$	102.7 ± 22.3^{b}	<.001
Fractionated potential	251 /1630 (15.4%)$^{\alpha}$	92 /302 (30.5%)$^{\beta}$	30 /94 (31.9%)$^{\beta,\gamma}$	216 /487 (44.4%)$^{\gamma}$	115 /190 (60.5%)$^{\delta}$	<.001
Late potential or LAVA	62 /1630 (3.8%)$^{\alpha}$	8 /302 (2.6%)$^{\alpha}$	10 /94 (10.6%)$^{\beta}$	124 /487 (25.5%)$^{\gamma}$	4 /190 (2.1%)$^{\alpha}$	<.001
Critical VT site	8 /114 (7.0%)$^{\alpha}$	4 /24 (16.7%)$^{\alpha,\beta}$	4 /11 (36.4%)$^{\beta}$	3 /58 (5.2%)$^{\alpha}$	4 /17 (26.3%)$^{\alpha,\beta}$	0.005
Exit	6	4	3	2	3	
Central isthmus	1	0	0	0	1	
Entrance	1	0	1	1	0	

Note: Critical VT sites were quantified both as total number and percentage of pacing points. Same superscript letters indicate no statistical difference between groups.

Abbreviations: CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; VT, ventricular tachycardia.

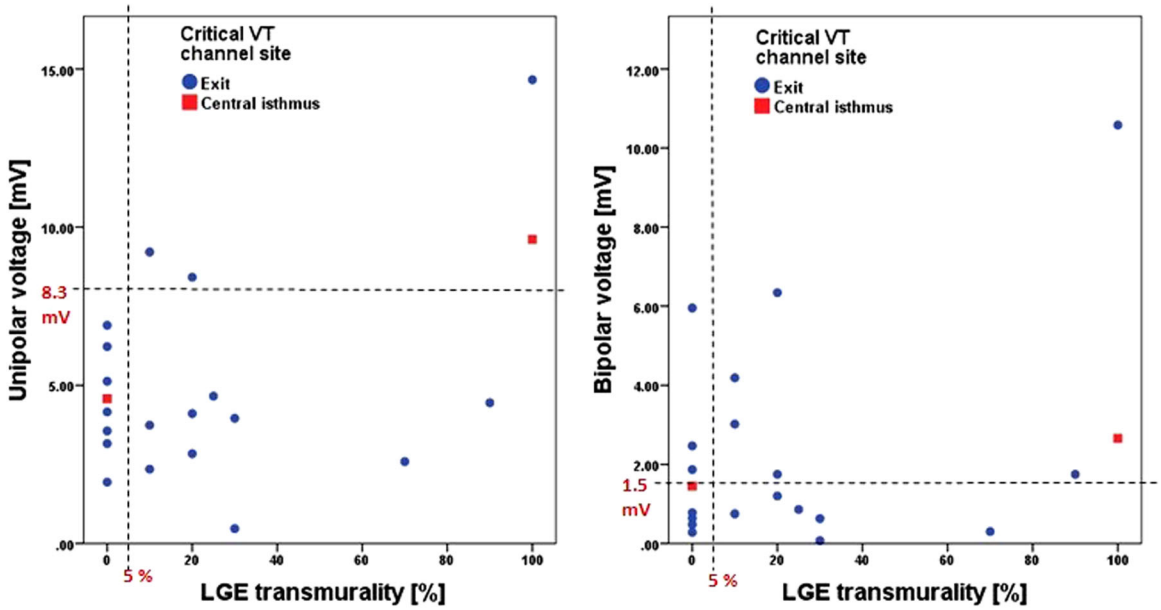

FIGURE 3 Distribution of electrogram voltage measures and LGE transmurality at critical VT sites. The figure illustrates the myocardial voltage and LGE characteristics adjacent to 21 critical VT sites with available voltage and LGE data. LGE, late gadolinium enhancement; VT, ventricular tachycardia

were found more frequently in midmyocardial and subepicardial LGE locations, but not in transmural LGE location.

3.4 | Distribution of critical VT sites according to LGE transmurality and intramural location

A total of 39 critical VT sites were identified (16 endocardial and 23 epicardial EAM points) and had LGE transmurality of 28.5 ± 30.6%. Figure 2 shows that more critical VT sites were found at EAM points with nontransmural LGE (1–25%, 26–50%, and 51–75% LGE) compared to transmural LGE ($N = 24$ vs. 5). Table 2 shows that more critical VT sites related to subendocardial LGE were found by endocardial pacing ($N = 11$ vs. 4 by epicardial pacing), while more critical VT sites related to midmyocardial, subepicardial, or transmural LGE were found by epicardial pacing ($N = 11$ vs. 3 by endocardial pacing). Figure 3 shows the distribution of electrogram voltage measures and LGE transmurality at 21 critical VT sites. Notably, 4 of 21 (19.0%) critical sites were located in regions with LGE, but normal unipolar and bipolar voltage. However, all 21 critical VT sites were located in regions with low unipolar voltage or LGE.

3.5 | Patient and pacing location predictors of exit site QRS duration

Baseline patient-level factors such as age, sex, previous use of β-blocker or antiarrhythmic drugs did not show any association with paced QRS duration. As noted in Table 3, paced QRS duration was associated with LGE transmurality and intramural location at the impulse origin. However, total LGE mass was not associated with paced QRS duration. In multivariable analysis, baseline QRS duration, LGE transmurality, LGE intramural location, and pacing site were independently associated with paced QRS duration. LGE intramural location and endocardial pacing at points with subendocardial or transmural LGE location were associated with prolonged paced QRS duration, but not at points with subepicardial LGE location. In contrast, epicardial pacing at points with subendocardial, subepicardial or transmural LGE location were associated with prolonged paced QRS duration. Pacing at the lateral wall was associated with longer paced QRS duration, whereas pacing at the septal wall was associated with shorter paced QRS duration compared to pacing at the inferior wall. Pacing rate was unassociated with paced QRS duration. In sensitivity analysis, excluding points with LGE to avoid a confounding effect of presumed scar, viable wall thickness was not associated with paced QRS duration.

4 | DISCUSSION

The main findings of the present study in a cohort of NICM patients with VT are: (1) Longer electrogram duration and more fractionated potentials were associated with higher LGE transmurality, while late potentials or LAVA were more prevalent in nontransmural LGE regions; (2) Almost a fifth of critical VT channels sites were located in regions with LGE but normal unipolar and bipolar voltage; and (3) QRS duration is affected by LGE transmurality and intramural location, but not by wall thickness, at the impulse origin or exit.

TABLE 3 Univariable and multivariable linear mixed analysis for patient-level and pacing location-level predictors of exit site QRS duration

	Endo or epi points		Endocardial points		Epicardial points		Endocardial points		Epicardial points	
	Univariable		Multivariable		Multivariable		Multivariable		Multivariable	
Variable	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*
Baseline QRS duration, ms	0.427	.004	0.375	.041	0.329	.039	0.371	.040	0.351	.029
LV ejection fraction, %	−0.698	.066	−0.098	.809	−0.822	.037	−0.049	.903	−0.792	.044
Wall thickness, mm	−0.663	.161	−0.315	.534	−0.789	.245	−0.084	.872	−0.545	.416
Total LGE volume, %	−1.108	.429								
LGE transmurality at pacing site, %	0.092	.003	0.111	.003	0.113	.005	[a]	[a]	[a]	[a]
LGE intramural location at pacing site		<.001	[a]	[a]	[a]	[a]		.002		<.001
No LGE	Reference		[a]	[a]	[a]	[a]	Reference		Reference	
Subendocardial	8.368	.001	[a]	[a]	[a]	[a]	8.477	.003	8.863	.008
Midmyocardial	6.532	.083	[a]	[a]	[a]	[a]	5.063	.225	7.390	.089
Subepicardial	4.377	.070	[a]	[a]	[a]	[a]	0.029	.993	10.938	<.001
Transmural	11.028	.001	[a]	[a]	[a]	[a]	12.690	.001	8.167	.041
Pacing site		<.001		<.001		<.001		<.001		<.001
Septum	−8.362	.014	−12.223	.002			−11.382	.003		
Anterior wall	1.945	.578	9.137	.031	−11.835	.020	9.295	.036	−8.943	.069
Anterolateral wall	15.185	<.001	14.297	<.001	11.109	.001	14.572	<.001	13.623	<.001
Inferolateral wall	17.529	<.001	17.015	<.001	10.453	<.001	17.132	<.001	10.890	<0.001
Inferior wall	Reference		Reference		Reference		Reference		Reference	
Apex	−2.091	.754	−8.299	.273	12.501	.223	−7.454	.320	16.214	.106
Pacing rate	−0.005	.627	0.017	.109	−0.016	.149	0.013	.235	−0.023	.044
Epicardial pacing	8.936	<.001			4.603	.006[b]			5.369	.001[b]

Note: Clinical variables including age, sex, use of beta-blocker, or antiarrhythmic drug showing no association are not shown. EAM variables including electrogram bipolar and unipolar voltage, electrogram duration, fractionated potential, late potential or LAVA, and stimulus-QRS interval were omitted because of lack of association or collinearity with other variables.

Abbreviations: EAM, electroanatomic map; LGE, late gadolinium enhancement; LV, left ventricular.

[a]LGE variables included separately in the multivariable analysis because of collinearity.

[b]The coefficient and *p* value from multivariable analysis with both endocardial and epicardial pacing points.

4.1 | Association of electrogram features with intramural LGE

LGE architectural features including its heterogeneity and intramural location have been established as important determinants of VT inducibility and patient prognosis in NICM.[1-3,5] Recent studies have demonstrated an indirect association between the extent of LGE and voltage amplitude in patients with ischemic and NICM with the point-by-point comparison following coregistration of EAM and CMR.[11-13] Our study expands upon prior findings by extending these associations in a relatively larger cohort of NICM patients with concurrent epicardial mapping. Importantly, our study suggests limited ability of endocardial mapping to distinguish intramural LGE location. For example, endocardial unipolar voltage mapping revealed abnormal values adjacent to subendocardial or midmyocardial LGE regions, but subepicardial LGE regions exhibited normal endocardial unipolar voltage. In contrast, epicardial unipolar voltage identified remote midmyocardial and subendocardial LGE. In addition to utility for identification of free wall midmyocardial substrates, this finding is applicable for identification of endocardial substrates during an epicardial only ablation approach, which is utilized in the setting of mobile intracardiac thrombus. Regarding localization of midmyocardial LGE, endocardial bipolar voltage was normal whereas endocardial unipolar voltage was abnormal; however, unipolar voltage was less diminished and fractionated potentials were less prevalent compared to subendocardial LGE. Therefore, midmyocardial scar remains challenging to localize by voltage mapping, and LGE-CMR enables a complementary and important role in mapping complex VT substrates. The present study also showed that 19% of critical VT sites were located adjacent to regions with LGE but normal bipolar and unipolar voltage. This is likely explained by cardiac remodeling and hypertrophy in scar border zones, which masks the presence of scar on voltage assessment. However, the utility of ablation in regions with LGE in the absence of unipolar and bipolar voltage abnormalities must be prospectively studied.

4.2 | Impact of LGE architecture at exit site upon global impulse propagation

The present study demonstrates that LGE transmurality and intramural location at the impulse origin or exit are important determinants of QRS duration. However, despite our prior expectation, wall thickness at the impulse origin or exit is not associated with QRS duration on multivariable analysis. Endocardial paced QRS duration was only associated with LGE involving the subendocardial layer. In contrast, epicardial paced QRS duration was associated with any intramural scar location. These observations are consistent with the knowledge that an endocardial impulse immediately engages the remaining myocardium through the adjacent endocardial His-Purkinje network and is only disrupted by subendocardial scar. In contrast, an epicardial impulse must travel to the endocardium before engaging the His-Purkinje network and the remaining myocardium and can be disrupted by any intramural scar location.

4.3 | Clinical implications

The findings of this study have several implications for understanding the substrate for VT in patients with NICM. First, the associations of EAM characteristics with LGE distribution reported in the present study sheds light on the strengths and limitations of voltage mapping and underscore the importance of CMR as an adjunct for determining the VT substrate in difficult NICM cases. Second, global myocardial impulse propagation is affected by LGE transmurality and intramural location at the impulse origin or exit. This finding may refine our understanding of 12-lead ECG morphology variations for premature ventricular complex (PVC) and VT exit site determination, as well as the limitations of global impulse propagation following LV lead placement epicardial to LGE regions.

4.4 | Study limitations

This is a retrospective study from a referral VT ablation center and thus may be subject to selection bias. Although the sample size is limited, it is larger in terms of patients and the number of EAM and pacing points analyzed when compared with previous studies in the setting of NICM. LGE-CMR images have limitations in spatial resolution, signal to noise ratio, and partial volume effects. Results may also be limited by positional errors from coregistration of EAM and CMR. Multielectrode mapping catheters with small electrodes and interelectrode distance provide higher density maps and higher sensitivity to near-field signals.[14] The use of multielectrode mapping catheters in future studies may refine these results. While the incidence of fractionated and late potentials or LAVA was associated with LGE distribution, a relatively high proportion of fractionated and, to a lesser extent, late potentials or LAVA were noted in regions without adjacent LGE. This finding may be due to abnormal conduction due to heterogeneous fiber orientation, diffuse fibrosis in the absence of cohesive fibrosis, or in some cases due to registration inaccuracies. Further studies that incorporate diffusor tension fiber orientation analyses and T1 mapping are warranted.

5 | CONCLUSIONS

In patients with NICM and VT, LGE-CMR findings are associated with electrogram features. Exit site QRS duration is affected by LGE transmurality and intramural location, but not by wall thickness, at the impulse origin or exit. These findings have implications for preprocedural planning with regard to epicardial access and for understanding 12-lead ECG morphology variations for PVC and VT exit site determination, as well as the limitations of global impulse propagation following LV lead placement epicardial to LGE regions.

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ORCID

Jaeseok Park http://orcid.org/0000-0002-5264-1235
Jackson J. Liang http://orcid.org/0000-0001-8608-8899
Shuanglun Xie http://orcid.org/0000-0003-2985-9946
Erica Zado http://orcid.org/0000-0001-7331-448X
Pasquale Santangeli http://orcid.org/0000-0002-0023-9666
David S. Frankel http://orcid.org/0000-0001-9276-4857
David J. Callans http://orcid.org/0000-0001-6823-6149
Francis E. Marchlinski http://orcid.org/0000-0001-7962-9423
Saman Nazarian http://orcid.org/0000-0002-8369-0259

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