Clinical Research

The Extent of Left Atrial Low-Voltage Areas Included in Pulmonary Vein Isolation Is Associated With Freedom from Recurrent Atrial Arrhythmia

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ABSTRACT

Background: The extent of left atrial (LA) baseline low-voltage areas (LVA-B), which may be a surrogate for fibrosis, is associated with recurrent atrial fibrillation (AF) after ablation. This study aimed to assess the relationship between the extent of LVA-B isolated by ablation (LVA-I) and AF recurrence.

Methods: The study cohort included 159 consecutive patients with drug-refractory AF who underwent an initial AF ablation with LA voltage mapping during sinus rhythm. The extent of LVA-B was quantified while excluding the pulmonary veins, LA appendage, and mitral valve area. LVA-I was quantified as the percentage of LVA-B encircled by pulmonary vein isolation. Surveillance and symptom-prompted electrocardiograms, Holter monitors, and event monitors were used to document atrial arrhythmia recurrence for a median follow-up of 712 days (1.95 years).

Pulmonary vein isolation (PVI) is the cornerstone of atrial fibrillation (AF) ablation. However, long-term AF suppression after PVI for persistent AF remains unsatisfactory. The baseline extent of low-voltage areas (LVA-B) on point by point intracardiac bipolar voltage mapping, as a surrogate of atrial scarring, appears to be associated with atrial arrhythmia recurrence. The extent of left atrial (LA) scar examined by other modalities also is associated with atrial arrhythmia recurrence after ablation. The Substrate and Trigger Ablation for Reduction of AF II (STAR AF II) trial and the corresponding meta-analysis showed no added benefit of empirical linear and complex fractionated atrial electrogram ablations over PVI alone in patients with persistent AF. Consequently, any ablation strategies in addition to PVI must be scrutinized to prove benefit that outweighs increased complication rates and unnecessarily prolonged procedures and fluoroscopy exposure to the patient and staff. A previous study showed that LVA-B ablation as an adjunct to PVI improved procedural outcomes in patients with persistent AF and LVA. Whether LVA isolation as part of the PVI strategy leads to lower complication rates while achieving increased success in treating AF.

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Results: Of 159 patients, 72% were men and 27% had persistent AF. The mean number of sampled bipolar voltage points was 119 ± 56. The mean LA surface area was 102.3 ± 37.3 cm², and the mean LVA-B was 1.9 ± 3.8 cm². The mean LVA-I was 51.05% ± 36.8% of LVA-B. In the multivariable Cox proportional hazards model adjusted for LA volume, CHA2DS2-VASc (Congestive Heart Failure, Hypertension, Age [≥ 75 years], Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age [65-74 years], Sex [Female] score), LVA-B, and AF type, LVA-I was inversely associated with recurrent atrial arrhythmia after the blanking period (hazard ratio, 0.42/percent LVA isolated; P = 0.037).

Conclusions: The extent of LVA-I is independently associated with freedom from atrial arrhythmias after AF ablation, supporting ongoing efforts to target low LA voltage areas and other fibrosis indicators to improve ablation outcomes.

remains to be examined. Additionally, the exact anatomic placement of PVI with respect to venous ostia and LVA-B is subjective and varies according to individual physician strategies and patient anatomy. In this study, we sought to evaluate the association between the percentage of LVA-B isolated by PVI (LVA-I) and freedom from AF.

Methods

Patient population

We retrospectively studied patients with symptomatic drug-refractory AF who underwent an initial PVI at Johns Hopkins Hospital between 2011 and 2015. Study cohort inclusion criteria included consistent follow-up for > 1 year, a minimum of 100 voltage mapping points obtained during sinus rhythm, and a lack of previous ablation procedures or cardiac surgery. Of 2162 patients identified in the source cohort, 159 met the inclusion criteria and composed the study cohort. The Johns Hopkins Institutional Review Board approved the study protocol, and all participants provided written informed consent. Persistent and paroxysmal AF were defined according to the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society and 2016 Focused Update of the Canadian Cardiovascular Society guidelines for the management of patients with AF. LA volume was quantified from 64-slice computed tomography or 1.5 T magnetic resonance imaging using ITK-SNAP software, version 3.4 (www.itksnap.org).  

Ablation procedure

The ablation procedure was performed using general anesthesia in all cases. Patients with AF at the beginning of the procedure underwent external cardioversion before catheter mapping and ablation, allowing for a waiting period of ≥ 5 minutes to ensure a stable rhythm before voltage mapping. After heparin infusion, confirmation of activated clotting time > 350 seconds, and attainment of double atrial transseptal puncture, a detailed bipolar voltage map was acquired during sinus rhythm. Our mapping process focused on obtaining the greatest sampling density surrounding the pulmonary veins to optimize the accuracy of electroanatomic map registration with LA image segmentations. Thus, sampling density was highest in the venous ostial regions under study. Bipolar electrograms were filtered at 30-500 Hz. Mapping points were acquired using an electrode catheter with a 3.5-mm tip, a 1-mm ring electrode, and a 1-mm interelectrode distance (THERMOCOOL; Biosense Webster, Diamond Bar, CA). Adequate endocardial contact was established by the stability of electrogram signals for at least 2 beats and < 2 mm distance to a registered geometry surface.

All patients underwent radiofrequency ablation–based PVI. The ablation catheter was used to collect geometry and voltage data from the entire left atrium. An interpolation threshold of 10 mm was used for surface color projection. Ablation was performed with the 3.5-mm, irrigated-tip catheter (THERMOCOOL). Standard ablation settings consisted of a radiofrequency power of 25 W (posterior left atrium) to 30 W (anterior left atrium). No linear lesions or additional substrate or trigger-based ablation was performed in this cohort. A circular multipolar electrode-mapping catheter (LASSO, Biosense Webster) was used to confirm PVI by the presence of entrance block.

Clinical follow-up

After the procedure, patients were observed for 24 hours. In the absence of atrial arrhythmia recurrence, antiarrhythmic medications were discontinued after 3 months. Close communication through routine clinic visits and symptom-prompted telephone calls or in-person visits, or both, was
maintained with all patients after the ablation procedure. If symptoms suggestive of an arrhythmia occurred, patients were asked to undergo 24-hour Holter monitoring or 30-day event monitoring depending on symptom frequency. In the absence of reported symptoms, patients were evaluated for recurrence at 6 and 12 months with 24-hour Holter monitoring and at 3 and 9 months with 12-lead electrocardiography. Recurrences were defined as electrocardiographic or Holter-documented AF, atrial flutter, or atrial tachycardia > 30 seconds occurring beyond a 3-month blanking period after the procedure. Freedom from AF was defined as lack of recurrence while receiving antiarrhythmic drug therapy after a single procedure.

LVA measurements

All mapping points were manually reviewed. Electrogram quality was assessed by consensus of 2 experienced observers. Points that displayed poor contact or an unstable electrogram signal were excluded. In accordance with previous studies, peak to peak amplitude of the electrogram was categorized as signal were excluded. In accordance with previous studies, quality was assessed by consensus of 2 experienced observers.

LVA-B and LVA-I measurements

The extent of LVA-I was inversely associated with atrial arrhythmia after the blanking period (hazard ratio [HR], 0.31 mV; 95% CI, 0.17-0.57; P = 0.001). Patients with persistent AF were more likely to be men (83.7% vs 67.2%; P = 0.040) and to have a higher incidence of hypertension (72.1% vs 43.1%; P = 0.002) and CHF (34.9% vs 5.2%, P < 0.001). Patients with persistent AF had lower LVEFs (49.3% ± 10.8% vs 55.8% ± 8.4%; P = 0.008) and higher LA volumes (121.7 ± 40.6 cm³ vs 98.2 ± 38.6 cm³; P < 0.001).

LVA measurements

Of all patients, 41 had no LVA-B: 33 (80.5%) of these patients had paroxysmal AF and 8 (19.5%) had persistent AF. The mean LVA-B of the 118 patients with LVA was 1.9 ± 3.8 cm², and the mean percentage of LVA-I was 51.0% ± 36.8% of those with LVA-B. Among those with LVA-B, there was no significant difference in the LVA-B (2.2 ± 3.2 cm² vs 1.7 ± 3.8 cm²; P = 0.456) or the LVA-I (44.5% ± 32.0% vs 54.1% ± 38.1%; P = 0.143) of patients with persistent vs paroxysmal AF.

Procedural outcomes

Of 159 patients, 83 (52.2%) had an atrial arrhythmia recurrence during a median follow-up of 712 days (IQR, 346-1207 days), and 46 (28.9%) underwent redo procedures. Procedural complications included 1 (0.63%) right radial artery pseudoaneurysm, 1 (0.63%) transient phrenic nerve injury, and 1 (0.63%) urethral bleed. Follow-up information is displayed in Table 2. There was no significant difference between patients with and those without atrial arrhythmia recurrence regarding sex, race, AF type, AF duration, hypertension, BMI, CHF, LVEF, or CHA2DS2-VASc. Patients with atrial arrhythmia recurrence were, however, more likely to have a larger LA volume and LVA-B. Additionally, the extent of LVA-I was inversely associated with atrial arrhythmia recurrence.

Association of the extent of LVA included in PVI with freedom from atrial arrhythmia

In the multivariable Cox proportional hazard model adjusted for LA volume, CHA2DS2-VASc, LVA-B, and AF type, only LVA-I was associated with recurrent atrial arrhythmia after the blanking period (hazard ratio [HR], 0.42% of LVA-I; P = 0.057) (Table 3). As shown in Figure 2, the multivariable adjusted HR plot revealed no significant evidence for nonlinear effects. The HR for atrial arrhythmia recurrence decreased with increasing extent of LVA-I, with the upper 95% confidence interval decreasing to less than the unity line at > 45% scar isolation. There was no evidence of multiplicative interaction between LVA-I and AF type, LA volume, or LVA-B in the multivariable Cox proportional hazards model of the association between LVA-I and atrial arrhythmia recurrence (P = 0.944, P = 0.147, and P = 0.848, respectively).

Results

Patient characteristics

The median follow-up was 712 days (interquartile range [IQR], 346-1207 days). The mean number of voltage mapping sites was 119 ± 56 points. Detailed baseline characteristics are summarized in Table 1. Of 159 patients, 114 (72%) were men and 43 (27%) had persistent AF. The mean age and body mass index (BMI) were 60.2 ± 9.2 years and 29.0 ± 5.7 kg/m², respectively. The mean LA volume was 105.0 ± 40.6 cm³, and the mean left ventricular ejection fraction (LVEF) was 54.1% ± 9.5%. Of all patients, 81 (50.9%) had hypertension, 21 (12.8%) had congestive heart failure (CHF), and 79 (49.1%) had a CHA2DS2-VASc ≥ 2. Patients with persistent AF were more likely to be men (83.7% vs 67.2%; P = 0.040) and to have a higher incidence of hypertension (72.1% vs 43.1%; P = 0.002) and CHF (34.9% vs 5.2%, P < 0.001). Patients with persistent AF had lower LVEFs (49.3% ± 10.8% vs 55.8% ± 8.4%; P = 0.008) and higher LA volumes (121.7 ± 40.6 cm³ vs 98.2 ± 38.6 cm³; P < 0.001).
Major findings
The main finding of the present study is that regardless of AF type, LA volume, CHA2DS2-VASc, and LVA-B, the percentage LVA-I as part of PVI is inversely associated with atrial arrhythmia recurrence after an initial ablation. Interestingly, the extent of LVA-B in patients with paroxysmal AF was not statistically different from that in those with persistent AF, thus generalizing the findings to the entire AF ablation population. Our findings differ from previous studies that showed LVA-B extent to be significantly greater in patients with persistent AF.6-8 One explanation could be the definition of LVA-B as < 0.3 mV in contrast to the < 0.5 mV threshold used in other studies.12,13

Association of extent of LVA included in PVI with freedom from AF
The histologic correlation of LVA-B with atrial fibrosis, as well as its detrimental association with AF ablation outcomes, is well established.6-8 In fact, the extent of LVA-B appears to be a strong predictor of atrial arrhythmia recurrence after PVI even after adjustment for known risk factors, such as advanced age, persistent AF, low ejection fraction, or large LA size.8

In the present study, we found that the CHA2DS2-VASc, LVA-B, and percentage of LVA-I were associated with atrial arrhythmia recurrence on univariable analyses. On multivariable analysis, only the extent of LVA-I was associated with freedom from AF after an initial ablation. Thus, the extent of LVA-I was more closely associated with outcome than the mere extent of LVA-B. Yamaguchi et al.13 previously showed that additional LVA-based substrate modification after PVI improved ablation outcomes in patients with persistent AF, supporting our previously mentioned findings. Jadidi et al.21 suggested that ablation of sites within/at border zones of LVA-B in addition to PVI is more effective than a conventional PVI-only strategy for persistent AF. Importantly, in a recent study by Schreiber et al.,22 box isolation of fibrotic areas in patients with mild to moderate LA size resulted in success rates comparable to those in patients without atrial cardiomyopathy.23

Although atrial structural remodelling involving atrial scar is a well-recognized factor in AF pathogenesis,12 patient selection for additional atrial substrate modification is usually based on AF persistence rather than the underlying substrate.
Additionally, currently used extended AF therapies increase procedure duration, fluoroscopy exposure, proarrhythmia, and time/ablation-dependent complications, without proven efficacy. LA scar can be detected noninvasively and confirmed, when necessary, by endocardial voltage mapping.\(^2\)\(^,\)\(^3\)\(^,\)\(^23\) LVA-B has previously been shown to be a powerful predictor of arrhythmia recurrence after AF ablation.\(^5\)\(^,\)\(^6\) Our results suggest that routine voltage mapping and inclusion of LVA-B by patient-specific design of PVI finds results similar to those of other studies that investigated the correlation between isolation of LA scar and freedom from AF,\(^2\)\(^4\)\(^,\)\(^25\) and this point warrants further investigation.

### Clinical implications: LVA-guided catheter ablation strategy for AF

An ablation strategy of voltage-based substrate modification after AF has been proposed by Rolf et al.,\(^12\) yielding improved AF-free survival 1 year after ablation. Similarly, our study shows that the extent of LVA-B included in PVI is associated with freedom from AF after an initial ablation regardless of AF type. Inclusion of LVA in PVI provides an individualized substrate-based AF ablation strategy that minimizes additional lines and ablations.

### Study limitations

This study is limited by its retrospective design, which may have led to selection bias. The cohort included patients with symptomatic drug-refractory AF and those with >100-point electrogram acquisitions; thus, the results may not be generalizable to other AF cohorts. Our sample size may have decreased the study power to detect statistical interaction between AF type, LVA-B, and LVA-I in their association with atrial arrhythmia recurrence. Additionally, the interaction of the overall PVI area with LVA-I in the context of their association with outcome was not analyzed. Limited point by point voltage mapping was performed with a standard catheter. Most points were attained from the venous ostia, providing adequate data for understanding the extent of perivenous LVA-B and LVA-I; however, our results may be refined by increased density of mapping with multipolar catheters. Although patients were closely monitored through

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**Table 2.** Characteristics of patients with vs those without atrial arrhythmia recurrence

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (N = 159)</th>
<th>Patients with AF/AFL/AT recurrence (n = 82)</th>
<th>Patients with no AF/AFL/AT recurrence (n = 77)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.2 ± 9.2</td>
<td>60.3 ± 8.9</td>
<td>60.0 ± 9.6</td>
<td>0.927</td>
</tr>
<tr>
<td>Male sex</td>
<td>114 (72.0%)</td>
<td>65 (78.1%)</td>
<td>49 (65.0%)</td>
<td>0.067</td>
</tr>
<tr>
<td>White ethnicity</td>
<td>142 (89.2%)</td>
<td>76 (91.2%)</td>
<td>66 (86.6%)</td>
<td>0.785</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>43 (27.0%)</td>
<td>27 (32.9%)</td>
<td>16 (20.8%)</td>
<td>0.085</td>
</tr>
<tr>
<td>AF duration, y</td>
<td>4.8 ± 5.6</td>
<td>4.8 ± 5.4</td>
<td>4.7 ± 5.8</td>
<td>0.919</td>
</tr>
<tr>
<td>Hypertension</td>
<td>81 (50.9%)</td>
<td>43 (51.9%)</td>
<td>38 (50.0%)</td>
<td>0.817</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>29.0 ± 5.7</td>
<td>29.2 ± 5.3</td>
<td>28.9 ± 6.1</td>
<td>0.461</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>21 (12.8%)</td>
<td>13 (15.9%)</td>
<td>8 (9.5%)</td>
<td>0.233</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>54.1 ± 9.3</td>
<td>53.9 ± 10.2</td>
<td>54.4 ± 8.5</td>
<td>0.823</td>
</tr>
<tr>
<td>CHA(_2)DS(_2)-VASc ≥ 2</td>
<td>79 (49.1%)</td>
<td>41 (48.8%)</td>
<td>38 (49.4%)</td>
<td>0.943</td>
</tr>
<tr>
<td>LA volume, cm(^3)</td>
<td>105.0 ± 40.6</td>
<td>112.5 ± 44.9</td>
<td>96.7 ± 33.7</td>
<td>0.021</td>
</tr>
<tr>
<td>Mean LVA, cm(^2)</td>
<td>1.9 ± 3.8</td>
<td>2.5 ± 4.5</td>
<td>1.3 ± 2.8</td>
<td>0.019</td>
</tr>
<tr>
<td>Mean LVA isolated, %*</td>
<td>51.0 ± 36.8</td>
<td>43.9 ± 34.7 (64)</td>
<td>59.4 ± 37.7 (54)</td>
<td>0.033</td>
</tr>
</tbody>
</table>

* P values in bold are significant at the < 0.05 level.

AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; CHA\(_2\)DS\(_2\)-VASc, Congestive Heart Failure, Hypertension, Age (≥ 75 years), Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age (65-74 years), Sex (Female) score; LA, left atrial; LVA, low-voltage areas; LVEF, left ventricular ejection fraction.

* Calculated in patients with LVA > 0 cm\(^2\).

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**Table 3.** Multivariable Cox proportional hazard model of the association of LVA-I with freedom from AF

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA volume, cm(^2)</td>
<td>1.01</td>
</tr>
<tr>
<td>CHA(_2)DS(_2)-VASc score ≥ 2</td>
<td>0.65</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>0.98</td>
</tr>
<tr>
<td>LVA, cm(^2)</td>
<td>1.01</td>
</tr>
<tr>
<td>LVA isolated, %</td>
<td>0.42</td>
</tr>
</tbody>
</table>

* P values in bold are significant at the < 0.05 level.

AF, atrial fibrillation; CHA\(_2\)DS\(_2\)-VASc, Congestive Heart Failure, Hypertension, Age (≥ 75 years), Diabetes, Stroke/Transient Ischemic Attack, Vascular Disease, Age (65-74 years), Sex (Female) score; LA, left atrial; LVA, low-voltage areas.
symptom-prompted and routinely scheduled electrocardiographic monitoring, continuous monitoring was not performed, and some asymptomatic recurrences may have been missed. We have previously examined and reported our findings on the association between the extent of late gadolinium enhancement on magnetic resonance imaging and the extent of LVA by endocardial mapping and, therefore, did not re-examine the association in this study.\textsuperscript{28} Finally, patients in the present study were enrolled before contact force-sensing catheters were routinely used for AF ablation. It is possible that with the improved results observed using current technology, the effect size attributable to LVA isolation is smaller. The appropriate voltage threshold for delineation of scar is unknown. In this study and others,\textsuperscript{30,31} we adopted a threshold of 0.3 mV based on previous histologic and imaging observations.

**Conclusions**

Regardless of AF type, LA volume, mean LA area with low voltage, and CHA\textsubscript{2}DS\textsubscript{2}-VASc at baseline, the extent of LVA included in the left atrial pulmonary vein antrum is correlated with AF recurrence post-ablation. Further investigation is warranted to determine the optimal voltage cutoff for localization of LVA within the pulmonary vein antrum and the role of LVA isolation in achieving a durable clinical outcome.

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**Disclosures**

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**References**


