


Spatial correlation of left atrial low voltage substrate in sinus rhythm versus atrial fibrillation: The rhythm specificity of atrial low voltage substrate

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Abstract

Introduction: Improved sinus rhythm (SR) maintenance rates have been achieved in patients with persistent atrial fibrillation (AF) undergoing pulmonary vein isolation plus additional ablation of low voltage substrate (LVS) during SR. However, voltage mapping during SR may be hindered in persistent and long-persistent AF patients by immediate AF recurrence after electrical cardioversion. We assess correlations between LVS extent and location during SR and AF, aiming to identify regional voltage thresholds for rhythm-independent delineation/detection of LVS areas. (1) Identification of voltage dissimilarities between mapping in SR and AF. (2) Identification of regional voltage thresholds that improve cross-rhythm substrate detection. (3) Comparison of LVS between SR and native versus induced AF.

Methods: Forty-one ablation-naïve persistent AF patients underwent high-definition (1 mm electrodes; >1200 left atrial (LA) mapping sites per rhythm) voltage mapping in SR and AF. Global and regional voltage thresholds in AF were identified which best match LVS < 0.5 mV and < 1.0 mV in SR. Additionally, the correlation between SR-LVS with induced versus native AF-LVS was assessed.

Results: Substantial voltage differences (median: 0.52, interquartile range: 0.33–0.69, maximum: 1.19 mV) with a predominance of the posterior/inferior LA wall exist between the rhythms. An AF threshold of 0.34 mV for the entire left atrium provides an accuracy, sensitivity and specificity of 69%, 67%, and 69% to identify SR-LVS < 0.5 mV, respectively. Lower thresholds for the posterior wall

Abbreviations: AF, atrial fibrillation; IQR, interquartile range; LGE-MRI, late gadolinium-enhancement magnetic resonance imaging; LVS, low voltage substrate; PVI, pulmonary vein isolation; ROC, receiver operating characteristic; SR, sinus rhythm.

Deborah Nairn, Martin Eichenlaub, Amir Jadidi, and Axel Loewe contributed equally to this study.

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(0.27 mV) and inferior wall (0.3 mV) result in higher spatial concordance to SR-LVS (4% and 7% increase). Concordance with SR-LVS was higher for induced AF compared to native AF (area under the curve[AUC]: 0.80 vs. 0.73). AF-LVS < 0.5 mV corresponds to SR-LVS < 0.97 mV (AUC: 0.73).

Conclusion: Although the proposed region-specific voltage thresholds during AF improve the consistency of LVS identification as determined during SR, the concordance in LVS between SR and AF remains moderate, with larger LVS detection during AF. Voltage-based substrate ablation should preferentially be performed during SR to limit the amount of ablated atrial myocardium.

KEYWORDS

atrial fibrillation, induced AF, low voltage substrate, regional analysis, sinus rhythm

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia associated with an increased risk for stroke and heart failure.¹ The pulmonary veins are the primary trigger site of AF. Isolating the pulmonary veins can yield a high rate of arrhythmia freedom in paroxysmal AF patients.² However, the success rate is often lower in persistent AF patients due to atrial remodeling and additional pathological substrate contributing to arrhythmia maintenance.^{3,4}

Electroanatomical mapping to identify low bipolar voltages (peak-to-peak amplitudes) <0.5 or 1 mV during sinus rhythm (SR) has been shown to be a promising technique to identify the additional pathological substrate.^{3,5-7} However, mapping in SR is not always feasible: for example, when AF reoccurs shortly after electrical cardioversion due to recurrent/sustained fibrillatory trigger activity. Moreover, electrophysiologists may choose to perform mapping during AF to identify both the potential arrhythmogenic rapid trigger sites and the underlying pathological substrate.^{8,9}

Two widely accepted voltage cutoff values have been reported in SR that allow the identification of potentially proarrhythmogenic tissue: <1¹⁰ and <0.5 mV.^{5,7} When mapping is done in AF, atrial areas displaying LVS < 0.5 mV have been reported as potential arrhythmogenic sites.³ Uncertainties remain regarding which cutoff values should be applied when mapping during AF and how the voltages in both rhythms relate to one another. The current study aimed to compare LVS in SR and AF and identify regional voltage thresholds to improve cross-rhythm substrate detection.

2 | METHODS

2.1 | Patient cohort

Forty-one patients with persistent AF presenting for their first AF ablation procedure were included in the study. Six weeks before AF ablation procedure, all patients were electrically cardioverted to SR to

enable favorable reverse electrical remodeling.¹¹ Patients presenting with SR on procedure date (11/41) underwent voltage and activation mapping in SR first, followed by voltage mapping during induced AF and subsequent pulmonary vein isolation (PVI). Patients with native AF on procedure date (30/41) first underwent voltage mapping in AF, followed by electrical cardioversion, electroanatomical mapping in SR, and finally PVI. Mapping was performed 5 min after AF induction and only if AF was maintained for the entire mapping time. In two patients (5% of patients) with important SR bradycardia and hypotension, pacing from the coronary sinus was performed. The study was approved by the institutional ethics committee of the University of Freiburg (Germany) and all patients provided written informed consent before enrollment.

2.2 | Electroanatomical mapping

High-density voltage mapping was performed using the CARTO-3 mapping system (Biosense Webster) and a 20-pole (electrode size: 1 mm, spacing: 2–6–2 mm) Lasso-Nav catheter.

To avoid including information from points with poor contact, measurements were disregarded if the electrodes were located >6 mm from the atrial surface.

Bandpass filtering at 16–500 Hz was applied to the bipolar electrograms. To calculate the voltage in SR and AF, a window of interest was chosen restricted to the PR interval in the electrocardiogram. Voltage values between the electrode positions were interpolated by the CARTO-3 system. Cutoff values of <0.5 and <1.0 mV were then applied to the bipolar SR voltage maps to define the low voltage substrate (LVS).^{3,6} Areas demonstrating LVS were confirmed using a separate contact force-sensing mapping catheter with a contact threshold of >5 g.

2.3 | Analysis

Using the Scalismo statistical shape modeling software,¹² the geometries of each patient were aligned and registered to a mean

left atrial (LA) geometry. This allowed the transfer of voltage information from each patient's geometry to a common geometry represented by the same number of surface points, which represent the same anatomical landmarks.

The voltage value for each point was calculated as the mean amplitude of all points within a 1.5 mm radius to compare local areas between the two rhythms. To investigate the correlation between SR and AF, receiver operation curves (ROCs) were created across the whole patient cohort, with the SR map being considered as the reference condition. The optimal AF thresholds for both SR cutoff values (0.5 and 1 mV) were identified and the sensitivity, specificity, and accuracy were computed for each patient. In a subsequent local analysis, the percentage of patients showing consistent classification as low or high voltage in both rhythms per point was determined to identify the spatial concordance pattern.

A map of the median voltage values was constructed across the entire patient cohort for both rhythms. Additionally, a map showing the difference between SR and AF median voltage values across all patients was computed.

The atrium was split into anatomical regions to examine the difference between SR and AF voltage mapping and identify optimal voltage thresholds for different atrial regions: inferior wall, lateral wall, posterior wall, anterior wall, and roof. The optimal threshold for each region was identified as the top left-hand corner of the ROC curve when comparing the identification of low voltage regions between rhythms in that region.

Finally, the patient cohort was split into two groups: (1) where induced AF was mapped (patients presenting in SR) and (2) where native AF was mapped (patients presenting in AF). The two patients where the coronary sinus (CS) was paced to maintain SR were removed from this part of the study due to the unknown effect of how different fast pacing from the CS relates to AF. A two-sample *t* test was performed to investigate if the voltage values between the two groups were significantly different. The two groups were then compared to their respective SR maps and ROC curves were computed. Since more patients were mapped with native AF (65%), a leave-*p*-out (*p* = 11) cross-validation was performed for the native ROC curve. A two-sample *t* test was additionally performed between the distance of the two ROC curves with respect to the top left-hand corner.

3 | RESULTS

3.1 | Patient characteristics

Forty-one persistent AF patients (63 ± 11.1 years old, 43.9% female) presenting for their first AF ablation procedure were included. On the procedure date, 30 of 41 (73%) patients recurred with persistent AF. Table 1 describes further details regarding the patients' characteristics.

TABLE 1 Patient clinical demographics.

Patient characteristics	Total = 41
Age (years)	63 ± 11.1
Female (%)	18 (43.9)
BMI (kg/m ²)	27.8 ± 6.1
Arterial hypertension (%)	23 (56.1)
Diabetes mellitus (%)	5 (12.2)
Prior stroke (%)	1 (2.4)
Structural CMP (%)	12 (29.2)
Coronary artery disease (%)	6 (14.6)
Persistent atrial fibrillation (%)	41 (100)
CHA ₂ DS ₂ -VASc score	1.7 ± 1.4
Initial rhythm SR (%)	11 (26.8)
History of AF (months since diagnosis) (%)	38 ± 41
AA therapy on admission (%)	17 (41.5)
Betablocker therapy only (%)	18 (43.9)
Amiodarone (%)	11 (26.8)
Flecainide (%)	3 (7.3)
Sotalol (%)	1 (2.1)
Dronedarone (%)	2 (4.8)
LA diameter (AP, mm)	42.8 ± 6.9
LVEF (%)	50.4 ± 4.1
LV dysfunction (LVEF < 50%)	6 (14.6)
LVEDD (mm)	48.7 ± 6.1
LA dilatation (>40 mm) (%)	28 (68)
Creatinine clearance (mL/min/1.73 m ²)	74.1 ± 16.7

Abbreviations: AA, antiarrhythmic; AF, atrial fibrillation; AP, anteroposterior; BMI, body mass index; LA, left atrial; LV, left ventricle; LVEDD, left-ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; SR, sinus rhythm.

3.2 | Spatial distribution of LA voltage during SR and AF

Figure 1 shows the distribution of LVS for a representative patient for mapping both during SR and AF. While the location of the LVS matches well between the rhythms on both the anterior and posterior wall, the extent is bigger in the AF map when using a cutoff value of 0.5 mV for both maps. The voltage maps for all patients are shown in the Supporting Information Material (Figure S1).

Figure 2 shows the spatial distribution of the median voltages across the entire patient cohort during both SR and AF. Voltages are lower across the entire atrium in AF (0.48 ± 0.32 mV) than in SR (0.93 ± 0.40 mV). The biggest differences between the median voltages

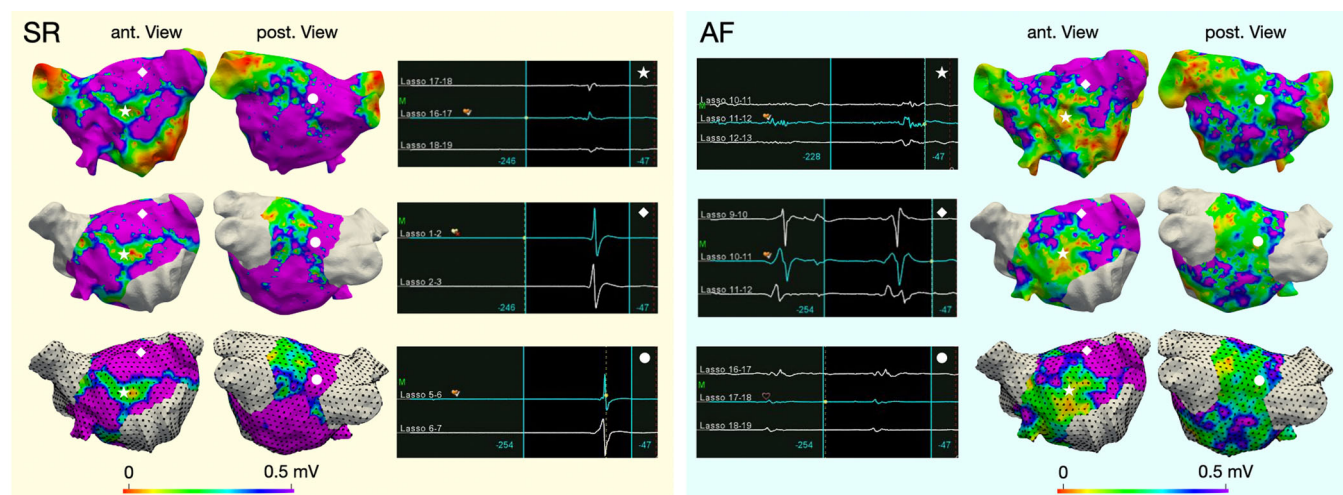


FIGURE 1 Spatial distribution of low voltage in SR and AF in one patient. Voltage maps in the top row are shown on the patient's geometry. The middle row shows the voltage projected onto the joint geometry after the exclusion of the pulmonary vein and mitral valve areas. The bottom row shows the equidistant points (black dots) where the mean amplitude of all points within a 1.5 mm radius was considered. SR voltage map and relating signals are shown on the left (yellow box), and AF on the right (blue box). The icons mark spatial points on the atrial geometry for which the corresponding signals are shown in the middle columns. AF, atrial fibrillation; SR, sinus rhythm.

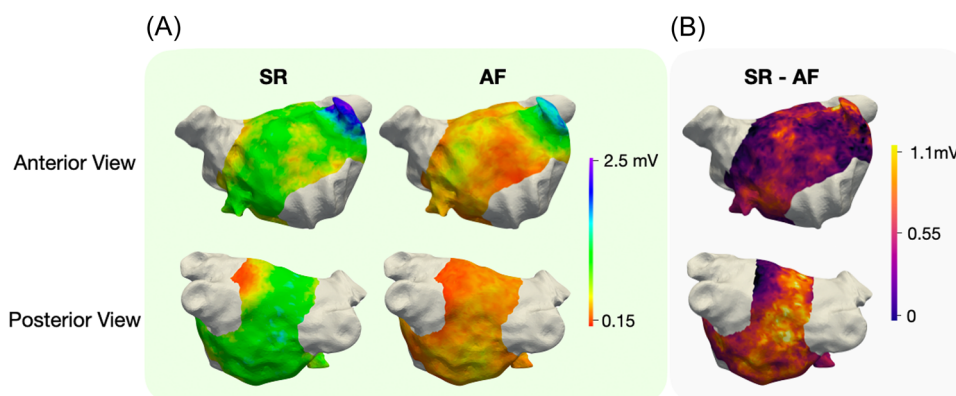


FIGURE 2 (A) Median voltage across all patients during SR and AF and (B) the difference of median voltage between the two rhythms. AF, atrial fibrillation; SR, sinus rhythm.

in SR and AF of up to 1.1 mV are seen on the posterior and inferior walls. On the anterior wall, differences are smaller (0.35 ± 0.14 mV). In both maps, the lowest voltages occur around the PVs and on the anterior wall (mean \pm standard deviation: 0.77 ± 0.19 mV), with the highest voltages in the LAA (1.87 ± 0.27 mV).

3.3 | Global AF thresholds for the detection of SR-LVS

ROC curve analysis provided the optimal threshold in AF for identifying LVS in SR. AF thresholds 0.34 and 0.45 mV for SR < 0.5 and < 1 mV provided the best balance between high sensitivity and specificity as identified by the top left-hand corner of the ROC curve (Figure 3A). The percentage of concordance was moderate with a sensitivity of 67% (< 0.5 mV) and 66% (< 1 mV), specificity of 69%

(< 0.5 mV) and 68% (< 1 mV), and accuracy of 69% (< 0.5 mV) and 65% (< 1 mV). The performance of the new AF voltage thresholds varied between patients with per-patient accuracy ranging between 53% and 94% (mean $69 \pm 11\%$ for SR < 0.5 mV, mean $67 \pm 11\%$ for SR < 1 mV) (Figure 3B). In Supporting Information Material: Figure S2, the ROC curve identifying the optimal threshold in SR for AF < 0.5 mV is shown.

Figure 4 shows the spatial distribution of the percentage of patients who demonstrate agreement with LVS areas in both SR and AF in a local neighborhood. The agreement was high in the LAA ($88 \pm 3\%$ of patients). When using 0.5 mV as the cutoff value in both SR and AF, there is agreement on the anterior wall ($62 \pm 8\%$). However, the agreement is substantially smaller on the inferior and posterior walls ($48 \pm 8\%$). By lowering the AF voltage thresholds to the values identified by the ROC curve analysis (Figure 3A), the agreement on the anterior wall and inferior increased ($69 \pm 8\%$ and $61 \pm 8\%$).

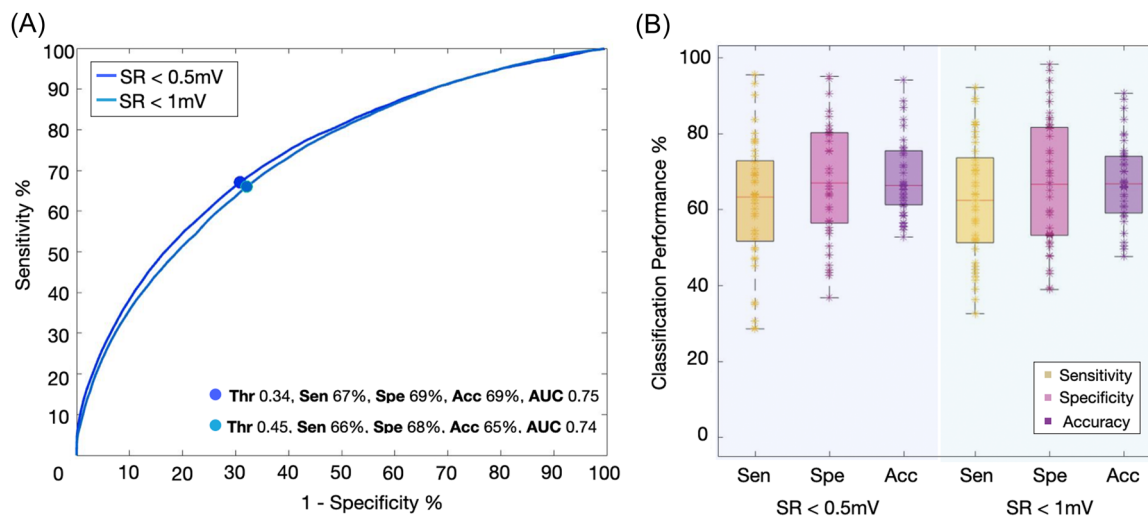


FIGURE 3 Cross-rhythm classification consistency. (A) ROC curve comparing LVS as identified during SR for bipolar thresholds <0.5 and 1 mV and during AF. The optimal AF thresholds across all patients and corresponding performance metrics are given in the legend. (B) classification performance parameters for each patient using the threshold obtained from the ROC curve. AF, atrial fibrillation; LVS, low voltage substrate; ROC, receiver operating characteristic; SR, sinus rhythm.

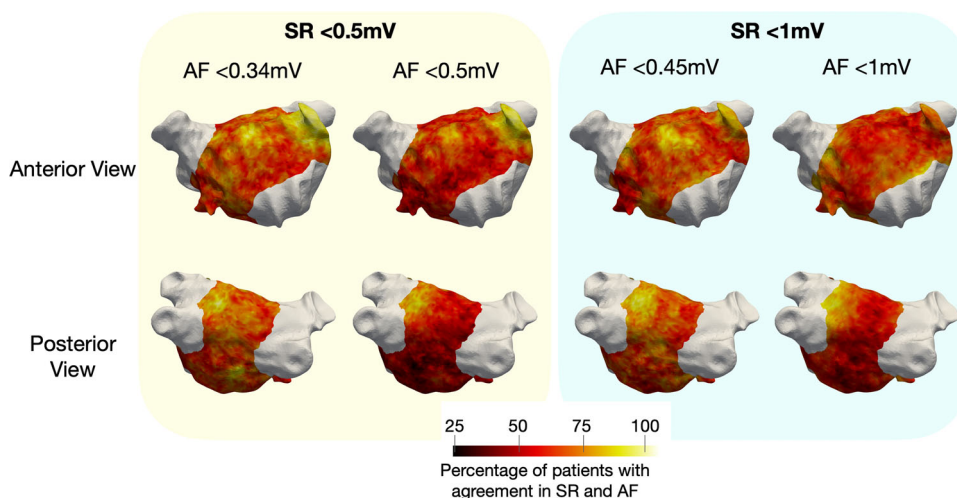


FIGURE 4 Agreement map between SR and AF. Each map shows the percentage of patients in which both voltage maps in SR and AF agree that low or high voltage is located within a local neighborhood. The yellow box shows the agreement with SR < 0.5 mV, and the light blue box with SR < 1 mV. In each box, the left column uses the optimal AF voltage thresholds as identified by the ROC curve analysis (Figure 3A). AF, atrial fibrillation; ROC, receiver operating characteristic; SR, sinus rhythm.

3.4 | Regional AF thresholds for the detection of SR-LVS

The lowest concordance between SR and AF using the global optimal threshold for the entire atrium was found at the inferior wall (accuracy: 62%) Figure 5. By applying a regional AF threshold (0.3 mV), the accuracy on the inferior wall increased by 4%. For the posterior wall, an even lower AF threshold (0.27 mV) increased the accuracy from 69% to 76%. In both regions, the new regional thresholds decreased the sensitivity and increased the specificity.

From Figure 2, it can be seen that the voltage values are markedly higher on the posterior/inferior wall in SR than in AF. The entire atrium threshold is therefore too sensitive for these regions. On the other hand, on the anterior and lateral walls, a slightly higher threshold (0.36 and 0.39 mV, respectively) can optimally locate the regions of SR-LVS using the AF voltage map. The optimal AF regional thresholds, which correspond to SR < 1 mV are shown in the Supporting Information Material (Figure S3). The ROC curves used to find the optimal regional thresholds are shown in Supporting Information: Figure S4.

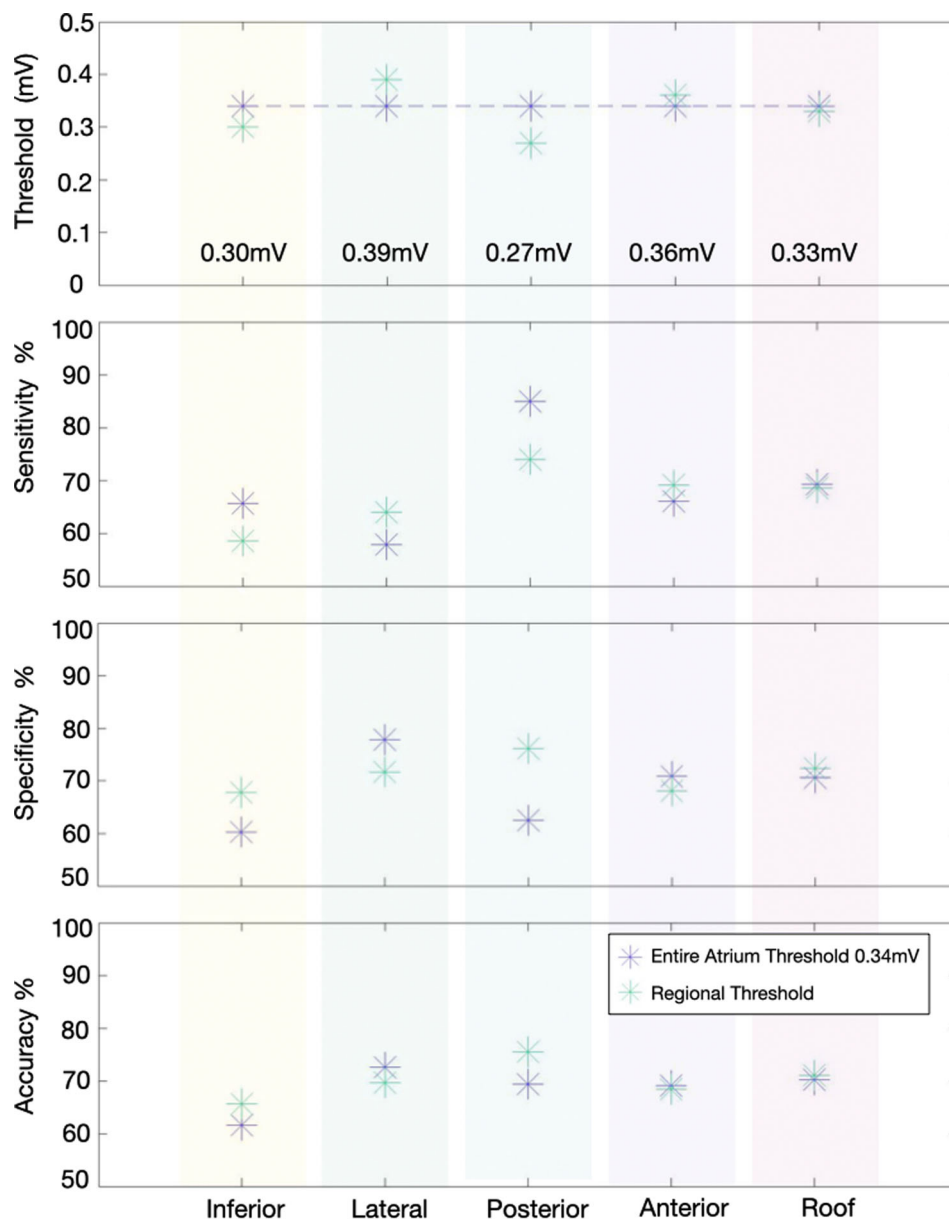


FIGURE 5 Optimal AF threshold and the corresponding sensitivity, specificity, and accuracy for each anatomical region of the LA compared to SR < 0.5 mV. The previously defined global threshold for the entire atria is shown by the purple asterisk while the green asterisk represents the regional threshold. AF, atrial fibrillation; LA, left atrial; SR, sinus rhythm.

3.5 | Impact of inducing AF

The voltage was slightly higher in native AF patients than in patients in whom AF was induced (Figure 6A, not significant). The ROC curves (Figure 6B) show that the correlation between AF-LVS and SR-LVS is significantly ($p < .05$) better in patients in whom AF was induced (area under the curve: 0.80 vs. 0.73). The optimal AF threshold for identifying SR-LVS < 0.5 mV was lower for patients in whom AF was induced (0.3 mV). In Supporting Information Material: Figure S5, the boxplots and histograms can be seen for SR voltage values for patients who were cardioverted after mapping native AF versus first mapping native SR and then inducing AF. Although the difference was also not significant, the voltage values were typically higher in

the patients mapped first in SR than those who presented in AF (median 1.66 vs. 0.77 mV).

4 | DISCUSSION

4.1 | Main findings

This study investigated the differences in LVS identification for mapping during SR and AF. Three key findings can be reported:

1. The overall correspondence of LVS mapped in SR and in AF is moderate.

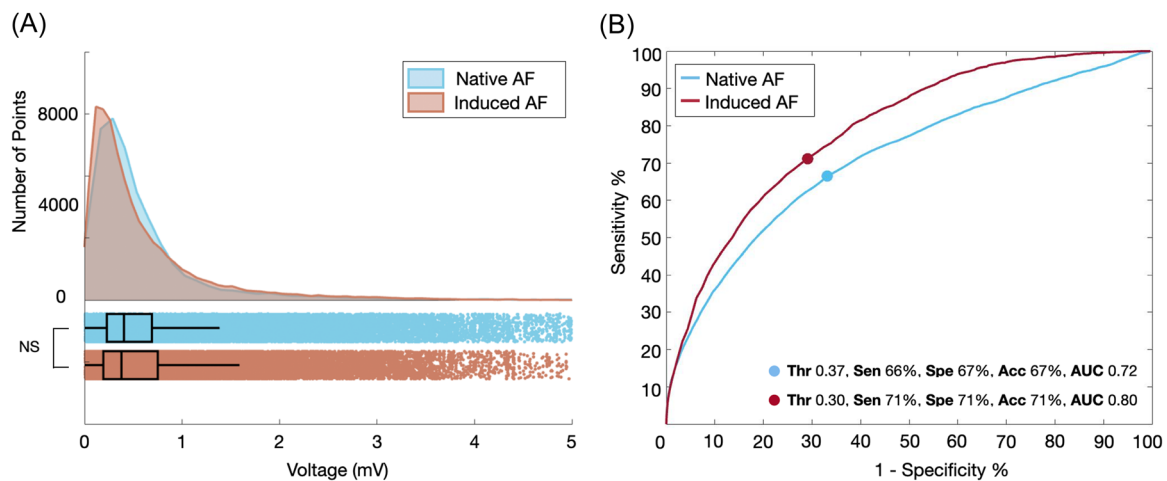


FIGURE 6 Histogram and boxplot of the voltage distribution in patients in whom AF was induced versus native AF. ROC curves comparing the AF-LVS in each group to SR-LVS. Blue: patients which presented with native AF, red: patients with induced AF. AF, atrial fibrillation; LVS, low voltage substrate; ROC, receiver operating characteristic; SR, sinus rhythm.

- Discrepancies exist between mapping in SR and AF, specifically on the posterior and inferior LA walls.
- New regional AF cutoff values improve cross-rhythm substrate detection.
- The concordance of SR and AF voltage maps is higher when AF was induced compared to native AF.

This study addresses whether the same LVS sites can be identified irrespective of rhythm by adaptations of the thresholds. However, to enable both a sensitive and specific detection of trigger sites for AF, additional markers for arrhythmogenesis, besides low voltage areas and late gadolinium-enhancement (LGE) areas (e.g., rapid repetitive activity in AF or atrial late potentials in SR⁹) need to be considered.

4.2 | AF cutoff values for identifying LVS

A recent study using generalized additive models in a cohort of 31 patients found that a cut-off value of 0.31 mV in AF was best for predicting <0.5 mV SR-LVS.¹³ However, a point-by-point analysis was performed, which could have been affected by undetected map shifts. To counter this problem, our study analyzed the data in small equidistant regions with a radius of 3 mm. Regardless, a similar cut-off value (0.34 mV) was found based on ROC curve analysis. When examining LVS in AF as identified by regions <1 mV in SR, a cut-off value of 0.45 mV is optimal. However, pronounced differences between the rhythms are present on the posterior and inferior walls (Figure 2). By adjusting the threshold for each region, the extent and location of SR-LVS can be better estimated when mapping during AF. Given the positive results of recent studies including the ERASE-AF RCT,^{7,14} the SR cut-off of 0.5 mV (best corresponding to 0.34 mV in AF) might be more relevant than the SR-LVS < 1 mV (best corresponding to 0.45 mV in AF).

4.3 | Differences in SR and AF voltage mapping

While the voltage is typically lower in AF than SR, this study identified that this difference is not uniform across the entire atrium. The differences between rhythms were found to be much higher on the posterior and inferior LA wall (difference typically >0.55 mV) than on the anterior (difference typically <0.55 mV). Kurata et al. also reported higher voltages in the posterior region than the anterior region in both patients with and without low voltage areas.¹⁵ Butcher et al. showed that omnipolar AF-LVS < 0.5 remarkably resembles bipolar SR-LVS < 0.5 mV,¹⁶ partly capitalizing on the compensation of lower voltages in AF versus SR by higher voltages in omnipolar versus bipolar electrograms. Additionally, a recent study comparing voltage maps to LGE magnetic resonance imaging (MRI) identified that the correlation between the two modalities was significantly better on the posterior wall when the voltage map was acquired during AF versus SR.¹⁷ One explanation drawn is that when activation rates are more rapid during AF, nontransmural or patchy fibrotic tissue may be more susceptible to functional reentry, slow conduction or conduction block, which results in low voltage areas.¹⁸ Further computational studies may elucidate the mechanisms of rhythm-dependent voltage discrepancies on the posterior wall.

4.4 | Influence of AF induction on detected LVS

The correlation between SR and AF voltage mapping was higher when AF was induced in the patients. One hypothesis is that native AF is on average more complex, with high levels of electrical remodeling, endoepicardial dissociations of wavelet activities, and more wavefronts approaching from multiple directions than in induced AF, which is mapped few minutes after its initiation.¹⁹ Alternatively, patients who presented with AF on the procedure day may have a more advanced form of electrical and structural LA

remodeling than those who maintained SR.²⁰ Thus, they may present with more complex propagation patterns, such as multiple wavefronts and reentries. In this study, the mean voltages during SR are higher in the patients who presented with SR (median: 1.16 mV, IQR: 0.51–2.18 mV) than those who presented in AF (median: 0.77 mV, IQR: 0.37–1.44 mV). A recent study reported that patients with extensive mean regional voltage reductions demonstrated whole LA degeneration.¹⁵ This indicates a more advanced stage of arrhythmic remodeling in patients with AF recurrence 6 weeks after cardioversion to SR.

4.5 | Applicability to other systems

The CARTO-3 mapping system was used for this study with a 20-pole Lasso catheter with electrodes of size 1 mm, and interelectrode spacing 2–5–2 mm, which is a commonly used configuration. Similar findings are expected for other mapping catheters (e.g., Orion); however, with electrode size-adapted voltage thresholds.²¹

The current study used high-density bipolar voltage mapping to compare LVS in SR and AF. The impact of omnipolar voltage mapping was not evaluated. However, it has been reported that with high-density mapping where the catheter is allowed to rove the direction of activation front to mapping electrodes does not significantly influence the extent and localization of detected LVS (both for SR and AF).^{6,22}

5 | LIMITATIONS

In some patients, AF was mapped first before cardioverting to SR, potentially affecting the results by undetected map shifts. To counteract this, all patients' voltage information was mapped to a joint geometry, and analysis points comprised of the mean voltage in a 1.5 mm radius. The size of the subcohort in which AF was induced is comparatively small ($n = 11$). Additionally, SR and AF LVS were not correlated to imaging modalities such as MRI, as the aim of this paper is not to provide a tool for AF-guided ablation but to identify if similar low-voltage sites can be found irrespective of rhythm. Further studies should be performed to identify the importance of the newly proposed thresholds for LVS ablation.

6 | CONCLUSION

The extent and distribution of LVS are different in SR and AF. The proposed AF thresholds improve the identification of SR-LVS when mapping is performed during AF. However, a global threshold for the entire atria can lead to over- or underestimation of LVS, which can be corrected only to some extent by applying the reported regional thresholds. When mapping in AF may be necessary for patients who cannot be cardioverted or maintained in SR or when AF mapping for detection of rapid activity sites is chosen, further electrogram or

activation characteristics might be useful to localize the arrhythmogenic substrate.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The figures within the article and Supporting Information: Material show detailed analyses for all patients used. Raw patient data cannot be shared without additional Institutional Review Board (IRB) approval and patient consent. Requests should be directed to the IRB of Freiburg University Hospital.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Freiburg University Hospital ethics committee. The patients provided written informed consent to participate in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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