Discordance in Scar Detection Between Electroanatomical Mapping and Cardiac MRI in an Infarct Swine Model

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ABSTRACT

OBJECTIVES This study sought to investigate the sensitivity of electroanatomical mapping (EAM) to detect scar as identified by late gadolinium enhancement (LGE) cardiac magnetic resonance (CMR).

BACKGROUND Previous studies have shown correlation between low voltage electrogram amplitude and myocardial scar. However, voltage amplitude is influenced by the distance between the scar and the mapping surface and its extent. The aim of this study is to examine the reliability of low voltage EAM as a surrogate for myocardial scar using LGE-derived scar as the reference.

METHODS Twelve swine underwent anterior wall infarction by occlusion of the left anterior descending artery (LAD) (n = 6) or inferior wall infarction by occlusion of the left circumflex artery (LCx) (n = 6). Subsequently, animals underwent CMR and EAM using a multielectrode mapping catheter. CMR characteristics, including wall thickness, LGE location and extent, and EAM maps, were independently analyzed, and concordance between voltage maps and CMR characteristics was assessed.

RESULTS LGE volume was similar between the LCx and LAD groups (8.5 ± 2.2 ml vs. 8.3 ± 2.5 ml, respectively; p = 0.852). LGE scarring in the LAD group was more subendocardial, affected a larger surface area, and resulted in significant wall thinning (4.88 ± 0.43 mm). LGE scarring in the LCx group extended from the endocardium to the epicardium with minimal reduction in wall thickness (scarred: 5.4 ± 0.67 mm vs. remote: 6.75 ± 0.38 mm). In all the animals in the LAD group, areas of low voltage corresponded with LGE and wall thinning, whereas only 2 of 6 animals in the LCx group had low voltage areas on EAM. Bipolar and unipolar voltage amplitudes were higher in thick inferior walls in the LCx group than in thin anterior walls in the LAD group, despite a similar LGE volume.

CONCLUSIONS Discordances between LGE-detected scar areas and low voltage areas by EAM highlighted the limitations of the current EAM system to detect scar in thick myocardial wall regions. (J Am Coll Cardiol EP 2020;6:1452–64) © 2020 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the JACC: Clinical Electrophysiology author instructions page.

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Ventricular tachycardia (VT) activation mapping is the gold standard for mapping scar-related re-entry circuits, yet it is rarely achieved due to long mapping times and/or hemodynamic intolerance (1). Substrate mapping during sinus rhythm has evolved as an alternative to activation and/or entrainment mapping to manage hemodynamically unstable VTs (2) by reducing the need for mapping during prolonged periods of VT. However, substrate mapping techniques during sinus rhythm are often associated with substantial recurrence rates (3,4). Higher rates are partially due to assumptions and misconceptions related to substrate mapping techniques, such as the assumption that low voltage equals scar or the misconception that mapping of the ventricular surface provides accurate information of the much larger unmapped intramural volume (5,6).

The relationship between low voltage amplitude and the VT isthmus was initially established in arrhythmia surgeries of patients with large anterior wall infarctions and aneurysms (1). Bipolar voltage amplitude <1.5 mV recorded with a quadripolar non-steerable woven catheter with a 2-mm tip, 1-mm ring, and 5-mm interelectrode spacing was associated with the location of the VT isthmus (7). This threshold was later validated for a standard 4-mm tip, 1-mm ring, and 2-mm interelectrode spacing mapping catheter, and, more recently, for multielectrode mapping catheters in animal studies (8,9). Similar to the original patients who underwent arrhythmia surgery, these animal models had anterior infarctions by left anterior descending artery (LAD) occlusion in which the anterior wall underwent remodeling with transmural scarring, significant wall thinning, and preservation of a thin endocardial layer (8-13). Infarctions at other territories, particularly at the left circumflex artery (LCx), often produced a more heterogeneous scar without significant wall thinning (14,15). In humans, such infarctions often result in patchy patterns of bipolar voltage abnormalities, which may suggest overall smaller infarct sizes, lower collagen content relative to cardiomyocytes, larger areas of preserved sub-endocardium, and relative differences in scar-to-wall thickness ratios (16,17).

Cardiac magnetic resonance (CMR) imaging has become an integral evaluation component in patients undergoing VT ablation (18-20). Late gadolinium enhancement (LGE) identifies scar regions associated with the ventricular substrate. In addition to the scar, wall thickness and strain can be accurately measured via cine images to better assess left ventricular (LV) remodeling and anatomical functional effects of the scar (10,21,22). Numerous studies have correlated scar regions on LGE images to areas of low voltage on substrate mapping (6,9,21,23-28), and it is well accepted that EAM can detect scarring observed on LGE. However, voltage maps only represent tissue characteristics within a few millimeters of the catheter tip, limiting their sensitivity to detect mid-myocardial scar (29). In contrast, LGE is not capable of identifying scar within 1 to 2 mm (i.e., 1 to 2 pixels) of the blood pool due to blood–myocardium partial voluming (30,31). These limitations have raised concerns regarding the sensitivity of current EAM technologies to detect myocardial scar.

We sought to investigate the concordance between myocardial scar detection by LGE and voltage amplitude in a swine model of anterior and inferior healed myocardial infarction.

**METHODS**

**EXPERIMENTAL STUDY DESIGN.** This study included 12 Yorkshire swine of either sex weighing 35 to 40 kg. The animals were divided into 2 groups and underwent infarction in either the LAD (n = 6) or the LCx (n = 6) using balloon occlusion as previously described (32). Differences between the procedures included 1) balloon occlusion time (180 min for LAD, 60 to 120 min for LCx); and 2) targeted coronary arteries (occlusion of the LAD was performed after the second diagonal branch and occlusion of the LCx was performed after the second obtuse marginal branch to reduce mortality and allow a similar territory of ischemia). Animals then lived for 8 to 10 weeks before CMR and electrophysiology studies. CMR and electrophysiology studies were performed under general anesthesia with mechanical ventilation. The study was conducted at Beth Israel Deaconess Medical Center and approved by the Institutional Animal Care and Use Committee.

**CMR IMAGING.** CMR was performed using a 3-T cardiac magnetic resonance scanner (Siemens Vida, Erlangen, Germany) with an 18-channel body receiver coil. Animals underwent in vivo CMR 1 week before terminal mapping and ex vivo CMR immediately after being killed. The CMR protocol included evaluation of function using short- and long-axis slices with balanced steady-state free-precession imaging (TR = 3.2 ms; TE = 1.4 ms; flip angle = 40 degrees; voxel size = 0.9 × 0.9 × 8.0 mm³; field of view = 360 × 270 mm²). Ten to 15 min after administration of 0.2 mmol/kg of intravenous gadobutrol (Gadavist, Bayer HealthCare, Berlin, Germany), 3-dimensional LGE imaging was performed using an inversion-
Table 1: Cardiac Magnetic Resonance Imaging Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LAD (n = 6)</th>
<th>LCx (n = 6)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV, ml</td>
<td>209 ± 17</td>
<td>172 ± 21</td>
<td>0.009</td>
</tr>
<tr>
<td>ESV, ml</td>
<td>116 ± 10</td>
<td>91 ± 16</td>
<td>0.011</td>
</tr>
<tr>
<td>SV, ml</td>
<td>92 ± 12</td>
<td>81 ± 6</td>
<td>0.074</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>44 ± 3.7</td>
<td>47 ± 3.0</td>
<td>0.160</td>
</tr>
<tr>
<td>CO, l/ml</td>
<td>7.9 ± 0.9</td>
<td>6.9 ± 0.8</td>
<td>0.081</td>
</tr>
<tr>
<td>CI, l/ml/m²</td>
<td>3.8 ± 0.4</td>
<td>3.6 ± 0.3</td>
<td>0.252</td>
</tr>
<tr>
<td>HR, min</td>
<td>85 ± 10</td>
<td>84 ± 5</td>
<td>0.788</td>
</tr>
<tr>
<td>Total mass, g</td>
<td>98 ± 10</td>
<td>99 ± 13</td>
<td>0.967</td>
</tr>
<tr>
<td>Tissue tracking (global systolic peak strain)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial, %</td>
<td>15 ± 4.2</td>
<td>15 ± 4.0</td>
<td>0.799</td>
</tr>
<tr>
<td>Circumferential, %</td>
<td>10 ± 2.2</td>
<td>11 ± 2.2</td>
<td>0.821</td>
</tr>
<tr>
<td>Longitudinal, %</td>
<td>12.0 ± 3.1</td>
<td>12.5 ± 2.5</td>
<td>0.783</td>
</tr>
<tr>
<td>LGE (in vivo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total volume, ml</td>
<td>8.6 ± 2.2</td>
<td>8.3 ± 2.5</td>
<td>0.852</td>
</tr>
<tr>
<td>Total mass, g</td>
<td>9.0 ± 2.3</td>
<td>8.7 ± 2.6</td>
<td>0.851</td>
</tr>
<tr>
<td>LGE burden, %</td>
<td>8.2 ± 2</td>
<td>8.9 ± 2</td>
<td>0.540</td>
</tr>
<tr>
<td>Area of subendocardial LGE bordering LV blood pool, cm²</td>
<td>12.5 ± 3.1</td>
<td>4.1 ± 1.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LGE (ex-vivo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total volume, ml</td>
<td>9.0 ± 1.8</td>
<td>8.5 ± 2.1</td>
<td>0.711</td>
</tr>
<tr>
<td>Total mass, g</td>
<td>9.5 ± 1.9</td>
<td>9.1 ± 2.2</td>
<td>0.688</td>
</tr>
<tr>
<td>LGE burden, %</td>
<td>7.9 ± 1.6</td>
<td>8.3 ± 1.8</td>
<td>0.802</td>
</tr>
<tr>
<td>Wall thickness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean wall thickness of remote myocardium, mm</td>
<td>6.6 ± 0.4</td>
<td>6.7 ± 0.4</td>
<td>0.703</td>
</tr>
<tr>
<td>Mean wall thickness of scarred segments, mm</td>
<td>1.8 ± 0.3</td>
<td>5.4 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Wall thinning percentage on scarred segments, %</td>
<td>73 ± 40</td>
<td>20 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean amount of thinning, mm</td>
<td>4.9 ± 0.4</td>
<td>1.4 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

CI = cardiac index; CO = cardiac output; EDV = end-diastolic volume; ESV = end-systolic volume; HR = heart rate; LAD = left anterior descending; LCx = left circumflex; LGE = late gadolinium enhanced; LGE burden = LGE volume to LV volume ratio; LV = left ventricular; LVEF = left ventricle ejection fraction; SV = stroke volume.

The recovery sequence with gradient-echo imaging (TR = 3.85 ms; TE = 1.7 ms; flip angle = 18 degrees; voxel size = 1.5 × 1.5 × 1.5 mm³; field of view = 385 × 288 × 96 mm³).

For ex vivo CMR imaging, 0.2 mmol/kg gadobutrol (Gadavist, Bayer HealthCare) was administered intravenously 15 min before the animals were killed during the mapping procedure. Imaging commenced within 1 h of heart removal using an isotropic 3-dimensional T₁-weighted spoiled gradient-echo sequence with the following parameters: TR = 27 ms; TE = 4.9 ms; flip angle = 25 degrees; voxel size = 0.4 × 0.4 × 0.5 mm³.

Image analysis was performed using CVI42 application (version 5.11, Circle Cardiovascular Imaging Inc., Calgary, Ontario, Canada). LV and right ventricular (RV) volumes were quantified by manually tracing the end-diastolic and end-systolic endocardial contours. For global strain measurement, LV endocardial and epicardial borders were manually traced at end-diastole in electrocardiographically gated balanced steady-state free precession 4⁻, 3⁻, and 2-chamber long-axis sequences using a point-and-click approach. The automatic border tracking algorithm was applied to track image features throughout the cardiac cycle. Tracking was visually reviewed and manually corrected. For LGE quantification, endocardial and epicardial borders were first manually contoured. LGE scar was defined as areas with signal >3 SDs above the healthy remote region. LV volume, mass, and burden (i.e., percentage of LV scar to LV volume) were calculated. The surface area of the LGE bordering the LV blood pool was measured by calculating LGE scar length in contact with the LV blood pool, multiplied by slice thickness (Supplemental Figure 1). The regional wall thickness was measured by dividing the balanced steady-state free precession cine short-axis images of the myocardium into 100 equally distributed segments using CVI42 (Circle Cardiovascular Imaging Inc.) (Supplemental Figure 2). Wall thinning was calculated as the percentage—thinning rate of the scarred region versus the healthy remote myocardium (Supplemental Figure 2). All analyses were performed by S.K. (with 5 years of experience in CMR); an additional reviewer (F.P. with 10 years of experience) repeated the measurements of 4 variables to assess interobserver reproducibility: 1) remote wall thickness; 2) scarred wall thickness; 3) LGE volume; and 4) subendocardial LGE area.

EAM Protocol. All animals underwent EAM following a 10-week survival period and ≥1 week after CMR by an experienced electrophysiologist with >15 years of experience treating patients with ventricular arrhythmias and 7 years of experience with large animal models of arrhythmia. A 6-F pentapolar catheter (Bard EP, Lowell, Massachusetts) was placed in the RV apex for pacing and as an intracardiac activation reference. An intracardiac echocardiography catheter was positioned in the right atrium or RV and routinely used for each procedure. EAM was performed using Carto3 ( Biosense Webster Inc, Diamond Bar, California) and a multi-electrode bidirectional mapping catheter (Octaray; Biosense Webster Inc,) that including 8 splines and 48 electrodes (26, 33). The performance of this catheter, including its bipolar and unipolar voltage cutoffs for scar tissue, were recently reported. Specifically, the fifth percentile of the bipolar voltage amplitude recorded in healthy ventricles with this catheter was 1.34 mV, which was similar to the cutoff of other catheters (~1.5 mV). Similarly, its mean unipolar voltage amplitude in healthy ventricles was relatively similar to that of the PentaRay catheter ( Biosense Webster Inc; 5.2 ± 1.9 mV [median: 5.2 mV] vs. 5.6 ± 2.1 mV [median: 5.5 mV]) (33).
EAM of the LV was performed via a retrograde aortic approach during RV pacing at a cycle length of 450 to 550 ms using a fill threshold of <5 mm. The high-pass filter was 0.5 Hz for unipolar and 30 Hz for bipolar electrograms (EGMs). The low-pass filter was 500 Hz for both. Data acquisition was automated using the following inclusion criteria: 1) QRS morphology stability defined as ≥95% morphology compared with the paced QRS configuration; 2) activation time stability of ≤5 ms between 2 consecutive beats; and 3) maximal distance ≤3 mm from the pre-made anatomical shell. In 2 LAD and 4 LCx cases, the epicardium was mapped by accessing the pericardial space using the modified Sosa technique (34).

EGM analysis was performed off-line at a sweep speed of 200 to 400 mm/s on either Carto3 or the LabSystem Pro EP recording system (Bard, Boston Scientific, Lowell, Massachusetts). The minimum bipolar voltage amplitude of collected EGMs was 30 mV, which is twice the voltage level in our laboratories. All EGMs were manually reviewed to exclude ectopic beats and artifacts. Activation time was annotated to the near-field potential as determined by presence of high-frequency potentials exhibiting spatiotemporal propagation across multiple electrodes at a similar acquired beat (1).

Low voltage areas were measured using the standard surface area measurement tool on the Carto3 system. The border of the low voltage area on each

Reformatted 3-dimensional (3D) late gadolinium enhancement (LGE) images from 2 animals with (A and B) left anterior descending (LAD) and (C and D) left circumflex (LCx) occlusion. Arrows show areas of scar in LGE images. Scar in LAD animals was mainly localized in the sub-endocardial region in areas with significant wall thinning on cine images and in areas with low unipolar and bipolar voltages on electro-anatomical mapping (EAM) as well, but scar extended from the endocardium to epicardium in LCx animals with preserved wall thickness and showed normal unipolar and bipolar voltages on EAM.
map was manually traced using Carto3 area measurement software. The low voltage burden was calculated using the mesh feature on the Carto3 software (endocardial low voltage area/total endocardial voltage area percentage). Low voltage cutoffs were set at 1.5 mV for bipolar amplitude.

**HISTOLOGY DATA.** In 1 animal from each group, the heart was harvested and placed in a 10% buffered formalin solution for >1 week. After tissue fixation, 1 heart from each group was serially sectioned parallel to the atrioventricular groove into 1-cm-thick slices starting from the apex. Tissue samples were paraffin embedded and sectioned at 5-μm thickness perpendicular to the epicardial surface so each section showed the full thickness of the ventricular wall from the epicardium to the endocardium. Slides were stained with Masson’s trichrome to detect collagen and subsequently scanned and digitized. The histology technique was not systematically examined; it was only used to validate the scar features.

**STATISTICAL ANALYSIS.** Continuous variables with normal distribution are expressed as mean ± SD. Categorical variables are expressed as percentages. The independent sample Student’s t-test and Pearson’s chi-square test were used to compare normally distributed continuous and dichotomous variables, respectively. For multiple group comparisons, 1-way analysis of variance was used with post hoc Bonferroni’s correction. The intraclass correlation coefficient was used to assess intra- and interobserver agreement.
reliability. Analyses were performed using SPSS software v.25.0 (IBM Corporation, Armonk, New York) and GraphPad Prism software v.8.0 (GraphPad Software, San Diego, California). p Values <0.05 were considered statistically significant.

RESULTS

CMR ANALYSIS. All animals underwent in vivo CMR at a mean day of 60 ± 3.6 following myocardial infarction and at a mean day of 6 ± 1.6 before the EAM procedure.

Table 1 summarizes the comprehensive CMR data. LV end-diastolic and end-systolic volumes were greater in the LAD group than those in the LCx group. LV mass and LV ejection fraction were similar in both groups. The global radial, circumferential, and longitudinal systolic peak strain values were also similar in both of the LAD and LCx groups.

In LAD animals, LGE was present mostly in the anterior myocardial segments, extending from the apex (Figures 1A and 1B). In LCx animals, LGE was observed on the inferior myocardial segments, extending from the base to the apex (Figures 1C and 1D). LGE scar volume, mass, and burden in vivo and ex vivo 3-dimensional LGE images were similar for both groups (Table 1). To avoid false-positive image results, we also analyzed ex vivo images thoroughly and compared in vivo and ex vivo images head-to-head (Supplemental Figure S3 and Supplemental Table 1).

Areas of LGE scar bordering the blood pool were significantly different between the LAD (12.5 ± 3.1 cm²) and LCx (4.1 ± 1.2 cm²) groups (p < 0.0001). Although LGE scar was more subendocardial in the LAD group, LCx animals had LGE scars that extended from the endocardium to the epicardium with a significant presence in the mid-myocardium (Supplemental Figure 5). There were significant changes in wall thickness between LCx and LAD animals (Figure 2). Although average wall thickness in healthy remote regions was similar between groups (LCx: 6.75 ± 0.38 mm vs. LAD: 6.66 ± 0.42 mm; p = 0.703), wall thickness in scarred segments was significantly affected in the LAD group (1.78 ± 0.26 mm), but the scarred region was similar to healthy remote regions in the LCx animals (5.38 ± 0.67 mm). The extent of wall thinning was significant in the LAD group, whereas 73 ± 40% of the wall had reduced thickness, consistent with our previous experience (10).

Intra- and interobserver reliability correlation coefficients for each group were 0.97 (95% confidence interval: [CI]: 0.95 to 0.98) and 0.94 (95% CI: 0.88 to 0.99) for remote wall thickness measurements, 0.97 (95% CI: 0.95 to 0.98) and 0.87 (95% CI: 0.80 to 0.91) for scarred wall thickness, 0.95 (95% CI: 0.91 to 0.97) and 0.86 (95% CI: 0.78 to 0.93) for LGE volume, and 0.95 (95% CI: 0.97 to 0.99) and 0.95 (95% CI: 0.94 to 0.99) for the subendocardial LGE area, respectively (Supplemental Table 2).

EAM ANALYSIS. Animals underwent EAM at a mean day of 59.5 (range 56 to 68 days) after infarct induction, with the same survival period for LAD and LCx animals. We analyzed EGMs on the scar-related walls: anterior wall for the LAD group and inferior wall for the LCx group (1,533 ± 543 vs. 618 ± 192 EGMs, respectively; p = 0.01) during RV pacing.

Table 2 shows EGM data for the anterior wall, inferior wall, and EAM-derived scar parameters. For scar-related walls, the mean bipolar (1.77 ± 0.3 mV vs. 2.8 ± 0.2 mV; p < 0.0001) and unipolar voltages (3.83 ± 0.9 mV vs. 9.25 ± 2.1 mV; p < 0.0001) were lower in the LAD group. The mean voltage within the EAM-derived scar was higher in the LCx group than that in the LAD group: 1.12 ± 0.2 mV versus 0.7 ± 0.1 mV (p = 0.001) for bipolar voltage, and 4.63 ± 0.6 mV versus 2.3 ± 0.3 mV (p = 0.001) for unipolar voltage, respectively.

The low bipolar voltage (<1.5 mV) area and low voltage burden were 13.8 ± 1.7 cm² and 7 ± 0.7% of the LV in LAD animals compared with 3.8 ± 2.9 cm² and 1.8 ± 0.2% of the LV in LCx animals (p < 0.0001 for both).

Epicardial EAM was performed in 6 of 12 animals (2 in LAD and 4 in LCx). Small areas of low bipolar voltage corresponding to LGE were seen in the LAD group, indicating LGE presence on the endocardial anteroseptal location in both swine. However, there were no areas of low bipolar or unipolar voltage in the LCx group corresponding to LGE scar (Supplemental Figure 6).

CONCORDANCE BETWEEN SCAR DETECTION USING CMR AND EAM. In an all-swine analysis, wall
thinning percentage (graded: <25% [mild], 25% to 75% [moderate], >75% [severe]) was inversely associated with mean bipolar voltage (mild vs. moderate: 2.70 ± 1.4 mV vs. 2.26 ± 1.4 mV; p < 0.0001; mild vs. severe: 2.70 ± 1.4 mV vs. 1.14 ± 1.2 mV; p < 0.0001; moderate vs. severe: 2.26 ± 1.4 mV vs. 1.14 ± 1.2 mV; p < 0.0001) (Figure 3A) and with mean unipolar voltage (between mild and moderate: 7.14 ± 2.9 mV vs. 6.23 ± 3.5 mV; p < 0.0001; between mild and severe: 7.14 ± 2.9 mV vs. 3.33 ± 2.3 mV; p < 0.0001; between moderate and severe: 6.23 ± 3.5 mV vs. 3.33 ± 2.3 mV; p < 0.0001) (Figure 3B). There were significant differences in mean bipolar (0.63 ± 0.69 mV vs. 2.52 ± 1.35 mV; p < 0.0001) (Figure 3A) and unipolar voltages (2.28 ± 0.84 mV vs. 7.23 ± 2.94 mV; p < 0.0001) (Figure 3B) between scar-related LV walls for both groups (anterior wall for LAD, inferior wall for LCx).

On EAM, all LAD animals had a large low bipolar voltage area compatible with LGE-derived scar features. However, only 2 of 6 animals in the LCx group had low bipolar voltage areas, despite having a similar large LGE scar on in vivo and ex vivo CMR, and histopathological gross as well (Figure 4, Supplemental Figure 6-8 and Supplemental Table 3). LGE scar in the LAD group corresponded with low voltage areas on EAM, whereas LGE scar in the LCx group did not correspond with low voltage EAM areas (Central Illustration). Full dataset for each pig is also available in the Supplemental Tables 4 and 5.

HISTOPATHOLOGICAL ASSESSMENT. LGE-derived scar was validated histologically in both groups. In addition, 1 swine from each group showed visual correlation between histology samples and CMR images in both in vivo and ex vivo scans with respect to scar extension into the myocardial segment from 1 swine for each group (Supplemental Figures 4 and 9). Preserved myocardial tissue was more notable in a slice from the LCx animal.

DISCUSSION

In this preclinical study, we demonstrated the limitations of EAM in identifying LGE scar. The discordance between low voltage EGMs on EAM and LGE scar highlighted the limitation of catheter mapping to identify large scar extending from the endocardium to epicardium within a normal wall thickness.

Despite similar LGE scar sizes between both animal groups, there were differences in LGE scar characteristics. Infarction in the LAD group caused significant remodeling with greater wall thinning, which resulted in better LGE scar detection by catheter
FIGURE 4  Electroanatomic Characterization of Post-Infarct Scars

EAM bipolar and unipolar voltage maps for each animal (left column for LAD group and right column for LCx group) showing extensive low voltage areas in the LAD group (anterior view) but limited low voltage areas in the LCx group (inferior view). Only 2 animals had EAM-derived scar areas that were mostly mismatched with LGE-derived scar. Abbreviations as in Figure 1.
mapping. However, wall thickness was considerably preserved in the LCx group and in cases in which LGE scars extended from the subendocardial to epicardium regions. These differences contributed to the limitations of catheter mapping in identifying LGE scar.

We and others have extensively used the anterior myocardial infarction (MI) swine model for investigation of ventricular arrhythmia (25,35–38). However, scars in this model were large and caused wall thinning and significant remodeling of the heart (10). With advances in acute MI guidelines and shorter door-to-balloon times (39), scars in patients with MI are often much smaller, with preserved wall thickness. Therefore, the LCx group might better represent scar characteristics in our patients.

Scar identification mismatch between CMR and EAM mismatch might be more common than
currently anticipated. Catheter mapping sensitivity to identify scars is highly dependent on the location and distance of the scar with respect to the epicardium (35). Wolf et al. (35) investigated the correlation between the endocardial potential and infarct transmurality in an anterior infarction dog model. They demonstrated that the extent of infarct transmurality could be accurately assessed in vivo using electrical parameters derived from the endocardial surface. Codreanu et al. (19) investigated the correlation of LGE- and EAM-derived scar in 10 patients who underwent post-infarct VT ablation and reported a mismatch in infarct surfaces between voltage maps and LGE in one-third of infarcted areas. Takigawa et al. (40) used a previous version of the mapping catheter we used to evaluate EGM amplitudes within the scar, including near- and far-field components based on bipolar spacing in thin and thick myocardial walls. They discovered that far-field voltages had a positive correlation with wall thickness; in contrast, near-field voltages had no correlation with wall thickness. This annotation issue was reported as an important limitation of current EAM systems to explain why an important number of EGMs showed normal voltages even in transmural scars on CMR (40). Desjardins et al. (41) correlated LGE with EAM in post-infarct patients and demonstrated a somewhat significant correlation between unipolar voltage and scar depth \( R = -0.61 \) but a weak correlation with bipolar voltage \( R = -0.47 \). In post-MI patients, Wijnmaalen et al. (46) showed strong correlation between transmural infarcts and low voltage areas on EAM. Despite this correlation, visual analysis, particularly in patients with inferior MI, showed a mismatch between EAM- and LGE-derived scar areas. In these patients with inferior MI, they reported larger LGE-derived scar areas than low voltage areas on EAM and several scar areas that were not detected by EAM (16). Unlike the bipolar EGM, the usefulness of the unipolar EGM to localize scar is not well defined (42). Unipolar signals have been suggested to have a larger field of view than bipolar signals, which allows detection of subepicardial scars during endocardial EAM (35,42,43). Hutchinson et al. (42) described endocardial unipolar signal characteristics in patients with epicardial scars. They identified abnormal epicardium using an endocardial unipolar voltage of <8.3 mV in patients with nonischemic cardiomyopathy and normal LV endocardial bipolar voltage. Compared with these previous studies (35,42,43), our unipolar voltage cutoff of 5.5 mV was lower. This difference in unipolar voltage cutoff might be related to the smaller electrode size of the multielectrode catheter or differences in the scar-related wall thicknesses between LAD and LCx animals. However, the mean unipolar voltage amplitudes on scar-related walls in the LAD group were >8.3 mV in our study.

A novel mapping method technique for characterizing and targeting the intramural substrate using a retractable needle within an endocardial catheter is emerging as an effective approach for intramyocardial mapping and ablation (44–46). Infusion needle catheters were developed by modifying a catheter originally designed for intramyocardial drug delivery (47). Unipolar EGMs can thus be recorded from the needle, and bipolar EGMs can be recorded between the needle and the tip of the catheter. This approach also allows unipolar pacing and radiofrequency delivery (44–49). There are some studies that evaluated the safety and effectiveness of intramural needle ablation (45,46,49). A larger multicenter study of patients with treatment-refractory ventricular arrhythmias resulted in arrhythmia elimination in 48% of patients and improvement in arrhythmia burden (49). Although these novel techniques for targeting intramural sources of VT are promising, their long-term effectiveness, safety, and cardiac complications warrant additional study.

Another mapping challenge with respect to inferior infarcts is the presence of scar tissue adjacent to or just behind papillary muscles. EAM and ablation procedures in patients in this region may be difficult due to the lack of contact between the catheter tip and the tissue (50,51). However, this can be potentially overcome by flexible bidirectional catheters and adjunct imaging guidance (e.g., intracardiac echocardiography), which was used for each animal in this study to avoid false-negative voltage mapping results and to improve success rates (50–52).

Several studies reported that advanced cardiac imaging integration techniques resulted in accurate characterization of the arrhythmogenic substrate and enhanced ablation procedure efficiency and safety (18,53–55). A total of 157 consecutive patients with ventricular arrhythmias were prospectively enrolled by Hennig et al. (53). Diagnosis before performing CMR was based on standard diagnostic tests (echocardiography, stress test, and invasive angiography), yet the implementation of CMR determined a new diagnosis or a diagnostic change in 48 patients. Njeim et al. (54) observed similar findings in 20 patients with a history of failed ablation who underwent CMR for substrate identification before a repeat ablation procedure. In these patients, CMR identified both epicardial and mid-myocardial scars, indicating that epicardial mapping might not be effective in patients with only a mid-myocardial substrate. Similarly, our
Our preclinical study demonstrated the limitations of current state-of-the-art catheter mapping systems to identify scarred regions extending from sub-endocardial to epicardial regions because of discrepancies between low voltage areas in EAM and scarring on CMR. Furthermore, voltage maps could vary significantly between areas of reduced or preserved wall thickness, regardless of the presence or the extent of scar.

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Key Words: Cardiac cardiac magnetic resonance, electroanatomical mapping, myocardial infarction model, wall thickness

Appendix: For supplemental figures and tables, please see the online version of this paper.