Voltage during atrial fibrillation is superior to voltage during sinus rhythm in localizing areas of delayed enhancement on magnetic resonance imaging: An assessment of the posterior left atrium in patients with persistent atrial fibrillation

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BACKGROUND Bipolar electrogram voltage during sinus rhythm (VSR) has been used as a surrogate for atrial fibrosis in guiding catheter ablation of persistent atrial fibrillation (AF), but the fixed rate and wavefront characteristics present during sinus rhythm may not accurately reflect underlying functional vulnerabilities responsible for AF maintenance.

OBJECTIVE The purpose of this study was determine whether, given adequate temporal sampling, the spatial distribution of mean AF voltage (VmAF) better correlates with delayed-enhancement magnetic resonance imaging (MRI-DE)–detected atrial fibrosis than VSR.

METHODS AF was mapped (8 seconds) during index ablation for persistent AF (20 patients) using a 20-pole catheter (660 ± 28 points/map). After cardioversion, VSR was mapped (557 ± 326 points/map). Electroanatomic and MRI-DE maps were co-registered in 14 patients.

RESULTS The time course of VmAF was assessed from 1–40 AF cycles (~8 seconds) at 1113 locations. VmAF stabilized with sampling ≥4 seconds (mean voltage error 0.05 mV). Paired point analysis of VmAF from segments acquired 30 seconds apart (3667 sites; 15 patients) showed strong correlation (r = 0.95; P < .001). Delayed enhancement (DE) was assessed across the posterior left atrial (LA) wall, occupying 33% ± 13%. VmAF distributions were (median [IQR]) 0.21 [0.14–0.35] mV in DE vs 0.52 [0.34–0.77] mV in non-DE regions. VSR distributions were 1.34 [0.65–2.48] mV in DE vs 2.37 [1.27–3.97] mV in non-DE. VmAF threshold of 0.35 mV yielded sensitivity of 75% and specificity of 79% in detecting MRI-DE compared with 63% and 67%, respectively, for VSR (1.8-mV threshold).

CONCLUSION The correlation between low-voltage and posterior LA MRI-DE is significantly improved when acquired during AF vs sinus rhythm. With adequate sampling, mean AF voltage is a reproducible marker reflecting the functional response to the underlying persistent AF substrate.

KEYWORDS Atrial fibrillation; Atrial fibrosis; Atrial fibrillation voltage; Magnetic resonance imaging

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Introduction

Atrial fibrosis is known to play an important role in the maintenance of atrial fibrillation (AF). By interfering with electrical continuity, fibrotic tissue is vulnerable to slow conduction, refractory dispersion, and functional reentry, perpetuating AF. The optimal method of identifying de novo atrial fibrosis in persistent AF remains unclear. Delayed-enhancement magnetic resonance imaging (MRI-DE) has been used to visualize fibrotic remodeling but is limited by its current scale of resolution. More recently, low-amplitude bipolar electrograms (EGMs) have been used as an electrical surrogate for fibrosis while mapping during sinus rhythm (SR). However, EGM amplitudes can be influenced by many factors. In addition to recording electrode characteristics (size, spacing, bipole orientation), physiological rate and wavefront dynamics have a direct bearing on the resultant EGM characteristics. Hence, EGM amplitudes associated with fixed, directional conduction during SR can be misleading, presenting a major challenge to discrimination of the fibrotic substrate. In contrast, AF presents as a variable-rate and multidirectional rhythm. Being the clinical rhythm of interest, we hypothesized that AF provides the ideal paradigm for substrate interrogation in order to better resolve the underlying functional vulnerabilities most relevant to AF perpetuation. Given conditions of adequate sampling, EGM voltage measured during AF should be a reproducible marker of the underlying substrate, allowing for a more sensitive and specific measure of MRI-DE detected fibrosis compared to voltage acquired during SR.

Methods

Study population

The study comprised 20 patients presenting for persistent AF ablation (Table 1). Local Ethics Committee approval was obtained.

MRI-DE

All imaging was performed with a 1.5-T Philips Achieva MR system (Philips, the Netherlands) and a 5- or 32-element phased-array cardiac coil using a technique we previously reported (see Supplemental Material for details). The workflow is summarized in Figure 1.

Electrophysiological study

All procedures were performed after written informed consent was obtained from the patients. After transseptal puncture, electroanatomic maps (EnSite Velocity, Abbott, MN) were collected, with bipolar EGMs filtered at 30–500 Hz (without 50-Hz notch filter). With operators blinded to

Table 1  Patient clinical demographics, MRI, and mapping parameters of patients recruited into the study

| Patient characteristics (n = 20) |
|----------------------------------|
| Age (y)                          | 62 ± 11 |
| Male                             | 11 (55) |
| Mean LA size on TTE (mm)         | 41 ± 6  |
| Mean CHA2DS2VASc score           | 2.4 (0–6) |
| Hypertension                     | 8 (40)  |
| Diabetes mellitus                | 4 (20)  |
| Cerebrovascular disease          | 2 (10)  |
| History of heart failure         | 4 (20)  |
| Duration of persistent AF (mo)   | 21.3 ± 10 |

| MRI and electrophysiological parameters (n = 14)* |
|---------------------------------------------------|
| MRI surface area                                   |
| Left atrium (cm²) (%)                              | 37.6 ± 9.4 (27.0 ± 9.8) |
| Posterior LA (cm²) (%)                            | 20.1 ± 9.3 (33.4 ± 13.2) |
| Rhythm (n)                                        |
| AF† (14)                                          | Sinus rhythm (13) |
| Map points (density)                               |
| Left atrium (pts/cm²)                             | 660 ± 283 (4.6 ± 1.9) |
| Posterior LA (pts/cm²)                            | 306 ± 109 (5.0 ± 1.3) |
| Voltage (mV)                                      |
| Global                                            | 0.35 [0.19–0.61] |
| DE†                                               | 0.21 [0.14–0.35] |
| Non-DE                                           | 0.52 [0.34–0.77] |
| Cycle length (ms) (rate [bpm])†                   | 161 ± 21 (379 ± 44) |

*Includes subset of patients analyzed for MRI-DE vs voltage correlation.
†As determined by MRI-DE ≥2 SD above mean blood pool intensity.
‡Eight-second acquisition, resulting in $V_{mAF-8}$.
MRI-DE results, data acquisition was performed according to study protocol before radiofrequency ablation.

**Study protocol**

All patients presented in AF on the day of the procedure. Left atrial (LA) geometry and subsequent data were acquired using a double-loop catheter (AFocusII™, Abbott) with 20-ring electrodes (1-mm length, 4-mm spacing). For comparative assessment of AF vs SR voltage in the LA, baseline AF maps were collected in 14 patients via 8-second complex fractionated EGM mapping (EnSite™ Velocity™, Abbott). In a subset of 13 of 14 patients, SR was additionally maintained after external DC cardioversion, and SR voltage maps were created. Before each acquisition, the AFocusII catheter was held tangentially to the endocardial surface, enabling stable tissue contact. EGMs >5 mm from the geometry surface were automatically excluded. For subsequent quantitative analysis, all points within the pulmonary veins and LA appendage were excluded (Table 1).

**Criteria for mean AF voltage**

The criteria used for determination of mean AF voltage ($V_{mAF}$) was based on detection of the maximum peak-to-peak (P-P) voltage per atrial fibrillation cycle length (AFCL), followed by statistical averaging of all AF peaks detected across the sampling interval. P-P detection criteria for any candidate deflection required a voltage threshold $>0.04$ mV, slew rate $<10$ ms, and used a 100-ms refractory window (Figures 2A and 2B). In subsequent phases of AF voltage analyses, an index sampling interval of 8 seconds was used as the nominal sampling interval ($V_{mAF-8}$) (for details see Supplemental Material).

To facilitate $V_{mAF}$ analysis, 2 independent software modules were used: (1) HEART (High-density Electrogram Analysis Research Tool) in-house software allowed for signal analysis into the temporal variability of AF (Figure 2C); and (2) EnSite Velocity Research Module (V1.1), Abbott, MN, served as an interactive 3-dimensional platform for assessment of the spatial distribution of $V_{mAF}$, $V_{SR}$, and subsequent correlation with MRI-DE (Figures 2D and 3). Although the implementation details for the $V_{mAF}$ metric varied slightly on each platform, the general methodologies used for peak detection and $V_{mAF}$ were consistent.

**Assessing temporal variability of mean AF voltage**

In 20 patients, 160 epochs of AF were recorded from the LA surface (360 ± 35 EGMs per patient; 100 ± 15 cm²/patient) over a 40-second duration, in order to assess the temporal
variability of VmAF and determine sampling adequacy. All AF segments were exported into HEART for analysis. The dominant deflection within each AFCL was detected according to the criteria described earlier, and VmAF was statistically calculated over sampling intervals ranging from 0.5–8 seconds at 1113 locations (Figure 3A). The coefficient of variation of AF voltage, a measure based on the SD/mean of individual AF voltage peaks (1 peak per AFCL), was derived. Intraclass correlation coefficients (ICCs) of sampled VmAF vs index VmAF-8 were assessed. In order to determine the minimum sampling duration sufficient to yield a statistically meaningful VmAF result, the time course of VmAF was generated for each EGM. Global mean voltage error (VME) was computed as the difference between sampled VmAF vs index VmAF-8. The sampling duration was determined such that VME was reduced to 0.05 mV, equivalent to the recording system noise level. The impact of sampling error on the spatial distribution of VmAF was assessed (Figure 3A).

Evaluating spatial reproducibility of mean AF voltage over time

In 15 of 20 patients, 3450 AF EGMs (244 ± 101 EGMs per patient) were acquired over a 40-second duration, enabling analysis into the spatial reproducibility of AF voltage via the EnSite Velocity research module. Time-shifted VmAF-8 maps were subsequently created by initiating 2 separate acquisitions per fixed catheter location separated by 30 seconds. The resulting “paired-point” VmAF-8 maps allowed for correlative assessment of spatial reproducibility of VmAF-8 across temporal epochs of AF (Figure 3B). In a subset of 2 of 15 cases, VmAF-8 maps were acquired sequentially, separated by a longer 20-minute waiting period. Although not a systematic study, these examples were assessed for visual evidence of spatial reproducibility of mean AF voltage.

Correlating MRI-DE with mean AF and SR voltage

In 14 of 20 patients, spatial correlative analyses were performed for comparing distributions of low voltage during AF (VmAF-8) and SR (VSR) with regions of MRI-DE. Electroanatomic maps were coregistered with MRI-DE models using the EnSite Fusion tool in a blinded fashion, such that voltage and MRI-DE data were not projected onto the respective surfaces. LA subregions occupied by normalized intensities ≥2 SD above mean blood pool intensity (Mbp) were assigned as delayed enhancement (DE), whereas regions with intensities <2 SD Mbp were categorized as normal (non-DE), consistent with previously described image intensity thresholds. Any points determined to be on

Figure 2 Criteria for determination of mean AF voltage (VmAF). A: Inclusion/exclusion criteria for AF peak-to-peak detection per AF cycle length. B: AF electrogram (1 second) illustrating implementation of P-P detection criteria in the Velocity research module. C: AF electrogram (8 seconds) from the HEART software module. D: AF electrogram (8 seconds) from the Velocity research module. AF voltage statistics are computed based on the distribution of all peak-to-peak voltage detections (right).
the border between binarized regions were included in both subgroups (Figure 3C).

Distributions for both VmAF-8 (4279 EGM sites) and VSR (3694 EGM sites) were sampled from both DE and non-DE regions of the LA posterior wall (Table 1). Comparative voltage distribution curves were generated for both VmAF and VSR in DE vs non-DE regions (Figure 3C, bottom). Receiver operating characteristic (ROC) curves were derived to assess sensitivity/speciﬁcity of VmAF and VSR for detection of MRI-DE, allowing for determination of optimal voltage cutoffs.

Statistical analysis
All normal variables are expressed as mean ± SD. The Shapiro-Wilk test was used to determine the normality of the distributions of voltages. Nonparametric distributions of VmAF-8 and VSR are given as median (interquartile range [IQR]). Paired and unpaired t tests were used when appropriate, with Bonferroni correction for multiple tests. Correlation of continuous variables was examined with Pearson and Spearman correlation coefficients for parametric and nonparametric data respectively. ROC curves were compared using the DeLong test. P <.05 was considered significant.

Results
Patient characteristics are listed in Table 1.

Sampling adequacy of mean AF voltage
The global coefﬁcient of variation of P-P AF voltage was 45% for 2 sampled AFCLs. Sampling 10, 20, and 40 AFCLs reduced coefﬁcient of variation to 18%, 12%, and 9%, respectively.

In representative data from a single patient, individual VmAF traces are plotted as a function of time, indicating that beyond 4 seconds, VmAF has stabilized (Figures 4A and 4B). Global results (3450 EGMs) quantifying the trend of VmAF stabilization are presented graphically, showing that as the sampling window reaches 4 seconds, VME approaches 0.05 mV (Figure 4C). Sampling beyond 4 seconds yields diminishing returns, with VME lowered ∼0.01 mV for each additional 1 second of sampling (Figure 4C, inset).
Global ICCs of sampled $V_{mAF}$ vs index $V_{mAF,8}$ show improving correlation with increased sampling. Increasing the sampling window in 1-second increments (1–7 seconds) yields respective ICC values of 0.88, 0.94, 0.96, 0.98, 0.99, and 1.00 (Figure 4D).

The spatial impact of sampling duration on $V_{mAF}$ is shown in Figure 3A. In this representative case, the spatial distribution of $V_{mAF}$ was rendered at sampling intervals ranging from 1 AFCL–8 seconds. Beyond a sampling interval of 4 seconds, the $V_{mAF}$ maps were visually similar, matching the MRI-DE distribution.

**Spatial reproducibility of mean AF voltage across epochs**

Time-shifted (30 seconds) $V_{mAF,8}$ maps revealed visually similar spatial distributions. Global analyses of all point-pairs (3450 EGM locations; $n = 15$) resulted in a high degree of correlation between the 2 distinct temporal epochs of AF (Pearson correlation coefficient $r = 0.95; r^2 = 0.89; P < .001$) (Figure 5A). Additionally, 2 sequentially acquired $V_{mAF,8}$ maps, separated by a 20-minute waiting period, illustrate visual similarity in $V_{mAF}$ distribution (Figure 5B).

**MRI-DE correlation with mean AF vs SR voltage**

Global median voltage was 0.35 [0.19–0.61] mV during AF vs 1.81 [0.90–3.31] mV during SR, resulting in $V_{mAF}/V_{SR}$ ratio of 1.518 (19.3%) (Table 1).

During AF, voltage distributions in DE vs non-DE regions were 0.21 [0.14–0.35] mV vs 0.52 [0.34–0.77] mV, respectively ($P < .0001$), showing minimal overlap in the intraquartile range (0.34–0.35 mV) (Figure 6A). During SR, voltage distributions in DE vs non-DE regions were 1.34 [0.65–2.48] mV vs 2.37 [1.27–3.97] mV, respectively ($P < .0001$), showing a high degree of intraquartile overlap (1.3–2.5 mV) (Figure 6B).

Intrapatient variability of median AF voltage ($n = 14$) ranged from 0.14–0.37 mV in DE vs 0.24–1.16 mV in
non-DE. Median AF voltage <0.24 mV was specific to the DE subgroup, whereas >0.37 mV was specific to the non-DE subgroup (Figure 6C). During SR (n = 13), voltage ranges were 0.64–2.69 mV in DE vs 0.93–4.07 mV in non-DE. Median SR voltage <0.93 mV was specific to DE, whereas ≥2.69 mV was specific to non-DE (Figure 6D).

**Threshold discrimination of AF vs SR to match MRI-DE**

ROC results for threshold discrimination of AF and SR voltage to match MRI-DE are shown in Figure 6E.

$V_{\text{mAF}}$ detected for the presence of MRI-DE with sensitivity of 75% and specificity of 79% at voltage cutoff of 0.35 mV and area under the curve (AUC) of 0.82. A cutoff range of 0.3–0.4 mV preserved balanced sensitivity/specificity tradeoffs of 68%/84% at 0.3 mV and 78%/73% at 0.4 mV. $V_{\text{SR}}$ detected for the presence of MRI-DE with sensitivity of 63% and specificity of 67% at voltage cutoff of 1.8 mV and AUC of 0.70. Legacy $V_{\text{SR}}$ thresholds 0.5–1 mV resulted in high specificity (97% at 0.5 mV, 86% at 1 mV) but low sensitivity (18% at 0.5 mV, 39% at 1 mV) for detection of MRI-DE. AUCs were highly statistically significant ($P < .0001$).

The clinical impact of these results is shown in 4 case examples in which AF voltage (0.35-mV cutoff) can be visually appreciated as a better match to regions of MRI-DE than SR voltage (1.0-mV cutoff) (Figure 7).

**Discussion**

**Main findings**

Under conditions of adequate sampling (≥4 seconds), mean AF voltage is a stable, reproducible metric, yielding high sensitivity and specificity to MRI-DE as assessed from the posterior LA of our persistent AF cohort. SR voltage correlates poorly to MRI-DE, with legacy thresholds (0.5–1 mV) yielding good specificity but unacceptably low sensitivity to the de novo substrate as detected by MRI-DE.

**Implications for legacy SR voltage thresholds as a marker for fibrosis**

Previous studies have suggested that SR voltages <0.5–1.0 mV represent varying degrees of “diseased” regions and correlate with MRI-DE.$^{5,6}$ We showed that $V_{\text{SR}}$ threshold <1.0 mV failed to demonstrate meaningful sensitivity to regions enhanced by MRI-DE. By applying a 95% normal threshold criteria, Kapa et al$^{11}$ prescribed a conservative 0.2- to 0.45-mV $V_{\text{SR}}$ threshold range for the detection of atrial scar. Applying Kapa’s thresholds to our own ROC results, $V_{\text{SR}}$ was found to be highly specific (>97%) but insensitive (5%–15%) to the extent of de novo fibrosis as detected by MRI-DE. Any attempt to increase sensitivity by raising thresholds (eg, 2.0 mV: 67%; 2.5 mV: 75%) resulted in an unacceptable decrease in specificity (2.0 mV: 62%; 2.5 mV: 51%), increasing...
the likelihood of false-positive detection of normal tissue. We theorize that the difference between the Kapa VSR cut-offs and our own may lie in the fact that their cohort included patients with ablation-induced scar and was not exclusive to the de novo substrate.

**AF voltage for identification of the arrhythmogenic substrate**

Bipolar voltage has long been accepted for detection of scar in the context of ventricular tachycardia. Bipolar voltage has long been accepted for detection of scar in the context of ventricular tachycardia. More recently, low-voltage zones during SR and AF have been targeted.
Figure 7  Case examples of atrial fibrillation (AF) and sinus rhythm (SR) voltage vs delayed-enhancement magnetic resonance imaging (MRI-DE). A: Case examples of AF (V_{AF,a}) and SR voltage with varying degrees of MRI-DE–detected fibrosis. In all cases, the AF voltage map (left) (cutoff range 0.05–0.35 mV) provides a visual spatial match with MRI-DE (>2 SD Mpp). SR voltage maps set to the legacy cutoff range (0.1–1.0 mV; right) lack the sensitivity to detect MRI-DE. As the V_{SR} threshold is increased to the study-derived threshold (1.8 mV; middle), sensitivity for MRI-DE detection is improved, whereas specificity is reduced. Representative electrograms are displayed from both DE/non-DE regions of each map. B: Case example with simultaneous electrograms sampled across the DE/non-DE border during both AF (left) and SR (right). During AF, the transition from non-DE to DE can be seen in both the differential amplitude of electrograms and in the V_{AF,a} map (cutoff range 0.05–0.35 mV). In contrast, electrograms during SR reveal no obvious differential. The V_{SR} map (cutoff range 0.1–1.0 mV) has no low-voltage zones.
in patients with persistent AF, resulting in improved clinical outcomes.

During AF, slow conduction in diseased myocardium may be necessary for sustaining rotational activity, whether localized or macroreentrant. Regions of rotational activity have been shown to colocalize with low-voltage regions (<0.1 mV) during AF in some studies but not in others.15,16

MRI-defined burden of atrial fibrosis correlates with clinical indices of remodeling and outcomes of catheter ablation.17 Sites exhibiting high rotational activity have shown clustering around borders of fibrotic areas in noninvasive mapping.18 The DECAAF (Delayed-Enhancement MRI of Atrial Fibrillation) Investigators17 de

Pathophysiological basis of voltage during AF
The relationship between AF and the underlying setting of fibrosis is unclear. Pathophysiologically, fibrosis can present in a spectrum of textures, resulting in distinct arrhythmogenic profiles. Compact fibrosis comprises dense regions of collagen that are readily resolved by MRI, electrophysiologically resulting in low voltage associated with fixed conduction block. Noncompact fibrosis (interstitial/reparative) encompasses more diffuse textures at or below the margins of current MRI resolution and is associated with functional arrhythmogenic vulnerability. Interstitial fibrosis involves collagenous separation of muscle bundles, resulting in slow conduction and functional reentry, whereas reparative fibrosis involves diffuse cardiomyocyte replacement, rendering tissue susceptible to anisotropy and refractory dispersion.1,20,21

During SR, the underlying AF substrate is in an electrophysiologically passive state, featuring low rates and coordinated activation wavefronts. Under these conditions, low voltage is known to result as the propagating wavefront encounters conduction barriers associated with compact fibrosis. In this passive state, noncompact fibrotic regions susceptible to arrhythmogenic activity may lie dormant.

The effects of arrhythmia function on voltage are less well understood. In a series comparing voltage amplitudes during SR vs atrial flutter, Bradfield et al observed the discordance of voltage associated with functional effects of the underlying rhythm. In their series, rhythm-based voltage differences were attributed to rate/wavefront direction, resulting in variability of functional block. In a controlled pacing study, Iso et al further elaborated on the functional influences on LA voltage, finding site-specific EGM amplitudes to be both rate and direction dependent.

During AF, activation rates are more rapid than those associated with any organized rhythm. Ndrepepa et al reported on the association between regional AFCL and AF voltage, observing the greatest AF voltage reductions occur in regions of “faster and more disorganized activity.” Accordingly, we theorize that the higher intrinsic rates present during AF may be associated with underlying noncompact fibrotic regions vulnerable to slow conduction and functional reentry, resulting in the manifestation of low voltage.

Furthermore, during AF, regional wavefront multiplicities may arise in the wake of conduction disturbances resulting from tissue anisotropies and refractory dispersion in areas of noncompact fibrosis. Importantly, such wavefront scatter is less likely to present during SR, which could further explain SR’s poor voltage sensitivity to noncompact fibrosis. In a supporting finding, Masuda et al demonstrated that although colocalized AF and SR EGM voltage amplitudes were well correlated in locations with normal EGM morphologies, the correlation disappeared at locations where normal EGMs during SR became fractionated during AF.

In this series, we reported that AF voltage yielded significantly higher sensitivity and specificity to MRI-detected fibrosis than SR voltage. We theorize that although either rhythm condition may elicit a low-voltage response to compact fibrosis, the difference may lie in the voltage response to the noncompact spectrum of fibrosis. We propose that arrhythmogenic vulnerabilities (eg, conduction slowing, functional reentry, anisotropy, refractory dispersion) associated with the noncompact spectrum of fibrosis, although dormant during SR, become manifest during the functional circumstances encompassing AF. As susceptible regions are "activated," low voltage is an expression of the underlying electro-architectural substrate that can only be elucidated under conditions of electrophysiological stress. AF, being the clinical rhythm of interest, conveniently provides the ideal setting to explore this paradigm.

Study limitations
MRI-DE for detection of atrial fibrosis has faced criticism for its lack of resolution, susceptibility to artifact, and lack of standardization. It is important to note that current MRI resolution may not allow for the detection of more diffuse fibrotic change and also precludes the study of nontransmural (endo–epicardial) fibrosis. Although our imaging results have been validated for ablation-induced scar and reflect relative spatial distributions of LA MRI-DE, we acknowledge that reproducing absolute image intensity results across centers depends on increased standardization of MRI-DE postprocessing methodologies.

Absolute voltage thresholds are dependent on the bipole configuration of the mapping catheter used in addition to other factors such as bipole orientation/wavefront direction and filtering. We elected to use the AFocus™ catheter (1-mm electrodes, 4-mm spacing), which allowed for high sampling density and stable tissue contact. We believe the significance of our results lies less in the prescription of absolute voltage thresholds and more in the relative nature of the relationships established between AF/SR voltage and MRI-detected fibrosis.
We acknowledge that some of the discrepancy between SR voltage and MRI-DE may potentially result from the delay in electrical recovery after acute cardioversion of long-standing persistent AF.27

Several groups have reported on the intrinsic variability of atrial voltage amplitudes with anatomic location.11 In order to obtain highest fidelity EGMs, our electroanatomic data were limited to the posterior LA, which was (1) anatomically consistent, (2) conducive to placement of the mapping catheter tangent to the endocardial surface, and (3) contained a predilection of fibrosis. This choice allowed us to best meet the objective of assessing the relationship between voltage and fibrosis. However, we accept the limitation that the LA posterior wall does not comprise the global persistent AF substrate and that other regions of the left and right atria should be considered in future studies.

**Conclusion**

Mean AF voltage, when sampled for ≥4 seconds, is a statistically robust and reproducible metric as assessed in the de novo persistent AF substrate. Within the posterior LA, AF voltage, to a greater extent than SR voltage, is both sensitive and specific for detection of MRI-DE. Although legacy SR voltage thresholds (0.5–1 mV) exhibit poor sensitivity to MRI-DE, we theorize that AF voltage is sensitive to the substrate that can only be elucidated under conditions of functional electrophysiological stress. Assessment of mean AF voltage can potentially be implemented widely, which would enable broader investigation into its utility as a surrogate for fibrosis, potentially obviating the need for MRI-DE, in characterizing the structural arrhythmic substrate.

**Appendix**

**Supplementary data**

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2019.05.032.

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