The association of left atrial low-voltage regions on electroanatomic mapping with low attenuation regions on cardiac computed tomography perfusion imaging in patients with atrial fibrillation

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BACKGROUND Previous studies have shown that contrast-enhanced multidetector computed tomography (CE-MDCT) could identify ventricular fibrosis after myocardial infarction. However, whether CE-MDCT can characterize atrial low-voltage regions remains unknown.

OBJECTIVE The purpose of this study was to examine the association of CE-MDCT image attenuation with left atrial (LA) low bipolar voltage regions in patients undergoing repeat ablation for atrial fibrillation recurrence.

METHODS We enrolled 20 patients undergoing repeat ablation for atrial fibrillation recurrence. All patients underwent preprocedural 3-dimensional CE-MDCT of the LA, followed by voltage mapping (> 100 points) of the LA during the ablation procedure. Epicardial and endocardial contours were manually drawn around LA myocardium on multiplanar CE-MDCT axial images. Segmented 3-dimensional images of the LA myocardium were reconstructed. Electroanatomic map points were retrospectively registered to the corresponding CE-MDCT images.

RESULTS A total of 2028 electroanatomic map points obtained in sinus rhythm from the LA endocardium were registered to the segmented LA wall CE-MDCT images. In a linear mixed model, each unit increase in the local image attenuation ratio was associated with 25.2% increase in log bipolar voltage (P = .046) after adjusting for age, sex, body mass index, and LA volume, as well as clustering of data by patient and LA regions.

CONCLUSION We demonstrate that the image attenuation ratio derived from CE-MDCT is associated with LA bipolar voltage. The potential ability to image fibrosis via CE-MDCT may provide a useful alternative in patients with contraindications to magnetic resonance imaging.

KEYWORDS Atrial fibrillation; Cardiac computed tomography perfusion imaging; Electroanatomic mapping

ABBREVIATIONS 3-D = 3-dimensional; AF = atrial fibrillation; CE-MDCT = contrast-enhanced multidetector computed tomography; CI = confidence interval; CT = computed tomography; EAM = electroanatomic map; IAR = image attenuation ratio; LA = left atrium/atrial; LGE = late gadolinium enhancement; MRI = magnetic resonance imaging; PV = pulmonary vein

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is associated with increased risk of stroke, heart failure, and mortality.1–3 Although success rates for maintenance of sinus rhythm after ablation are reasonable,4 the procedure remains limited by recurrences.5–7 Atrial remodeling and fibrosis have been found to be associated with the recurrence of AF.5 The location and extent of late gadolinium enhancement (LGE) on magnetic resonance...
imaging (MRI) have been demonstrated to benefit patient selection and assessment of ablation efficacy. However, LGE MRI has limited spatial resolution, requires extensive expertise for proper image acquisition and analysis, is not tolerated by some patients owing to claustrophobia, and is contraindicated in patients with metallic implants. Recent studies have shown that contrast-enhanced multidetector computed tomography (CE-MDCT) can visualize ventricular fibrosis after myocardial infarction in experimental animals and patients. In patients with ischemic cardiomyopathy, hyperperfusion segments on CE-MDCT images matched well with abnormal voltage segments. We sought to test the hypothesis that low-voltage left atrial (LA) myocardium also has lower perfusion and consequently lower image attenuation on perfusion CE-MDCT.

Methods
Patient characteristics
The study cohort includes 20 patients who underwent repeat AF ablation at our institution from November 2012 to December 2013 for recurrence after the initial ablation. All 20 patients underwent preprocedural CE-MDCT. The Johns Hopkins Institutional Review Board approved the study protocol, and all subjects provided written informed consent. Follow-up entailed office visits at 3 and 6 months, as well as symptom-prompted electrocardiograms and Holter monitors.

Multislice computed tomography
CE-MDCT scans were performed with a commercially available 320-detector computed tomography (CT) scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) on the same day or <1 week before the repeat AF ablation procedure. Slice collimation ranged from 320 × 0.5 mm, and tube voltage was 80, 100, or 120 kV, depending on the body habitus. Tube amperage ranged from 320 to 580 mA, depending on the body habitus and heart rate. Image acquisition was gated to 40% of the R-R interval during a breath-hold. β-Blockers were used at the discretion of the performing cardiologist to decrease the heart rate below 80 beats/min. The triphase contrast protocol includes a total volume of 60 mL (70 mL if body mass index > 30 kg/m²) of the noniodinated contrast material iopamidol (Isovue 370, Bracco Diagnostics, Princeton, NJ) administered at a rate of 5–6 mL/s in the following sequence: 20 mL saline test injection, 50 mL (100% contrast), 20 mL (50% saline, 50% contrast), and followed by 30 mL saline flush. The images acquired during the first pass were used for later segmentation and analysis.

Electroanatomic mapping
The repeat ablation procedure was performed at 21.6 ± 15.9 months after the initial ablation. All procedures were performed using a 3-dimensional (3-D) electroanatomic mapping system (CARTO 3, Biosense Webster Inc, Diamond Bar, CA). Detailed endocardium voltage maps of the LA were obtained with a 3.5-mm-tip, with 2-mm interelectrode spacing, irrigated ablation catheter (ThermoCool, Biosense Webster) during sinus rhythm. To optimize ablation success, patients with persistent AF were referred for external cardioversion 3–4 weeks before CE-MDCT and AF ablation. Electrograms were filtered at 30–400 Hz (bipolar) and 1–240 Hz (unipolar). Myocardial regions were considered abnormal if the bipolar voltage was <0.5 mV and dense fibrosis if the bipolar voltage was <0.1 mV.

LA wall segmentation and graphical representations
The CE-MDCT–derived images were processed off-line using Seg3D software (version 2.1.4, University of Utah, Salt Lake City, UT). LA epicardial and endocardial borders were manually contoured on multiplanar axial images (Figure 1B). Care was taken in 2-D tracings of the endocardial and epicardial walls to confine the region of interest to only the LA wall and to avoid the blood pool and epicardial fat regions. The local mean LA wall attenuation measured in Hounsfield units (Hu) was obtained by using custom software written in MATLAB (MathWorks Inc, Natick, MA). The analysis software measures the geometric mean attenuation of 5-mm regions of the LA myocardium. For graphical representations (not statistical comparisons), the Otsu Threshold tool was used. The Otsu Threshold tool produces an image intensity histogram to allow the selection of histogram-based threshold levels. The threshold to display colors on the attenuation maps of Figure 2 (lower panels) was manually adjusted to highlight the lowest attenuation regions in red and the highest attenuation regions in purple, similar to the voltage maps (upper panels). The color bar at the right of each lower panel specifies the original CT data attenuation (in Hounsfield units).

Image and electrogram registration
Intra-atrial EAM points were registered to the 3-D CE-MDCT images by using a semiautomated, 3-step process. First, the pulmonary veins (PVs) were identified manually on the EAM and the image, and a similarity transform was applied to the EAM coordinates to minimize mean squared distance between the corresponding landmarks. Second, an iterative refinement to the similarity transform was used to minimize the mean squared distance between the EAM
Finally, a nonrigid transform to further reduce the mean squared distance was determined iteratively and applied to the EAM coordinates (Figure 1C). After registration, the CE-MDCT attenuation of each EAM point was determined by taking the geometric mean of each CE-MDCT image voxel, which was within 5 mm of the registered EAM point coordinates and within the manual segmentation of the LA myocardium.

The image attenuation ratio (IAR), similar to the image intensity ratio used for LGE MRI, defined as the local LA myocardial CE-MDCT attenuation divided by the mean LA blood pool attenuation during the first pass perfusion, was calculated. To account for the regional heterogeneity of CE-MDCT image attenuation in different regions of the LA, we divided the PVs and LA posterior wall into 13 segments: the 4 PVs; the antrum of each PV; and the upper posterior, middle posterior, lower posterior, mitral isthmus, and septal surfaces of the LA wall (Figure 1D).

Statistical analyses

Continuous variables are expressed as mean ± SD and categorical variables as numbers or percentages. Because of the skewed nature of bipolar voltage measures, log transformation was used to make the distribution more symmetrical and accommodate modeling within a linear normal framework. To account for intrapatient clustering of data and patient level differences in data clusters, a linear mixed model, clustered by patient, and adjusted by age, sex, body mass index, and LA volume as level 1 variables and LA regions as the level 2 variable, was used to examine the association of the LA IAR on CE-MDCT with log bipolar atrial electrogram amplitude measures. The intraclass correlation coefficients for inter- and intraobserver variability in measuring the IAR were calculated using 2-way random effects models. To estimate uncertainty associated with the sample size, we used a nonparametric bootstrap study to confirm the significance of the associations. Statistical analyses were performed using STATA software (version 12, StataCorp, College Station, TX).

Results

Patient characteristics

Twenty patients (age 60.8 ± 9.6 years; 10 (50%) men) with preprocedural CE-MDCT images were enrolled in the
study. Before the repeat procedure, 12 patients had recurrent episodes of paroxysmal AF and 8 had recurrent persistent AF. The clinical and procedural characteristics of the 20 patients are summarized in Table 1. An average number of 114.4 ± 23.8 EAM points were sampled per patient during sinus rhythm. All patients tolerated CE-MDCT and repeat PV isolation procedures without complications.

Table 1  Patient characteristics (N = 20)

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Male sex</th>
<th>AF type</th>
<th>Duration of AF (y)</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>Peripheral vascular disease</th>
<th>CHADS2 score</th>
<th>BMI (kg/m²)</th>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>0</td>
<td>20.4</td>
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AF = atrial fibrillation; BMI = body mass index.
Registration of 3-D CE-MDCT images and electroanatomic mapping

A total of 2140 slices in CE-MDCT axial planes from 20 patients were analyzed. A total of 2287 EAM points were registered to the 3-D CE-MDCT images. Of these, 259 points were excluded from the study owing to registration distance >5 mm from the LA myocardium or suboptimal catheter contact evident from the instability in the beat-to-beat electrogram signal. Consequently, 2028 EAM points obtained from the LA endocardium were evaluated and registered to the segmented LA wall on 3-D CE-MDCT images. The CE-MDCT image attenuation corresponding to each EAM point (measured in Hounsfield units) was obtained. After registration, the mean distance of EAM points from the LA myocardium was 0.82 ± 1.56 mm.

Association of the LA IAR with local bipolar electrograms

The average bipolar voltage was 0.65 ± 0.51 mV (0.46 between-patient and 0.67 within-patient SD). The average LA image attenuation was 140.09 ± 45.79 Hu, and the average IAR was 0.34 ± 0.12. In a linear mixed model, accounting for clustering of data by patients and adjusting for age, sex, body mass index and LA volume, the local LA wall CE-MDCT IAR had a positive association with log local bipolar LA voltage (P = .029) after adjusting for age, sex, body mass index, LA volume, as well as clustering of data by patients and adjusting for LA regions (as a level 2 variable).

We further examined this finding by using a nonparametric bootstrap method.23 This analysis is a type of resampling method that is useful in situations with small sample size or when the theoretical distribution of the statistic is complicated. By using this method, we created new samples of 19 patients. We then executed the multivariable analysis including those variables from the multivariable model in Table 2 and repeated the process 1000 times. These new samples were taken from the original data set by using sampling with replacement, so it is not identical to the original sample. This method confirmed the association between the IAR and the log bipolar voltage with a coefficient of 0.252 (95% confidence interval [CI] 0.026–0.478; P = .029) after adjusting for age, sex, body mass index, LA volume, as well as clustering of data by patient and adjustment for LA regions (as a level 2 variable).

Table 2 Linear mixed model results

<table>
<thead>
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<th>Log bipolar</th>
<th>Coefficients</th>
<th>P</th>
<th>95% confidence interval</th>
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<td>IAR</td>
<td>0.252</td>
<td>.046</td>
<td>0.005 to 0.499</td>
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<td>Age</td>
<td>0.004</td>
<td>.725</td>
<td>−0.018 to 0.026</td>
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<td>Sex: male</td>
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<td>.344</td>
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<td>BMI</td>
<td>0.007</td>
<td>.754</td>
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<td>LA volume</td>
<td>−0.001</td>
<td>.934</td>
<td>−0.009 to 0.008</td>
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</table>

Model clustered by patient and adjusted for the effects of left atrial regions as a level 2 variable.

BMI = body mass index; IAR = image attenuation ratio; LA = left atrium.

On qualitative graphical representations, the EAMs overall correlated well with the CT-generated maps. Specifically, about 80% of the maps exhibited good or intermediate qualitative similarity and 20% exhibited qualitative differences. Three sets of CE-MDCT–derived image attenuation maps and the corresponding EAMs from 3 patients in the study are illustrated in Figure 2. Figure 2A is an example of good qualitative agreement between low-voltage (<0.1 mV) regions on EAM and the image attenuation map from CT. Figure 2B is an example of intermediate qualitative agreement between low-voltage regions on EAM and the image attenuation map from CT, whereas the images in Figure 2C exhibit qualitative differences.

Inter- and intraobserver variability

A total of 535 CE-MDCT axial planes from 5 patients underwent repeat review by an independent observer. The intraclass correlation coefficient for the interreader variability in IAR measures was 0.905 for the reliability of observations (95% CI 0.903–0.908). The primary observer also repeated the manual contouring in 5 patients for intraobserver variability analysis. The intraclass correlation coefficient for the intraobserver variability in IAR measures was 0.940 for the reliability of observations (95% CI 0.938–0.943). The intra- and interobserver variability data are presented in Figures 3A and 3B, respectively.

Discussion

Main findings

To our knowledge, this is the first study comparing local LA endocardial bipolar voltage measures with local atrial myocardial image attenuation on CE-MDCT in patients with AF. The main finding of this study is that in patients with AF, after adjusting for confounders, the local LA IAR is independently associated with local atrial bipolar voltage.

LA wall CE-MDCT IAR and bipolar voltage

Studies have shown histological changes in the LA myocardium of patients with AF including inflammatory infiltrates, myocyte hypertrophy, and interstitial fibrosis.24–26 The increased interstitial fibrosis accompanied by reduced microvasculature in the fibrotic atrial myocardium results in decreased myocardial perfusion. Thus, the abnormalities of the fibrotic atrial myocardium may be noninvasively detected by contrast-enhanced CE-MDCT images. Recently, Dewland et al27 compared the LA wall thickness and density measured from contrast-enhanced CE-MDCT between 98 patients with AF and 89 controls. They found that AF was associated with reduced density in the LA anterior wall and increased density below the right inferior PV and in the LA appendage. Their study suggested that CE-MDCT might be used to noninvasively assess LA myocardial abnormalities by measurement of myocardial radiographic image attenuation on perfusion images.

In this study, we performed CE-MDCT in 20 patients before repeat AF ablation procedures. The extent of LA
fibrosis, native or created by the first radiofrequency ablation procedure, was quantified by high-density voltage mapping during the repeat procedure. We found that the local IAR near each EAM point is positively associated with the local bipolar voltage.

LGE MRI has been recognized as a validated imaging technique for the assessment of myocardial fibrosis. LGE MRI offers several advantages including an improved signal to noise ratio for the assessment of myocardial fibrosis without radiation exposure. However, LGE MRI has limitations, including limited spatial resolution, propensity to motion artifacts, and imaging contraindications and/or artifacts in the presence of cardiac implantable devices. In addition, LGE MRI acquisition and analysis requires extensive experience and suffers from poor generalizability to routine clinical practice, owing to poor image quality in patients with arrhythmia, with inability to hold the breath, and with pacemakers and implantable cardioverter-defibrillators. In contrast, cardiac CE-MDCT is fast, widely available, easy to perform, and offers reliable image quality. In addition, CE-MDCT can provide accurate images of the coronary arteries with a quantitative assessment of coronary calcification and epicardial adipose tissue. In contrast, CE-MDCT exposes the patient to radiation in addition to that received from fluoroscopy. In addition, while improving the spatial resolution, CE-MDCT has a lower soft tissue resolution and contrast to noise ratio than does LGE MRI. With advancing technologies and techniques, the radiation exposure for CE-MDCT is continually decreasing and the contrast to noise ratio is improving. As a preprocedural tool, CE-MDCT can provide valuable information about atrial tissue characterization in addition to 3-D anatomical images with greater spatial resolution than those obtained using MRI. Previous studies have demonstrated excellent association between myocardial infarct sizes on cardiac CE-MDCT, LGE MRI, and histopathology in animal models. Theoretically, first-pass CT imaging or MRI performed immediately after contrast material administration will also show relative hypoenhancement of infarcted or fibrotic myocardium caused by reduced microvascular perfusion of the affected tissue. Nieman et al confirmed this hypothesis in 21 patients with acute reperfused myocardial infarction, where early hypoenhancement was differentiated from the normal myocardium by both first-pass CT and MRI. We do not have direct histology evidence that CE-MDCT can identify LA fibrosis; however, this feasibility study shows that the LA IAR is associated with bipolar voltage as a surrogate of fibrosis.

Study limitations
This study had several limitations. First, the study sample size was small, which led to an inability to account for some patient level covariates. The small patient sample size is partially offset by the detailed high-quality CE-MDCT image analysis and accurate image registration with EAM, providing >2000 registered image and electrogram points for quantitative analyses. However, future studies with a larger number of patients with AF undergoing CE-MDCT before ablation may refine these results. Second, although care was taken to be as accurate as possible with segmentation, because of inherently thin walls of the LA it is likely that segmentation may have included pixels with volume averaging of periatrial fat and endoluminal contrast. This volume averaging is unavoidable; however, it is expected to be uniform across the entire atrium and would equally impact the IAR from both fibrotic and nonfibrotic atrial walls. Third, the anterior LA wall and the LA appendage electrograms were not densely sampled, and the association between the CE-MDCT IAR and the local voltage in these regions may differ from that in other LA sites. Our patients had all undergone previous catheter ablation of AF and so likely had a mixture of native and ablation-induced fibrosis. The ability of CE-MDCT to identify only native LA fibrosis needs to be validated in other patient cohorts. Finally, the study did not contain an external validation set; however, we implemented
a resampling simulation study that confirmed the significance of the association.

Conclusion
We demonstrate that the local atrial IAR derived from CE-MDCT significantly associates with local atrial bipolar voltage. Although the signal to noise ratio of images obtained by CE-MDCT does not equal that obtained by LGE MRI, the improved spatial resolution and the ease of image acquisition and analysis impart significant advantages for CE-MDCT as a useful imaging alternative for tissue characterization in patients with AF.

References
CLINICAL PERSPECTIVES

Despite advancements in atrial fibrillation (AF) catheter ablation, reported recurrence rates after ablation remain high, especially in patients with extensive left atrial fibrosis. Late gadolinium enhancement magnetic resonance imaging has been recognized as a validated imaging technique for the assessment of myocardial fibrosis. However, magnetic resonance imaging has limitations, including limited spatial resolution, propensity to motion artifacts, and imaging contraindications and/or artifacts in the presence of cardiac implantable devices. In this study, we demonstrate an association between local left atrial endocardial bipolar voltage measures and atrial myocardial image attenuation ratio on contrast-enhanced multidetector computed tomography in patients with AF. On the basis of these results, contrast-enhanced multidetector computed tomography may provide a useful alternative for risk stratification and/or procedural planning in patients with AF.

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