Regional heterogeneity in left atrial (LA) conduction velocity (CV) is an important substrate for the development of functional reentry and atrial fibrillation (AF). 1 Myocardial fibrosis can contribute to decreased regional CV2–4 and is associated with the initiation and perpetuation of AF. 5–8 Late gadolinium enhancement (LGE) magnetic resonance imaging (MRI) 9,10 has been proposed as a useful tool for visualization of atrial fibrosis. 11 We have previously reported the association of a normalized parameter, the image intensity ratio (IIR), with local bipolar voltage and established quantitative thresholds of >0.97 and >1.61 corresponding to local bipolar voltage of <0.5 and <0.1 mV, respectively.12 Prior studies have uncovered an association between CV and myocardial fibrosis in the atria of animal models.2,4 However, no clinical studies have demonstrated an association between local CV and LA LGE. We sought to investigate the in vivo association between local CV during sinus rhythm and myocardial LGE in the human LA.

**Background**—Prior studies have demonstrated regional left atrial late gadolinium enhancement (LGE) heterogeneity on magnetic resonance imaging. Heterogeneity in regional conduction velocities is a critical substrate for functional reentry. We sought to examine the association between left atrial conduction velocity and LGE in patients with atrial fibrillation.

**Methods and Results**—LGE imaging and left atrial activation mapping were performed during sinus rhythm in 22 patients before pulmonary vein isolation. The locations of 1468 electroanatomic map points were registered to the corresponding anatomic sites on 469 axial LGE image planes. The local conduction velocity at each point was calculated using previously established methods. The myocardial wall thickness and image intensity ratio defined as left atrial myocardial LGE signal intensity divided by the mean left atrial blood pool intensity was calculated for each mapping site. The local conduction velocity and image intensity ratio in the left atrium (mean±SD) were 0.98±0.46 and 0.95±0.26 m/s, respectively. In multivariable regression analysis, clustered by patient, and adjusting for left atrial wall thickness, conduction velocity was associated with the local image intensity ratio (0.20 m/s decrease in conduction velocity per increase in unit image intensity ratio, \( P < 0.001 \)).

**Conclusions**—In this clinical in vivo study, we demonstrate that left atrial myocardium with increased gadolinium uptake has lower local conduction velocity. Identification of such regions may facilitate the targeting of the substrate for reentrant arrhythmias. (Circ Arrhythm Electrophysiol. 2016;9:e002897. DOI: 10.1161/CIRCEP.115.002897.)

**Key Words:** arrhythmias, cardiac ■ atrial fibrillation ■ fibrosis ■ magnetic resonance imaging ■ regression analysis
WHAT IS KNOWN

- Regional left atrial late gadolinium enhancement heterogeneity has been noted on magnetic resonance imaging of patients with atrial fibrillation.
- The extent of left atrial late gadolinium enhancement seems to be associated with atrial fibrillation persistence and failure of pulmonary vein isolation for arrhythmia suppression.

WHAT THE STUDY ADDS

- Left atrial regions, which exhibit late gadolinium enhancement, exhibit lower local conduction velocity.
- Conduction velocity heterogeneity may mediate the association of late gadolinium enhancement with atrial fibrillation persistence and recurrence after pulmonary vein isolation.

Atrial fibrillation persistence and recurrence after pulmonary vein isolation for atrial fibrillation seems to be associated with atrial fibrillation persistence and recurrence after pulmonary vein isolation.

Conduction velocity heterogeneity may mediate the association of late gadolinium enhancement with atrial fibrillation persistence and recurrence after pulmonary vein isolation.

Figure 1. Endocardial and epicardial left atrial (LA) contours and registration of electroanatomic mapping (EAM) data to late gadolinium enhancement (LGE)-magnetic resonance imaging (MRI) in a representative case. A, The endocardial (red) and epicardial (green) contours were drawn on LGE-MRI axial planes. LA myocardium between the 2 contours was divided into 20 sectors and the mean pixel intensity of each sector, defined as the mean pixel intensity of each sector divided by the mean pixel intensity of the entire LA blood pool, was calculated. Based on our prior data that examined the association of IIR with voltage mapping, image sectors with IIR > 0.97 were considered enhanced. The average LA wall thickness of each sector was calculated using QMass MR.

Electroanatomic Mapping

Before radiofrequency ablation, LA activation mapping was performed during sinus rhythm using an EAM system (CARTO3; Biosense Webster, Diamond Bar, CA) and a mapping catheter with a 3.5-mm distal tip (Navistar Thermocool, Biosense Webster). Endocardial contact during point acquisition was validated by recording of a stable contact signal for > 2 beats. Three-dimensional position coordinates and local electrograms of all mapping sites were recorded on CARTO. The timing reference for activation mapping was set as a stable coronary sinus electrogram. The local activation time of each EAM point was annotated. EAM points recorded during ectopic beats with different intracardiac sequences or different P-wave morphologies in surface electrocardiograms from those of sinus rhythm were excluded. If necessary, points were excluded by an observer that was masked to imaging data and before registration of EAM to images. Patients were observed for 24 hours after the procedure. No immediate postoperative complications were noted.

Local CV Analysis

The local CV for each point was calculated according to previously published methodology from prior studies. The local CV of each EAM point was defined as the average of the CV between that point and 5 adjacent points along the activation front, where the CV between each pair of points was defined as the linear distance between the points divided by the difference in activation times. To avoid the inclusion of CV measurements in a different direction than that of activation propagation, points with difference in local activation time < 5 ms from the index point were excluded from the CV calculation for that index point. Using this methodology the CV at all EAM points was automatically calculated with a custom calculating script written in Python.

Registration of EAM data and MRI

Using previously validated custom software (Volley; Johns Hopkins University, Baltimore, MD), the coordinates of activation map points on EAM were registered to the preprocedural LGE-MRI axial planes (Figure 1B). The IIR and LA wall thickness of LGE image sectors that corresponded to each EAM point were measured.

Image Analysis

QMass MR software (version 7.2; Leiden University Medical Center, Leiden, The Netherlands) was used to quantify scar extent on preoperative LGE-MRI by an observer that was masked to EAM results. Epicardial and endocardial contours were manually drawn around the LA myocardium on axial LGE-MRI planes (Figure 1A). The anatomic reference point was set at the LA posteroseptum, and the LA myocardium in each axial plane was divided into 20 sectors. The IIR for each sector, defined as the mean pixel intensity of each sector divided by the mean pixel intensity of the entire LA blood pool, was calculated. Based on our prior data that examined the association of IIR with voltage mapping, image sectors with IIR > 0.97 were considered enhanced. The average LA wall thickness of each sector was calculated using QMass MR.
Statistical Analyses
Continuous variables are expressed as means±SD and categorical data as numbers or percentages. The multivariable association of CV as dependent variable with IIR and thickness as independent variables was assessed using a multilevel multivariable regression model, clustered by patient. The multilevel model approach utilized here recognizes the existence of data clustering by allowing for patient-specific intercepts and slopes. Failure to account for data clustering and the between-patient variability in slopes and intercepts can result in incorrect inferences and overstatement of statistical significance. The possibility of multiplicative interaction between our main effect variable (IIR) and AF type was explored by subsequent addition of a multiplicative term, followed by stratification by AF type. To validate the reliability of our custom script for automated calculation of local CV, the automated results were compared with results from manual calculation using previously reported methodology. In a randomly selected sample of 5 patients (434 points). Inter- and intraobserver variability in measuring the IIR and wall thickness were also assessed by repeat review by a second reviewer and repeat review by the original reviewer, in a randomly selected sample of 5 patients. The intraobserver correlation coefficients for automated calculation versus manual CV measurements, and inter- and intraobserver variability of IIR and wall thickness were calculated using 2-way random effects models. Statistical analyses were performed using STATA (version 12; StataCorp, College Station, TX).

Results

Patient Characteristics
Twenty-two patients (17 men; age, 62±9.0 years; 13 paroxysmal; 9 persistent AF) were enrolled in this study. The mean left ventricular ejection fraction was 61±4.2% (limit, 55–68) and the mean CHA2DS2-V AS score was 1.9±1.8 (limit, 0–6). The paroxysmal and persistent AF groups were comparable with respect to age, BMI, and LA LGE and Local Conduction Velocity.

Conduction Velocity Analyses
A total of 2824 points were acquired on EAM of 22 patients. Of all points, 1356 were excluded because of catheter instability or ectopic beats during point acquisition, and the remaining 1468 points (67±30 points-per-patient) were included for local CV calculation. The mean local CV was 0.98±0.46 m/s (CV limit, 0.05–3.22 m/s; 0.24 between-patient and 0.40 within-patient SD).

EAM Coregistration and Analysis of LGE-MRI
Three-dimensional LGE-MRI with minimal artifacts was obtained in all 22 patients. A total of 9380 image sectors from 469 axial image planes were analyzed. The coordinates of all 1468 EAM points were registered to the LGE-MRI. The mean value of IIR and LA wall thickness of corresponding points were 0.95±0.26 (IIR limit, 0.21–2.24; 0.14 between-patient and 0.22 within-patient SD) and 1.9±0.5 mm (thickness limit, 0.40–3.63 mm; 0.31 between-patient and 0.39 within-patient SD), respectively. Figure 2 illustrates the activation propagation, local CV, IIR, and wall thickness in the LA in a representative case. In all patients, the LA posterior wall adjacent to the left pulmonary vein antra (septopulmonary bundle region) had lower local CV and higher IIR than other LA sites.

In multilevel multivariable linear regression analyses, clustered by patient, CV was associated with the local IIR (0.20 m/s decrease in CV per unit increase in IIR; P<0.001) after adjusting for LA wall thickness (0.03 m/s decrease in CV per mm increase in wall thickness; P=0.33).

When adding EAM point localization in the left LA posterior wall to the regression model, to adjust for the potential confounding effect of myocardial fiber orientation, both the IIR (0.10 m/s decrease in CV per unit increase in IIR; P=0.044) and left posterior LA localization (0.20 m/s decrease in CV; P<0.001) remained associated with CV after adjusting for LA wall thickness (0.01 m/s decrease in CV per mm increase in wall thickness; P=0.58).

We observed the presence of multiplicative interaction between IIR and AF type in their association with CV (Figure 3; P=0.002). After stratification by AF type, the magnitude of association between IIR and CV was higher in the setting of persistent AF (0.34 m/s decrease in CV per unit increase in IIR; P<0.001). Among the subgroup of patients with paroxysmal AF, there was no statistically significant association between IIR and CV (P=0.47).

Validation of Automated Calculation of Local CV
In a randomly selected sample of 5 patients (434 EAM points), the automated results were similar to results from manual calculation. The intraclass correlation coefficient for the reliability of automatic observations versus manual measurements was 0.93.

Inter- and Intraobserver Variability
For the assessment of inter- and intraobserver variability, repeat analyses by the same observer and the second observer were performed. A total of 407 EAM points and 2280 image sectors on 114 axial MRI planes from a randomly selected sample of 5 patients were analyzed. The intraclass correlation coefficients for intraobserver variability of the IIR and wall thickness were 0.99 and 0.92, respectively. The intraclass correlation coefficients for interobserver variability of the IIR and wall thickness were 0.98 and 0.69, respectively.

Discussion

Major Findings
The major finding of our study is that LA myocardium with increased gadolinium uptake, indicating increased extracellular volume content and slower contrast washout, exhibits lower local CV.

Table. Patient Characteristics (n=22)

<table>
<thead>
<tr>
<th>Table</th>
<th>Patient Characteristics (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62±9.0</td>
</tr>
<tr>
<td>Men</td>
<td>17 (77%)</td>
</tr>
<tr>
<td>BMI</td>
<td>29±5.8</td>
</tr>
<tr>
<td>Type of AF</td>
<td>13 (59%)</td>
</tr>
<tr>
<td>Persistent</td>
<td>9 (41%)</td>
</tr>
<tr>
<td>AF duration, y</td>
<td>4±4.5</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>61±4.2</td>
</tr>
<tr>
<td>CHA2DS2-V AS</td>
<td>1.9±1.8</td>
</tr>
<tr>
<td>Duration from preoperative MRI to ablation, d</td>
<td>Median 1, limit 0–9</td>
</tr>
</tbody>
</table>

Data are presented as means±SD, N (%), or median and limit. AF indicates atrial fibrillation; BMI, body mass index; LVEF, left ventricular ejection fraction; and MRI, magnetic resonance imaging.
Myocardial Fibrosis and CV

AF facilitates the expression of extracellular matrix proteins in the atrial myocardial tissue and promotes atrial fibrosis.\(^8,^{20}\) Additional stimuli such as mechanical stress, high rate cell depolarization, hypoxia, inflammation, and humoral factors also induce cardiac fibroblasts to proliferate and undergo phenotype-change into myofibroblasts, which stimulate other fibroblasts and exacerbate myocardial fibrosis by producing cytokines, growth factors, and extracellular matrix proteins.\(^{21–23}\) Myocardial fibrosis, in turn, causes decreased CV and regional conduction block, which promote functional reentry.\(^2,^{24}\) Interestingly, factors other than the lack of conduction by fibroblasts may explain decreased CV in fibrotic regions. Some evidence suggests that myocytes might form electric connections with fibroblasts\(^{3,5,23,25}\) and myofibroblasts\(^21\) through gap junctions. Heterogeneous cell-couplings have been shown to cause conduction slowing and excitation failure in cellular models\(^{25}\) and computer simulations.\(^{26}\)

In this study, we demonstrated that LA myocardium with increased LGE intensity has lower local CV than unenhanced areas. LA myocardium with fibrosis or increased myofibroblast content exhibits increased extracellular volume and prolonged contrast retention. The finding that LA regions with LGE conduct slowly provides additional evidence to validate the use of LGE and particularly IIR as a methodology for LA myocardial characterization and also suggests a mechanism for the observation that increased pre-existing LGE associates with persistent and recurrent AF.\(^{11}\)

Importantly, in our study, statistical interaction between IIR and AF type was noted in their association with CV. The association of IIR with CV was accentuated in patients with persistent AF.

<table>
<thead>
<tr>
<th>AF Type</th>
<th>Beta Estimate (95% CI)</th>
<th>P for Interaction=0.002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxysmal</td>
<td>-0.05 (-0.18, 0.09)</td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td>-0.34 (-0.46, -0.21)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>-0.20 (-0.29, -0.10)</td>
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**Figure 2.** Three-dimensional maps in a representative case. **Top** and **bottom**, The anterior and posterior projections of 3-dimensional LA images merged with the data of local activation time, local conduction velocity (CV), image intensity ratio (IIR), and wall thickness, respectively. Left atrial appendage was excluded from the figures.

**Figure 3.** Forest plot of beta estimates for the association of image intensity ratio (IIR) with conduction velocity (CV). The forest plot summarizes multivariable-adjusted beta estimates for the association of IIR with CV. Models were clustered by patient and adjusted for regional thickness. The association of IIR with CV was accentuated in patients with persistent atrial fibrillation (AF). In contrast, although the direction of association was consistent, the magnitude of association was lower and statistical significance was absent in the subgroup with paroxysmal AF.
persistent AF. In contrast, although the direction of association was consistent, the magnitude of association was lower and statistical significance was absent in the subgroup with paroxysmal AF. This may be because of progressive structural and electrophysiological remodeling in patients with more advanced arrhythmia.

In seeming contrast to our results, Krul et al reported that local longitudinal CV was faster in ex vivo perfused LA appendage specimens with thicker collagen bundles. In their study, the local CV was measured as the slope of the steepest upstroke of the action potential at each pixel of optical mapping. When examining conduction in larger regions more comparable with the scale of analysis in our in vivo study, the authors noted activation delay in preparations with a high amount of collagen because of areas of activation block and zigzag conduction. Thus, the primary difference between our results is likely a matter of scale of local CV. The different results may also be related to in vivo versus ex vivo perfused myocardial conditions, LA myocardial versus LA appendage conduction properties, and endocardial versus epicardial CV measurements.

Myocardial Fiber Orientation and Electric Conduction
Myocardial fiber architecture plays a prominent role in electric propagation. Consistent with De et al contact mapping results, we found that the earliest activation site within the LA is the anterosuperior breakthrough, which reflects conduction via Bachmann’s bundle.

In this study, left posterior LA CV was significantly lower than that of other LA areas. Myofibers of the left posterior LA (septopulmonary bundle) descend the posterior wall in a craniocaudal direction, whereas the atrial myocardium continuing into the muscular sleeves on the left pulmonary veins are different. These anatomic factors may contribute to the lower local CV in those regions. Increased extracellular volume (likely because of fibrosis) may also be responsible for the decreased local CV in the left posterior LA because the IIR in that region was higher than that of other LA areas. Importantly, in this study, localization in the left posterior LA, as well as IIR, was associated with CV. We used localization in the left posterior LA (septopulmonary bundle) as a surrogate of fiber orientation because current MRI resolution does not allow direct measurement of fiber orientation. Recently, Poveda et al succeeded in visualization of ventricular myocardial fiber architecture in the canine myocardium using diffusion tensor MRI and tractography reconstruction. Future MRI developments may enable advanced investigation of LA myofiber orientation and refine our results.

Limitations
This is a relatively small study and future studies with larger patient numbers and denser EAM may allow adjustment for other patient level confounders, which were not analyzed in this study. Mapping point density was reduced because of exclusion of points without a clear contact signal and with the evidence of ectopic activation. The routine use of force-sensing catheters will likely improve map density and reduce

Conclusions
Local in vivo CV measurements in the human LA are inversely associated with the IIR, a normalized measure of LGE-MRI intensity. This study provides further validation for the use of LA LGE for mechanistic studies of the substrate for arrhythmia. Additionally, noninvasive identification of regions with LGE may facilitate the localization of slow conduction zones as optimal targets for ablation in patients with reentrant tachyarrhythmias.

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Disclosures
Dr Nazarian is a consultant to Medtronic, CardioSolv, and Biosense-Webster Inc and principal investigator for research funding to Johns Hopkins University from Biosense-Webster Inc. The other authors report no conflicts.

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Association of Left Atrial Local Conduction Velocity With Late Gadolinium Enhancement on Cardiac Magnetic Resonance in Patients With Atrial Fibrillation

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