BACKGROUND: Conduction velocity (CV) is an important property that contributes to the arrhythmogenicity of the tissue substrate. The aim of this study was to investigate the association between local CV versus late gadolinium enhancement (LGE) and myocardial wall thickness in a swine model of healed left ventricular infarction.

METHODS: Six swine with healed myocardial infarction underwent cardiovascular magnetic resonance imaging and electroanatomic mapping. Two healthy controls (one treated with amiodarone and one unmedicated) underwent electroanatomic mapping with identical protocols to establish the baseline CV. CV was estimated using a triangulation technique. LGE+ regions were defined as signal intensity >2 SD than the mean of remote regions, wall thinning+ as those with wall thickness <2 SD than the mean of remote regions. LGE heterogeneity was defined as SD of LGE in the local neighborhood of 5 mm and wall thickness gradient as SD within 5 mm. Cardiovascular magnetic resonance and electroanatomic mapping data were registered, and hierarchical modeling was performed to estimate the mean difference of CV (LGE+/−, wall thinning+/−), or the change of the mean of CV per unit change (LGE heterogeneity, wall thickness gradient).

RESULTS: Significantly slower CV was observed in LGE+ (0.33±0.25 versus 0.54±0.36 m/s; P<0.001) and wall thinning+ regions (0.38±0.28 versus 0.55±0.37 m/s; P<0.001). Areas with greater LGE heterogeneity (P<0.001) and wall thickness gradient (P<0.001) exhibited slower CV.

CONCLUSIONS: Slower CV is observed in the presence of LGE, myocardial wall thinning, high LGE heterogeneity, and a high wall thickness gradient. Cardiovascular magnetic resonance may offer a valuable imaging surrogate for estimating CV, which may support noninvasive identification of the arrhythmogenic substrate.

VISUAL OVERVIEW: A visual overview is available for this article.
WHAT IS KNOWN?
- Slow conduction regions are necessary for initiation and maintenance of reentrant arrhythmias, which are responsible for the majority of arrhythmias observed in tissue damaged by prior myocardial infarction.

WHAT THE STUDY ADDS?
- In a swine model with healed myocardial infarction, conduction velocity measured using invasive catheter mapping is reduced in areas of signal enhancement and heterogeneity on late gadolinium enhancement and areas of left ventricular wall thinning and wall thickness gradient in cardiovascular magnetic resonance.
- Cardiovascular magnetic resonance may offer a valuable imaging surrogate for estimating conduction velocity, which may support noninvasive identification of the arrhythmogenic substrate.

Conduction velocity (CV) describes the speed and direction of cardiac electrical propagation within the myocardium and is an important property that contributes to the substrate arrhythmogenicity. Slow conduction regions are necessary for the initiation and maintenance of reentrant arrhythmias and are, therefore, critical components of pathological reentrant circuits. Reentry mechanism is the main cause of monomorphic ventricular tachycardia observed in tissue damaged by prior myocardial infarction (MI) and is a major cause for sudden cardiac death.

Various factors can affect CV in postinfarction ventricular tissue. Myocardial fibrosis reduces connectivity in myocyte-myocyte and myocyte-fibroblast coupleings and, therefore, slows CV. Tortuous or zigzag conduction through isolated bundles of surviving myocytes in and around infarcted regions represent a structural mechanism responsible for slow conduction in the scarred ventricular myocardium. Wavefront curvature also affects CV; a convex wavefront propagates more slowly than a planar wavefront due to a source-sink mismatch, a key mechanism responsible for the reduced CV observed around the infarcted border zone. Other factors including differences in transmembrane currents in the infarcted border zone resulting in excitability changes at a cellular level causing a slower upstroke of the cardiac action potential may also contribute to local differences in CV.

Due to the importance of cardiac conduction properties in determining the arrhythmogenicity of tissue, various studies have assessed CV. Prior investigators have directly estimated CV by using regularly spaced microelectrode arrays on exposed and smooth (usually epicardial) surfaces, where the distance between 2 microelectrodes is defined and the activation time is manually measured. CV can also be estimated in experimental settings using optical mapping systems. In the clinical setting, CV can be estimated based on planar wavefront propagation by applying a model based on the neighboring electrodes’ spatial locations and local activation times. The fitting can be performed either based on a predefined arrangement of measurement points depending on catheter design or more generalizable techniques such as polynomial surface fitting or triangulation. However, these CV measurements are intrinsically invasive since the electrodes require direct myocardial contact. Noninvasive techniques to identify regions of altered myocardial CV may offer a valuable tool for preprocedural planning and identification of the arrhythmogenic substrate, thereby reducing procedural duration and complexity.

Cardiovascular magnetic resonance (CMR) late gadolinium enhancement (LGE) imaging is the gold standard for visualizing and identifying the extent, volume, and characteristics of myocardial scar in patients with prior MI. The extent of LGE has been reported as a predictor for the arrhythmogenic substrate, adverse outcome, and appropriate implantable cardioverter defibrillator therapy in patients with ventricular arrhythmias. The presence of the scar border zone, as defined by LGE, correlates with ventricular tachycardia inducibility and mortality. Studies have also shown that decreased relative wall thickness is associated with an increased risk of ventricular arrhythmias. The association between the extent and the heterogeneity of myocardial fibrosis and decreased wall thickness with adverse outcomes in patients with arrhythmias are likely to reflect the importance of myocardial tissue structure on CV.

The association between LGE and CV has been studied in the human left atrium, where a negative association between LGE signal intensity (SI) and CV was shown during the sinus rhythm when clustered by patient, and adjusted for left atrial wall thickness. In the left ventricle (LV), LGE and wall thickness were reported to independently be associated with local intracardiac electrogram (EGM) duration and deflections, suggesting slower conduction in regions with higher scar transmurality. However, the association between CV and LGE or wall thickness in the LV has not yet been studied. Finally, although prior studies have reported association between LGE heterogeneity or wall thickness with adverse outcomes for arrhythmia, no study has investigated the direct association between CV and LGE heterogeneity or wall thickness gradient with CV.

In this study, we sought to investigate the association between CV and LGE, wall thinning, LGE heterogeneity, and wall thickness gradient in a swine model of healed anterior MI. With its ability to visualize and...
Five male and 3 female Yorkshire pigs from Parsons (3.5–4 months old; 35–40 kg) underwent balloon occlusion of the mid-left anterior descending artery as previously described.\textsuperscript{44,45} One female pig died at 15 days post-MI during its first CMR scan from an anesthetic-related bradycardic arrest and was excluded from the study. An angioplasty balloon was inflated in the mid-left anterior descending under fluoroscopic guidance. After 180 minutes, the balloon was deflated and withdrawn to create an ischemia-reperfusion mediated MI. Animals were treated with 800 mg twice daily oral amiodarone for 4 days after MI, which was then decreased to 400 mg once daily throughout the survival period to minimize the risk of death from spontaneous ventricular arrhythmias. To establish the baseline CV, 2 healthy control animals of comparable weights underwent the electrophysiology study using the identical protocol—one animal was medicated with oral amiodarone as per infarcted animal protocol (control\textsubscript{medicated}) and another animal was not medicated (control\textsubscript{nonmedicated}).

**CMR Imaging**

CMR imaging was performed using a 1.5T scanner (Philips Achieva, Best, the Netherlands) with a 32-element cardiac phased-array receiver coil. Scar imaging was performed using a dark-blood LGE sequence with an optimized joint inversion preparation and T\textsubscript{1} magnetization preparation to simultaneously suppress myocardial and blood signal and enhance blood-scar contrast.\textsuperscript{46,47} Imaging was performed 15 to 25 minutes after injection of 0.15 to 0.2 mmol/kg gadobenate dimeglumine (MultiHance; Bracco Imaging, Milan, Italy). A respiratory navigator with an adaptive acquisition window\textsuperscript{48} was used for prospective motion correction. Imaging was performed in short axis with the following parameters: gradient echo imaging sequence; spatial resolution = 1.3×1.3×1.3 mm\textsuperscript{3}; field of view = 320×335×90 mm\textsuperscript{3}; TR/TE/flip angle = 2.6/1.3 ms/55°; sensitivity encoding rate = 2; centric phase-encoding order.

**Electrophysiology Study**

Electrophysiology study was performed using the CARTO3 EAM system (Biosense Webster, Diamond Bar, CA) and standard electrophysiological recording system (LabSystem Pro, Bard, Lowell, MA). Twelve-lead surface ECG was recorded throughout all cases. High frequency (30 Hz) and low frequency (0.5 Hz) filters were applied to all surface ECG signals. Filters were applied to unipolar (low frequency filter: 0.5 Hz; high frequency filter 250 Hz) and bipolar (low frequency filter: 30 Hz; high frequency filter: 250 Hz) intracardiac EGMs before analysis. A sensor-enabled Thermocool (Biosense-Webster) ablation catheter was advanced to the aorta via the right femoral arterial sheath and used to acquire the aortic root and coronary ostia geometry before gaining retrograde LV access across the aortic valve. LV endocardial geometry was acquired using the fast anatomic mapping function within CARTO.

LV endocardial activation maps were acquired using a 5-spline 20-electrode mapping catheter (Pentaray, Biosense-Webster), with 1 mm electrodes and 2-6-2 mm electrode spacing introduced into the LV using a retrograde approach while pacing from the RV apex at a cycle length of 400 ms. A reference bipolar electrode pair was selected on the RV catheter and activation times of each acquired LV activation point

**METHODS**

The data that support the findings of this study are available from the corresponding author on reasonable request.

**Animal Study**

The protocol was approved by the Institutional Animal Care and Use Committee and conformed to the Position of the American Heart Association on Research Animal Use. All experiments were performed under general anesthesia with isoflurane inhalation (1.5%–2.5%) and mechanical ventilation (12–16 breaths/min with tidal volumes between 300 and 400 mL), and animals were euthanized with pentobarbital sodium. The animal study outline is summarized in Figure 1. In brief, ischemia-reperfusion MI was created by 180-minute balloon occlusion of the left anterior descending coronary artery. After a 9-week recovery, each animal underwent in vivo CMR. Zero to 5 days after in vivo CMR, invasive electrophysiology studies were performed as described below to collect activation maps during right ventricular (RV) apical pacing at cycle length of 400 ms. Inclusion criteria for enrollment into the study was defined as animals which completed the electrophysiology study protocol, and was set before the study. CMR and electroanatomic mapping (EAM) data were processed to extract CMR-derived tissue characteristics and to estimate CV. CMR and EAM data were spatially registered to study their associations.

**Animal Model**

Five male and 3 female Yorkshire pigs from Parsons (3.5–4 months old; 35–40 kg) underwent balloon occlusion...
assigned relative to the reference EGM. Individual activation times were automatically assigned within the EAM at the point of the highest rate of negative deflection of the bipolar EGM (−dV/dt max). Individual activation times were manually reviewed and reassigned after review of bipolar and unipolar EGM when necessary. Maps were considered complete when the point density allowed interpolation to be limited to <15 mm in normal region and <5 mm in regions of low bipolar voltage <1.5 mV.49 One animal did not complete the study protocol because of the repeated and prolonged episode of ventricular tachycardia, which resulted in metabolic state deterioration and was not recovered, and was excluded from the study.

Local CV Estimation
CV was estimated based on triangulation techniques1,26 (Figure 2A). We used a triangular mesh of local activation time (LAT) exported from the EAM system, after manual annotation as needed. LAT maps were automatically generated within CARTO using interpolation that was limited to a maximum of 15 mm from an acquired data point. An edge collapse decimation was performed to simplify and retriangulate meshes to improve triangular mesh quality. Triangulation techniques are based on the rules of trigonometry, and the coordinates of 3 points and their activation times were used to estimate the average CV within the triangle. When a wavefront is approximated as locally planar, from the earliest activation point to the next 2 points, the conduction speed and the direction is decided based on the activation time of the remaining 2 points. For example, when the earliest activation point is p, and the other points are q and r, the activation time difference between p to q is t a, and the orthogonal distance between p to q can be noted as |a|cos a. Then the CV can be defined as follows:

\[ v = \frac{|a| \cos \alpha}{t_a} \]

Likewise, for the third point, the activation time difference between p to r can be noted as t b, and the orthogonal
The distance separating the points can be noted as $|\delta| \cos b$, and the CV can be defined as follows as well:

$$v = \frac{|\delta| \cos b}{t_b}$$

Constraints were imposed on distance between each pair of points (1 < d < 20 mm), the difference in activation times (50 ms > LAT > 1 ms) to minimize measurement errors, and the ratio of circumcircle area to triangle area (<10) to penalize elongated triangles.26

**CMR Image Analysis**

CMR images were processed to generate LV endocardial surface projected CMR imaging feature maps shown in Figure 3. Conduction velocity (CV) and cardiovascular magnetic resonance (CMR) features from 2 animals. CV was estimated based on the local activation time (LAT). CV and CMR data were registered in the same spatial coordinates. Slower CV was observed in the region of hyperenhancement on late gadolinium enhancement (LGE) and wall thinning. The pattern of CV was inhomogeneous throughout the scar with maximal slowing in the region of dense scar with higher LGE heterogeneity or wall thickness gradient. SI indicates signal intensity.
Figure 2B. Endocardial and epicardial contours were manually delineated by an experienced reader with guidance from cine balanced steady-state free-precession images. For each slice, the center of the endocardial contour was selected, and the equiangular chord lines were drawn from endocardial to epicardial contours based on the number of pixels on the endocardial contour. Local tissue characterization parameters were defined for each chord line and were projected back to the endocardial points. Endocardial points from each slice were merged into a single point cloud data set, and a Poisson surface reconstruction was performed to reconstruct the LV endocardial surface. A second reader delineated endocardial and epicardial contours independently to study the interobserver reproducibility of the CMR measurements.

Late Gadolinium Enhancement
For LGE data, endocardial SI was defined using subendocardial lines automatically identified as one third from endocardial to epicardial chord lines. The LGE SI was then bimodal fitted, and LGE SI was normalized using the mean ($\mu_{remote}$) and SD ($\sigma_{remote}$) of remote regions, such that 0 in the normalized signal distribution was denoted as $\mu_{remote}$ and 1 as $\sigma_{remote}$. LGE+ was defined as any voxel with SI higher than $\mu_{remote} + 2\sigma_{remote}$.

Myocardial Wall Thickness
Myocardial wall thickness was calculated as the Euclidean distance between endocardial and epicardial contours of each chord line and was projected back to the endocardial points. Wall thickness was presented as the absolute value in millimeter. Wall thickness was bimodal fitted to define a region with wall thinning. Wall thinning+ was defined per chord line as wall thickness thinner than $\mu_{remote} - 2\sigma_{remote}$, such that 95% of the regions of remote wall thickness are thresholded.

LGE Heterogeneity
LGE heterogeneity was defined as the SD of the LGE SI of local neighbors in voxels that were within an Euclidean distance of 5 mm for each point, based on the minimal point density of EAM (49):

$$LGE_{heterogeneity} = \sqrt{\frac{\sum (LGE_{remote} - LGE_{remote})^2}{n}}$$

Figure 4. Scatter plots of late gadolinium enhancement (LGE), wall thickness, LGE heterogeneity, and wall thickness gradient vs. conduction velocity (CV) of all 6 animals. Smoothing splines of each animal are overlaid on the scatter plots. SI indicates signal intensity.
Wall Thickness Gradient

Wall thickness gradient was defined as the SD of the wall thickness of neighbors that were within an Euclidean distance of 5 mm for each point as follows:

$$\text{Wall thickness gradient} = SD_{\text{wall thickness}} = \sqrt{\frac{\sum_{n=1}^{N}(\text{wall thickness}_{n} - \text{wall thickness}_{\text{mean}})^2}{N}}$$

Data Registration

Imaging and EAM data were spatially aligned to study their associations as shown in Figure 2C. For spatial reference, the right coronary artery ostium, left main stem coronary artery ostium, and apex were manually marked both on EAM and CMR. Based on these 3 spatial reference points, fiducial registration was performed to align imaging and EAM data on the same spatial coordinates. Spatially registered EAM and imaging data were then 2-dimensionally projected onto the semihemisphere map to minimize surface area distortion using Hammer mapping (Figure 2C). All hammer maps were orientated consistently with the right coronary artery to apex axis along the center line. EAM and imaging data were projected onto the same hammer map, and for each data-containing EAM location, the closest point of imaging data was selected, and these spatially correlated values were paired for further analyses. All data processing analyses were performed using MATLAB (MathWorks, Natick, MA) and Meshlab (Visual Computing Lab—ISTI—CNR, Rome, Italy).

Statistical Analyses

Statistical analyses were performed to assess the association between CV and the other 4 parameters of (1) LGE, (2) wall thinning, (3) LGE heterogeneity, and (4) wall thickness gradient. First, we used the general linear models to analyze data for each animal. In each of these models, we reported the model coefficient and its 95% CI. For LGE and wall thinning where we dichotomized the data, the model coefficient represents the estimated mean difference of CV for each category (+/−). For LGE heterogeneity and wall thickness gradient, the model coefficient represents the slope (the change of the mean of CV per unit change of LGE heterogeneity or wall thickness gradient). For the modeling of all animals, we used hierarchical models (linear mixed effects models) where we captured the within-animal repeated/longitudinal measurements by modeling the within-animal correlation using the compound symmetry structure for the variance-covariance matrix of CV. The estimated variance-covariance parameters were used in the estimated fixed effects of the independent variables (LGE, wall thinning, LGE heterogeneity, and wall thickness gradient) and the models yielded the estimated mean difference (LGE and wall thinning) or the slope (LGE heterogeneity and wall thickness gradient). All statistical analyses were performed using SAS software (SAS Institute Inc, Cary, NC).

RESULTS

Six swine (4 male; median 82.9 kg [range 74.9–93.1 kg]) with healed MI 63.5 (63–64) days after infarction
and 2 healthy control animals (control medicated and control nonmedicated) were included in the study. The median number of data points per LV map was 296 (range 232–540) for post-MI animals, 265 for control medicated, and 140 for control nonmedicated. EAM and CMR data were successfully registered, and examples of CV and CMR features including LGE, wall thickness, LGE heterogeneity, and wall thickness gradient are shown in Figure 3. Scatter plots of CV versus LGE, CV versus wall thickness, CV versus LGE heterogeneity, and CV versus wall thickness gradient of all animals are shown in Figure 4, where smoothing splines of each scatter plots are overlaid. Interobserver reproducibility of CMR measurements was high with intraclass correlation coefficient of 0.95 for LGE scar volume and 0.86 for LV wall thickness.

Association Between CV and LGE

Extensive antero-septal scarring was observed in all post-MI animals on in vivo CMR. LGE distribution was mostly transmural with sparing of the sub-endocardium. Overall, the LGE scar volume was 24.0±7.8 % of the entire LV myocardial volume. The endocardial LGE scar volume was 29.0±10.7 % of the entire endocardial volume.

CV in post-MI animals was 0.38±0.28 m/s in the presence of LGE (LGE+) and 0.58±0.38 m/s in remote regions (LGE−; Figure 5; Table 1). CV was 0.65 m/s in the control medicated and 0.85 m/s in the control nonmedicated. For all animals, significantly lower CV was observed in LGE+ regions compared with LGE− regions with the estimated mean difference of −0.15 m/s (CI, −0.18 to −0.13; P <0.001, Table 1).

Association Between CV and Wall Thinning

The average LV wall thickness in CMR was 6.9±1.1 mm with substantial wall thinning observed in scarred regions (minimum wall thickness 1.2±0.7 mm). The average wall thickness was 5.1±1.2 mm in the region of hyperenhancement on LGE and 7.4±1.0 mm in the remote region.

CV in the post-MI animals were 0.38±0.28 m/s in the presence of wall thinning (wall thinning+) and 0.55±0.37 m/s in remote regions (wall thinning−; Figure 6; Table 2). CV in the control medicated was 0.65±0.36 m/s and 0.85±0.45 m/s in the control nonmedicated (Figure 6). Significantly slower CVs were observed in the presence of wall thinning with the estimated mean difference of −0.07 m/s (CI, −0.09 to −0.04; P <0.001, Table 2).

Table 1. Estimated Mean Differences in CV Between LGE+ and LGE−, 95% CI, and P Value of General Linear Modeling and of Multilevel Model of All Animals and Each Individual Animal

<table>
<thead>
<tr>
<th></th>
<th>CV in LGE+, m/s</th>
<th>CV in LGE−, m/s</th>
<th>Estimated Mean Difference, m/s</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All animals</td>
<td>0.38±0.28</td>
<td>0.58±0.38</td>
<td>−0.15</td>
<td>(−0.18 to −0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal 1</td>
<td>0.33±0.24</td>
<td>0.59±0.37</td>
<td>−0.09</td>
<td>(−0.14 to −0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal 2</td>
<td>0.35±0.29</td>
<td>0.58±0.37</td>
<td>−0.21</td>
<td>(−0.28 to −0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal 3</td>
<td>0.35±0.28</td>
<td>0.58±0.40</td>
<td>−0.23</td>
<td>(−0.28 to −0.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal 4</td>
<td>0.43±0.27</td>
<td>0.57±0.33</td>
<td>−0.03</td>
<td>(−0.10 to 0.03)</td>
<td>0.36</td>
</tr>
<tr>
<td>Animal 5</td>
<td>0.43±0.26</td>
<td>0.58±0.38</td>
<td>−0.16</td>
<td>(−0.24 to −0.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal 6</td>
<td>0.46±0.30</td>
<td>0.65±0.43</td>
<td>−0.15</td>
<td>(−0.21 to −0.09)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The model: CV = βLGE + βwall thinning + e. CV indicates conduction velocity; and LGE, late gadolinium enhancement.

Table 2. Estimated Mean Difference in CV Between Wall Thinning+ and Wall Thinning−, 95% CI, and P Value of General Linear Modeling and of Multilevel Model of All Animals and Each Individual Animal

<table>
<thead>
<tr>
<th></th>
<th>CV in Wall Thinning+, m/s</th>
<th>CV in Wall Thinning−, m/s</th>
<th>Estimated Mean Difference, m/s</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All animals</td>
<td>0.38±0.28</td>
<td>0.55±0.37</td>
<td>−0.07</td>
<td>(−0.09 to −0.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal 1</td>
<td>0.30±0.23</td>
<td>0.48±0.35</td>
<td>−0.13</td>
<td>(−0.18 to −0.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal 2</td>
<td>0.37±0.32</td>
<td>0.56±0.37</td>
<td>−0.04</td>
<td>(−0.13 to 0.04)</td>
<td>0.32</td>
</tr>
<tr>
<td>Animal 3</td>
<td>0.37±0.31</td>
<td>0.50±0.37</td>
<td>−0.01</td>
<td>(−0.07 to 0.05)</td>
<td>0.69</td>
</tr>
<tr>
<td>Animal 4</td>
<td>0.37±0.22</td>
<td>0.58±0.33</td>
<td>−0.18</td>
<td>(−0.26 to −0.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal 5</td>
<td>0.46±0.29</td>
<td>0.56±0.37</td>
<td>0.02</td>
<td>(−0.05 to 0.10)</td>
<td>0.52</td>
</tr>
<tr>
<td>Animal 6</td>
<td>0.43±0.29</td>
<td>0.62±0.41</td>
<td>−0.12</td>
<td>(−0.19 to −0.05)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The model: CV = βLGE + βwall thinning + e. CV indicates conduction velocity; and LGE, late gadolinium enhancement.
Association Between CV Versus LGE Heterogeneity and Wall Thickness Gradient

LGE heterogeneity and CV were negatively associated, where CV decreases 0.02 m/s per unit increase in LGE heterogeneity (CI, −0.04 to −0.01; *P*<0.001; Table 3). A negative relationship between CV and wall thickness gradient was also observed, where CV decreases 0.05 m/s per unit increase in wall thickness gradient (CI, −0.07 to −0.03; *P*<0.001; Table 4). The pattern of the CV was inhomogeneous throughout the scar, and the maximal slowing occurred in the area of dense scar with higher LGE heterogeneity or wall thickness gradient.

**DISCUSSION**

We investigated the association between EAM-defined CV with CMR-defined LGE and wall thickness in a swine model of healed LV infarction. We found that during steady state pacing from the RV apex, (1) CV is lower in LGE+ regions, (2) CV is lower in regions of wall thinning, and (3) CV is lower in regions with high LGE heterogeneity and steeper wall thickness gradient. CV exhibited inhomogeneous pattern with maximal slowing in the region of dense scar with higher LGE heterogeneity or wall thickness gradient.

Previous studies have reported associations between the extent and heterogeneity of LGE/wall thickness and adverse outcomes in patients with arrhythmias. Our study adds valuable insights by confirming a direct association between LGE/wall thickness with CV, highlighting an important mechanism by which CMR-defined tissue structural characteristics may promote arrhythmogenesis. This contributes to a deeper understanding of the previously reported association between the extent or heterogeneity of LGE/wall thickness and outcomes in patients with arrhythmias. CMR may offer a valuable imaging surrogate for estimating CV, which may support noninvasive identification of the arrhythmogenic substrate.

We found significantly slower CV in LGE+ regions, which is consistent with previous reports showing slower CV in the presence of myocardial fibrosis because of reduced connectivity in myocyte couplings. Our study shows significantly slower CV in the presence of wall thinning, which is as expected from previous stud-

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**Table 3.** The Regression Slope, 95% CI, and *P* Value of Generalized Linear Modeling of CV vs LGE Heterogeneity of Multilevel Model of All Animals and Each Individual Animal

<table>
<thead>
<tr>
<th>LGE Heterogeneity (Normalized SI)</th>
<th>Slope</th>
<th>95% CI</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All animals</td>
<td>−0.02</td>
<td>(−0.04 to −0.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal 1</td>
<td>−0.03</td>
<td>(−0.07 to 0.01)</td>
<td>0.18</td>
</tr>
<tr>
<td>Animal 2</td>
<td>−0.06</td>
<td>(−0.10 to −0.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal 3</td>
<td>0.02</td>
<td>(−0.01 to 0.04)</td>
<td>0.27</td>
</tr>
<tr>
<td>Animal 4</td>
<td>−0.01</td>
<td>(−0.04 to 0.02)</td>
<td>0.39</td>
</tr>
<tr>
<td>Animal 5</td>
<td>−0.05</td>
<td>(−0.09 to −0.02)</td>
<td>0.01</td>
</tr>
<tr>
<td>Animal 6</td>
<td>−0.06</td>
<td>(−0.10 to −0.01)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

The model: \( CV = \beta_1 \text{LGE} + \beta_2 \text{LGE heterogeneity} + \beta_3 \text{wall thickness} + \beta_4 \text{wall thickness gradient} + \epsilon \). CV indicates conduction velocity; LGE, late gadolinium enhancement; and SI, signal intensity.

**Table 4.** The Regression Slope, 95% CI, and *P* Value of Generalized Linear Modeling of CV vs Wall Thickness Gradient of Multilevel Model of All Animals and Each Individual Animal

<table>
<thead>
<tr>
<th>Wall Thickness Gradient, mm</th>
<th>Slope</th>
<th>95% CI</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All animals</td>
<td>−0.05</td>
<td>(−0.07 to −0.03)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal 1</td>
<td>0</td>
<td>(−0.07 to 0.06)</td>
<td>0.94</td>
</tr>
<tr>
<td>Animal 2</td>
<td>0.01</td>
<td>(−0.06 to 0.08)</td>
<td>0.84</td>
</tr>
<tr>
<td>Animal 3</td>
<td>−0.18</td>
<td>(−0.23 to −0.13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Animal 4</td>
<td>0.05</td>
<td>(−0.01 to 0.12)</td>
<td>0.11</td>
</tr>
<tr>
<td>Animal 5</td>
<td>0.05</td>
<td>(−0.03 to 0.13)</td>
<td>0.26</td>
</tr>
<tr>
<td>Animal 6</td>
<td>−0.05</td>
<td>(−0.12 to 0.02)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

The model: \( CV = \beta_1 \text{LGE} + \beta_2 \text{LGE heterogeneity} + \beta_3 \text{wall thickness} + \beta_4 \text{wall thickness gradient} + \epsilon \). CV indicates conduction velocity; and LGE, late gadolinium enhancement.
ies using multidetector computed tomography. Our result shows significantly slower CV in regions of high LGE heterogeneity, confirming slowing of CV in the presence of tissue heterogeneity, which is likely because of branching and merging bundles of surviving myocardial cells within infarcted tissue. Regions of steeper wall thickness gradient primarily represent the infarct border zone where the wavefront curvature changes, resulting in significantly slower CV as previously reported.

Our CVs are similar to those reported LV CV ranges in swine. In the swine ventricle, a range of 0.5±0.02 m/s in the longitudinal direction to the fiber orientation and 0.2±0.01 m/s in the transverse direction was reported in Langendorff-perfused hearts where CV was measured with multiple terminal electrodes in epicardial surface of the anterolateral LV wall. In another swine study during open-heart surgery, CV was estimated using polynomial surface fitting from 1.58±0.83 to 1.82±0.85 m/s depending on the sampling rate and activation threshold during sinus rhythm and 0.70±0.31 to 0.72±0.34 m/s during pacing with cycle length of 300 ms from RV epicardium.

In a swine LV where CV was measured using high-resolution basket catheter and triangulation technique, absolute conduction velocities in the infarct and peri-infarct zone ranged from 0.10 m/s in areas of conduction block to 0.88 m/s in healthy myocardium and conduction bundles. The CV estimated in our study was as low as 0.04 m/s in infarcted regions and 0.58 m/s in remote regions with pacing at cycle length of 400 ms, which lies within the expected range from the previous reports.

Our study has several limitations. The number of animals was small, though consistent with preclinical studies with large animal models. We did not study any factors that may contribute to functional aspects of CV such as restitution properties. Using EAM, LAT was measured only for voltage amplitude >0.1 mV. We did not acquire identical number of data points in all our animals during EAM. Only one control animal underwent CMR imaging, although we did not observe either LGE or wall thinning in this animal.

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**REFERENCES**


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