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ELECTROPHYSIOLOGY

Bi-atrial characterization of the electrical substrate in patients with atrial fibrillation

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Abstract

Background: Little is known regarding the characterization of electrical substrate in both atria in patients with atrial fibrillation (AF).

Methods: Eight consecutive patients undergoing AF ablation (five paroxysmal, three persistent) underwent electrical substrate characterization during sinus rhythm. Mapping of the left (LA) and right atrium (RA) was performed with the use of the HD Grid catheter (Abbott). Bipolar voltage maps were analyzed to search for low voltage areas (LVA), the following electrophysiological phenomena were assessed: (1) slow conduction corridors, and (2) lines of block. EGMs were characterized to search for fractionation. Electrical characteristics were compared between atria and between paroxysmal versus persistent AF patients.

Results: In the RA, LVAs were present in 60% of patients with paroxysmal AF and 100% of patients with persistent AF. In the LA, LVAs were present in 40% of patients with paroxysmal AF and 66% of patients with persistent AF. The areas of LVA in the RA and LA were 4.8±7.3 cm^2 and 7.8±13.6 cm^2 in patients with paroxysmal AF versus 11.7±3.0 cm^2 and 2.1±1.8 cm^2 in patients with persistent AF. In the RA, slow conduction corridors were present in 40.0% (paroxysmal AF) versus 66.7% (persistent AF) whereas in the LA, slow conduction corridors occurred in 20.0% versus 33.3% respectively (p = ns). EGM analysis showed more fractionation in persistent AF patients than paroxysmal (RA: persistent AF 10.8 vs. paroxysmal AF 4.7%, $p = .036$, LA: 10.3 vs. 4.1%, $p = .108$).

Conclusion: Bi-atrial involvement is present in patients with paroxysmal and persistent AF. This is expressed by low voltage areas and slow conduction corridors whose

extension progresses as the arrhythmia becomes persistent. This electrophysiological substrate demonstrates the important interplay with the pulmonary vein triggers to constitute the substrate for persistent arrhythmia.

KEYWORDS
atrial fibrillation, atrial substrate, Bi-atrial characterization, electrograms, slow conduction

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia worldwide and is associated with increased risk for ischemic stroke.[1] Catheter ablation (CA) of AF has achieved substantial improvement within the last years and may even be indicated as primary therapy in selected patients.[2] Circumferential pulmonary vein isolation (PVI) represents the most common therapeutic strategy for CA in patients with paroxysmal AF. However, PVI alone is often not sufficient in preventing recurrence of AF in a significant amount of patients with nonparoxysmal AF.[3] Atrial fibrosis is a very important histopathologic finding in these patients,[4] and in recent years, was shown to predict ablation failure associated with increased risk of arrhythmia recurrences after CA.[5]

Kottkamp and colleagues hypothesized a pathologic triangle consisting of the triggers for the initiation of the arrhythmia, a fibrotic substrate needed for the maintenance of AF, and various known modulators such as autonomous nervous system and others.[6] In this scenario, fibrotic atrial cardiomyopathy (FACM) is defined as a specific and progressive disease with mild to severe forms,[4] and AF is considered to be the arrhythmic manifestation of structural atrial disease.[7]

This may also explain the different clinical "phenotypes" of AF, between patients with relatively short episodes of paroxysmal AF for a long period of time and mild forms of FACM, versus patients that present with "early persistent" AF associated with severe forms of FACM.[2] Moreover, studies confirm that patients with history of AF have a 3–5-fold greater extent of fibrosis compared to patients without history of AF[8] with b-iatrial involvement documented by previous studies.[9]

Identification of the atrial substrate, including areas of low bipolar voltage and heterogeneous conduction properties is currently used in the risk stratification and to direct ablation strategies in patients with AF.[10] Even if ablation of LVA has been recently questioned by a randomized trial,[11] targeting the fibrotic substrate by CA has been advocated as an additional ablative target in persistent AF.[12]

The aim of the present study is to characterize bipolar LVA and functional electrophysiological mechanisms in patients with paroxysmal and persistent AF candidates undergoing RF ablation.

2 | METHODS

Eight consecutive patients undergoing ablation for AF (five paroxysmal, three persistent) were prospectively enrolled at our institution. The electro-anatomical maps of both atria were built using the HD Grid mapping catheter (Abbott Laboratories, North Chicago, IL, USA) ensuring a density of at least 1500 EGMs per chamber. Inclusion criteria were age > 18 years, documented AF episodes recorded on 12 lead ECG undergoing catheter ablation for clinical indication as per 2020 ESC guidelines.[13] Exclusion criteria were: previous left atrial catheter ablation, structural valvular disease, known primary electrical heart disease, thyroid and pulmonary disease, and use of amiodarone in the past 2 months. Each patient underwent a complete transthoracic echocardiography evaluation. Antiarrhythmic drugs were discontinued at least five half-lives before the procedure. Patients with persistent AF were cardioverted to sinus rhythm (SR) with external DC shock at the time of the procedure. The study was approved by the local Ethical Committee on Human Research.

2.1 | The electrophysiological study

Under conscious sedation, the following catheters were introduced via right femoral vein: (1) a decapolar catheter (Abbott Medical, MN, USA) within the coronary sinus, (2) a 3.5-mm open irrigated-tip ablation catheter (Flexability catheter, Abbott Medical, MN, USA). The multielectrode catheter HD Grid was utilized (Abbott Medical; MN, USA) for EGM acquisition. Every patient had given written informed consent before the study.

2.2 | Mapping and EGM collection

Bipolar EGMs were automatically collected during sinus rhythm. EGM analysis was performed off-line on the NAVX system (ABBOTT, Minnesota, USA) using electronic calipers at a speed of 100 mm/s. For our study, only the initial map and relative EGMs were considered for analysis prior to any radiofrequency (RF) ablation. Voltage maps of both atria were built according to threshold values of > 0.5 mV for healthy tissue. Low voltage tissue was defined as voltage lower than 0.05 mV. Border zones were defined as voltages in between the above-mentioned thresholds.

2.3 | Assessment of electrophysiological phenomena

All electrograms and propagation maps were reviewed offline by two electrophysiologists (A.F.; G.T.), blinded to each other's analysis, using electronic calipers at similar gain and speed of 100 mm/s. Bipolar signals were filtered from 30 to 250 Hz. When discrepancies occurred

between the two blinded reviewers, a third reviewer was consulted (A.H.). The P wave duration was measured from 12-lead surface ECG. From propagation maps, localization and time (corresponding to the beginning of the P wave) of the latest activation in the RA and the earliest activation in the LA were assessed. The following electrophysiological phenomena were assessed: (1) slow conduction corridors: defined as discrete zones with conduction velocity < 0.5 m/s[18,19] and (2) Lines of block: characterized by double potentials separated by an isoelectric line.

2.4 | Individual EGM assessment

All contact maps and respective EGM signals were exported to R 4.0.3 (The R Project, Vienna, Austria) using RStudio 1.3.1093 (RStudio PBC, Boston, MA). Using a custom-made script, all signals were reviewed in a random order and marked for fractionation and double potentials. Double potentials were automatically assigned to be either a line of block (defined as potentials separated by an isoelectric line of > 60 ms) or a wavefront collision (< 60 ms), respectively.

2.5 | Follow up

Follow-up was performed at 1 year from the index procedure. Arrhythmic recurrences were defined as episodes lasting more than 2 min and were assessed through: ECG during symptoms, loop-recorder interrogation or 24 or 48-h ambulatory Holter ECG monitoring.

2.6 | Statistical analysis

Categorical variables were expressed as numbers and percentages; continuous quantitative variables as mean ± standard deviation (SD). All analyses were performed in R using RStudio. Independent sample analyses in paroxysmal versus persistent AF patients and between patients with versus without arrhythmia occurrence were performed. The Kruskal–Wallis test was adopted for testing whether samples of different groups originated from the same distribution. Mann–Whitney U test was used to investigate whether the two groups had stochastically different distributions. The proportion of the categorical variables was compared using a Chi-square analysis. Furthermore, paired sample analyses were performed to detect differences between measurements in left versus right atrium using Student's T-test and Wilcoxon rank-sum test. A two-tailed p value < .05 was considered statistically significant.

3 | RESULTS

3.1 | Study population

The eight patients enrolled had a mean age of 67.4±4.9 years. Five (62.5%) patients had paroxysmal AF and were 68±5.6 years old while three (37.5%) patients had persistent AF with a mean age of 66.3±4.2 years. In the latter group, AF duration was 1.7±0.6 years. LV ejection fraction was 62.1±3%. CHA_2DS_2-VASc score in the paroxysmal AF group was 2.4±0.5 versus CHA_2DS_2-VASc of 1.3±1 in the persistent AF group. The total ablation procedure duration was 186.1±15.0 min for patients without differences between groups. Clinical characteristics are described in **Table 1**.

3.2 | Cardiac mapping

All patients underwent mapping of the left and right atrium. The mapping time was 12.4±8.7 min in the right atrium and 18.4±6.6 min in the left atrium without significant differences in both groups and between both atria ($p = .065$). The number of collected points in LA and RA were also similar (LA: paroxysmal 6826±4725 vs. persistent 8512±6535 points; RA: paroxysmal 7542±6253 vs. persistent 9482±3014 points, p = ns).

3.3 | Electrophysiological characteristics of atrial substrate

Three (60%) patients with paroxysmal AF and three (100%) patients with persistent AF presented LVA in the right atrium (RA), while two (40%) patients with paroxysmal AF and two (66%) patients with persistent AF presented LVA in the left atrium (LA). In patients with paroxysmal AF, the LVA was 4.8±7.3 cm^2 in the RA and 7.8±13.6 cm^2 in the LA, and in the persistent AF group 11.7±3.0 cm^2 and 2.1±1.8 cm^2, respectively. There was no significant difference in LVA extension between both atria ($p = .705$). LVAs in the paroxysmal AF patients were located in the anterior and septal wall of the RA and the anterior and posterior wall of the LA, while in the persistent AF patients, they were located in the anterior, septal, and inferior walls of the RA and in the mitral isthmus of the LA (Figure 2). **Figure 1** demonstrates a bipolar RA voltage map of a paroxysmal AF patient displaying normal voltage.

The P wave duration was 117.7±12 ms in patients with paroxysmal AF and 128.8±21.7 ms in persistent AF, with the latest activation of the RA occurring after 58.33±12.2 ms versus 68.8±9.7 ms in paroxysmal AF and persistent AF, respectively. The latest RA activation was on the anterior wall in all paroxysmal AF patients and inferoseptal in all persistent AF patients. The first LA activation corresponded to 11.7±2.3 ms after P wave onset in paroxysmal AF and 15.6±6.9 ms in persistent AF patients. First activated region was atrial septum in all patients (**Table 2**).

3.4 | Electrophysiological phenomena

Only one patient (20%) with paroxysmal AF presented a single area of slow conduction in the RA, located at the posteroseptal wall, while two (40%) patients with paroxysmal AF presented slow conduction in the LA with line of block, located at the anterior and posterior atrial wall. **Figure 3** shows the activation map during SR utilizing the HD grid

TABLE 1 Clinical characteristics of the study population

	Total	Paroxysmal	Persistent	*p*-value
Patients, n(%)	8	5(62.5%)	3 (37.5%)	N/A
Age, years	67.4±4.9	68.0±5.6	66.3±4.2	.650
Male gender	7 (87.5%)	4(80%)	3 (100%)	1.000
Hypertension	5 (62.5%)	4(80%)	1 (33%)	.464
Diabetes mellitus	3 (37.5%)	3(60%)	0	.196
CHA_2DS_2-VASc score	2.0±0.8	2.4±0.5	1.3±1	.245
AF duration, years	3.8±5.1	5.2±6.2	1.7±0.6	.274
LVEF,%	62.1±3.0	61.8±3.6	62.7±2.5	.702
LA volume, ml	70.5±9.7	71.0±9.1	69.7±12.7	.882
Antiarrhytmic therapy	6 (75%)	5 (83%)	1 (17%)	.107
B-blockers	4 (50%)	1 (20%)	3 (100%)	.143
RAAS agents	3 (37.5%)	2 (40%)	1 (33%)	1.000
Ca^{++} blockers	2 (25%)	2 (40%)	0 (0%)	.464

Abbreviations: NOAC, non vitamin-K oral anticoagulants; RAAS, renin angiotensin aldosterone system.

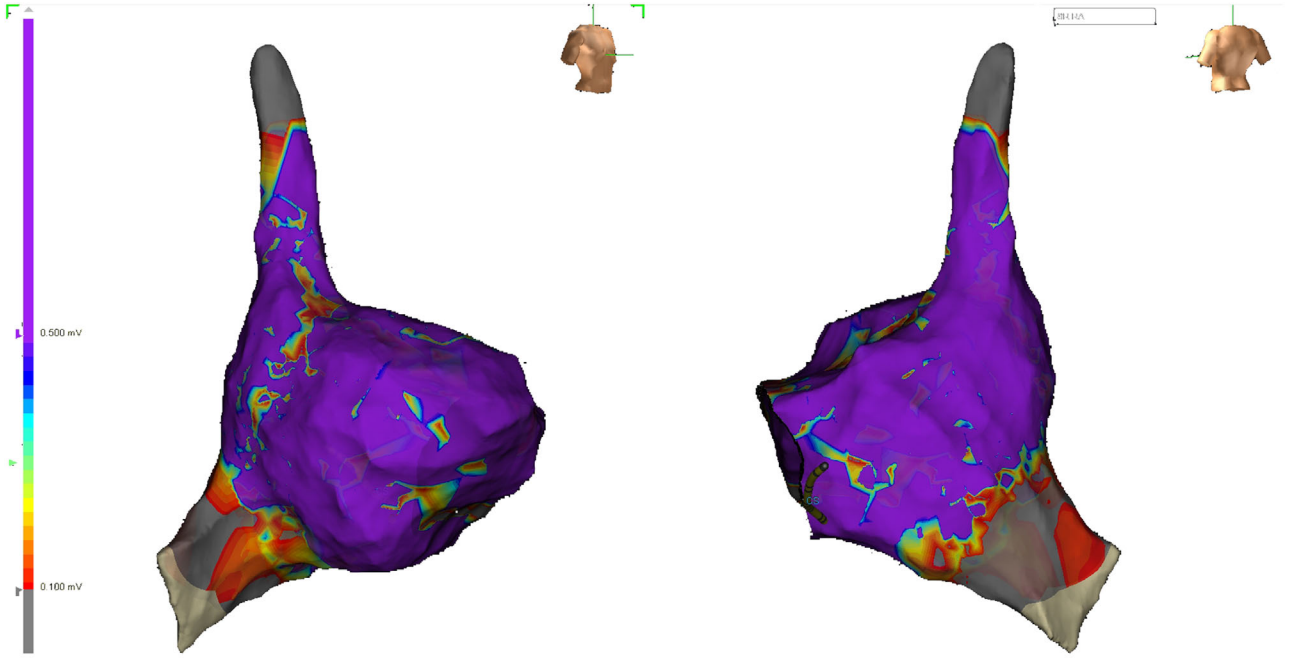

FIGURE 1 Voltage map of the right atrium of a paroxysmal AF patient with demonstration of almost complete normal voltage [Color figure can be viewed at wileyonlinelibrary.com]

catheter and isochronal timing in PA view. A line of block is evident on the posterior wall. **Figure** 4 demonstrates an anterior view of the LA of the same patient, also demonstrating a line of block at the anterior wall.

One (33%) patient with persistent AF had two slow conduction zones in the RA, situated at the posteroseptal atrial wall and the superior vena cava, without lines of block, while two patients (66%) with persistent AF demonstrated > 2 slow conduction corridors, located at the low septum and the anterior wall, respectively. Total number of slow conduction corridors at the RA were 3 versus five in the LA. A mean of 1.25±0.9 slow conduction corridors per patient were recorded in the RA (0.2±0.4 per patient with PAF and 0.6±0.9 per patient with persistent AF). A mean of 0.6±0.6 areas of slow conduction corridors per patient were recorded in the LA (0.6±0.8 per patient with PAF and 0.6±0.4 per patient with persistent AF).

TABLE 2 Electrophysiological atrial characteristics stratified by AF type

	Total	Paroxysmal	Persistent	*p*-value
Patients, n (%)	8	5 (62.5%)	3 (37.5%)	N/A
Procedure time (min±SD)	186.1±15.0	182.6±14.4	192.0±17.1	.472
Fluoro time (min±)	30.9±14.4	25.8±8.9	39.3±20.0	.221
RA LVA	6 (75%)	3 (60%)	3 (100%)	.464
LA LVA	4 (50%)	2 (40%)	2 (66%)	1.000
RA LVA area (cm^2)	7.4±6.7	4.8±7.3	11.7±3.0	.115
LA LVA area (cm^2)	5.7±10.7	7.8±13.6	2.1±1.8	.405
RA LVa	6 (75.0%)	3 (60.0%)	3 (100.0%)	.464
Septal	4 (50.0%)	1 (20.0%)	3 (100.0%)	
Anterior	3 (37.5%)	2 (40.0%)	1 (33.3%)	
Inferior	2 (25.0%)	1 (20.0%)	1 (33.3%)	
LA LVA	4 (50.0%)	2 (40.0%)	2 (66.7%)	1.000
Anterior	2 (25.0%)	2 (40.0%)	0 (0.0%)	
Posterior	2 (25.0%)	2 (40.0%)	0 (0.0%)	
Mitral istmus	2 (25.0%)	0 (0.0%)	2 (66.7%)	
P wave duration (ms)	124.6±18.5	117.7±12.0	128.8±21.7	.387
RA latest activation (ms)	64.9±11.2	58.3±12.2	68.8±9.7	.283
LA earliest activation (ms)	14.1±5.7	11.7±2.3	15.6±6.9	.293
RA slow conduction	2 (25.0%)	1 (20.0%)	1 (33.3%)	1.000
Location of RA slow conduction		Posteroseptal	Posteroseptal/Supe vena cava	N/A
RA lines of block	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.000
LA slow conduction	4 (50.0%)	2 (40.0%)	2 (66.7%)	1.000
Anterior	3 (37.5%)	2 (40.0%)	1 (33.3%)	
Posterior	1 (12.5%)	1 (20.0%)	0 (0.0%)	
Septum	1 (12.5%)	0 (0.0%)	1 (33.3%)	
Location of LA slow conduction		Anterior/posterior	Septum/anterior	N/A
LA lines of block	2 (25.0%)	2 (40.0%)	0 (0.0%)	.464
RA EGM analysis				
°Fractionation	7.00±3.77%	4.70±1.91%	10.83±2.68%	.036
°Line of block	1.01±1.47%	1.20±1.86%	0.70±0.66%	.610
°Wavefront collision	0.11±0.18%	0.04±0.09%	0.23±0.25%	.321
LA EGM analysis				
°Fractionation	6.39±4.25%	4.08±2.22%	10.26±4.19%	.108
°Line of block	1.99±2.22%	1.96±1.73%	2.03±0.34%	.975
°Wavefront collision	0.04±0.07%	0.02±0.04%	0.07±0.01%	.561

Abbreviation: LVA, Low voltage area.

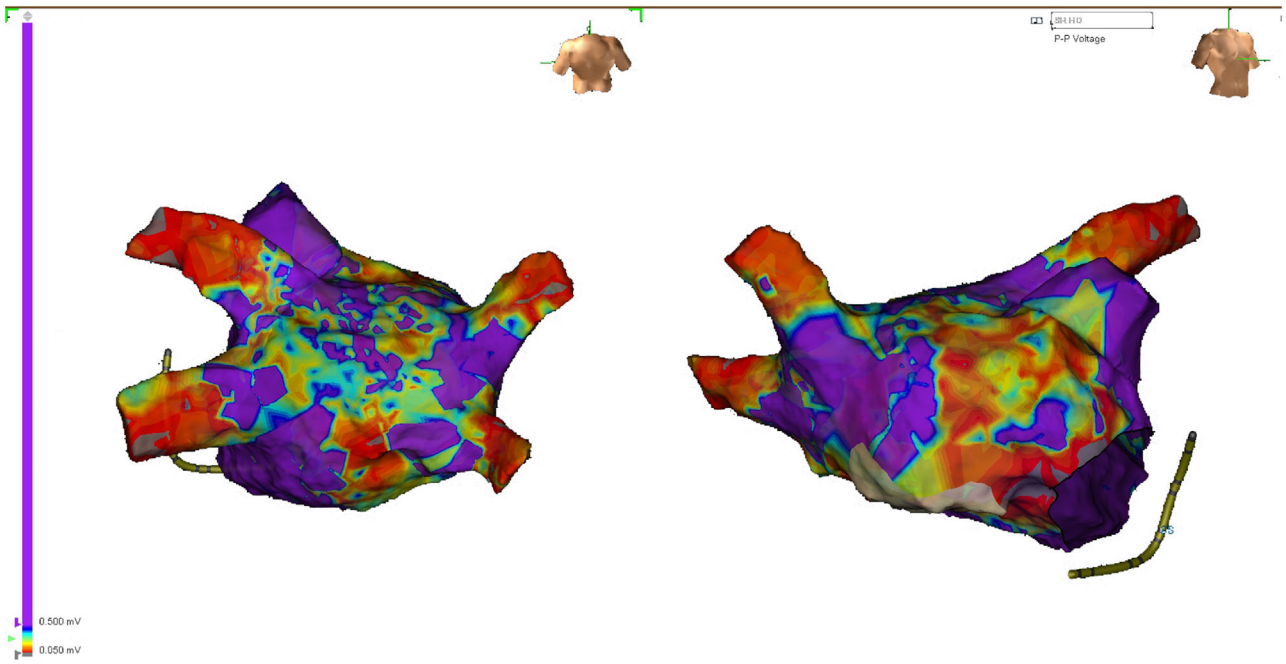

FIGURE 2 Voltage map of left atrium with patchy distribution on the anterior wall of the left atrium in patients with paroxysmal AF [Color figure can be viewed at wileyonlinelibrary.com]

3.5 | EGM analysis

Fractionation was detected in 6.7% of EGMs over a total of 1809±343 EGMs (per patient) analyzed. Prevalence of fractionated EGMs in the RA was 6.9% compared to 6.4% in the LA, a statistically non significant difference ($p = .769$), with slow conduction being the predominant phenomenon. (mean amplitude 0.26±0.07 mV). EGMs corresponding to double potentials were 1.7% (mean amplitude of 0.24±0.14 mV). Amongst double potentials signals, EGMs corresponding to line of block were 86.1% with a mean amplitude of 0.12±0.14 mV while those due to wavefront collision were 13.9% with a mean amplitude of 0.11±0.09 mV. The presence of fractionated signals was significantly greater in persistent AF versus paroxysmal cases (4.7 vs. 10.8%, $p = .036$, Figure 5). There was no significant difference in the occurrence of abnormal EGMs between the left and right atrium.

4 | DISCUSSION

The main findings of this study are: (I) bi-atrial disease exists in patients suffering from AF; and (II) slow conduction and extended areas of low voltage represent the common electrophysiological substrate.

4.1 | The electrophysiological substrate

AF is the result of the presence of a set of structural and functional factors that lead to the formation (induction) of microreentry circuits and subsequently to their sustainment. Structural factors, recognizable as slow conduction or blocking phenomena are observed on EGMs and activation patterns[5] and are the result of fibrosis. This in turn, induces changes in the conduction and refractory properties of the t issue.[25]

In our study, the number of slow conduction corridors was higher in the left atrium: this suggests the direct involvement of this chamber in the induction and maintenance of AF.[23] Patients with paroxysmal AF presented less areas of slow conduction in the RA, and, as expected, more areas of conduction slowing in the LA. The importance of slow conduction in the setting of paroxysmal AF is not known at the present time. It may represent a potential anchor for rotors in the development of microreentrant circuits which may form the base of persistent AF.[16–20] Slow conduction and lines of block play a significant role, particularly in persistent AF.[15] Our study recorded these phenomena at the low septum and the anterior wall. Such specific localization must be further investigated in future studies. The septum has been called a potential site of signal fractionation in the seminal works of Haïssaguerre.[26] The point-by-point EGM analysis showed that all patients already had a high prevalence of fractionated signals. Interestingly, prevalences were numerically higher in persistent AF patients. The greater prevalence of fractionated signals was seen in the right atrium as well, despite the low sample size and interestingly, was seen to reach statistical significance.

Surprisingly, no lines of block were recorded in the persistent group of our research study: this may either be due the low number of patients mapped and due to mapping being carried out in sinus rhythm. During faster paced rhythms, larger areas of slow conduction and lines

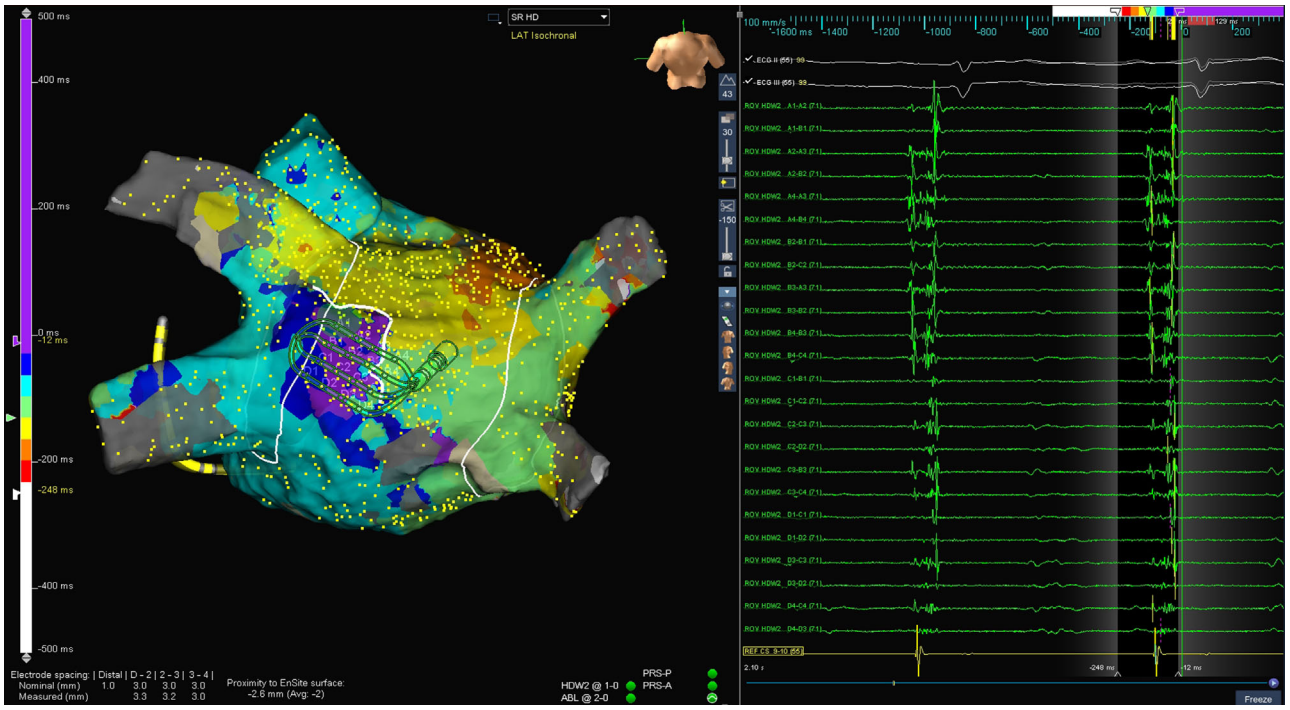

FIGURE 3 Activation mapping of the left atrium: a line of block is evident at the posterior wall [Color figure can be viewed at wileyonlinelibrary.com]

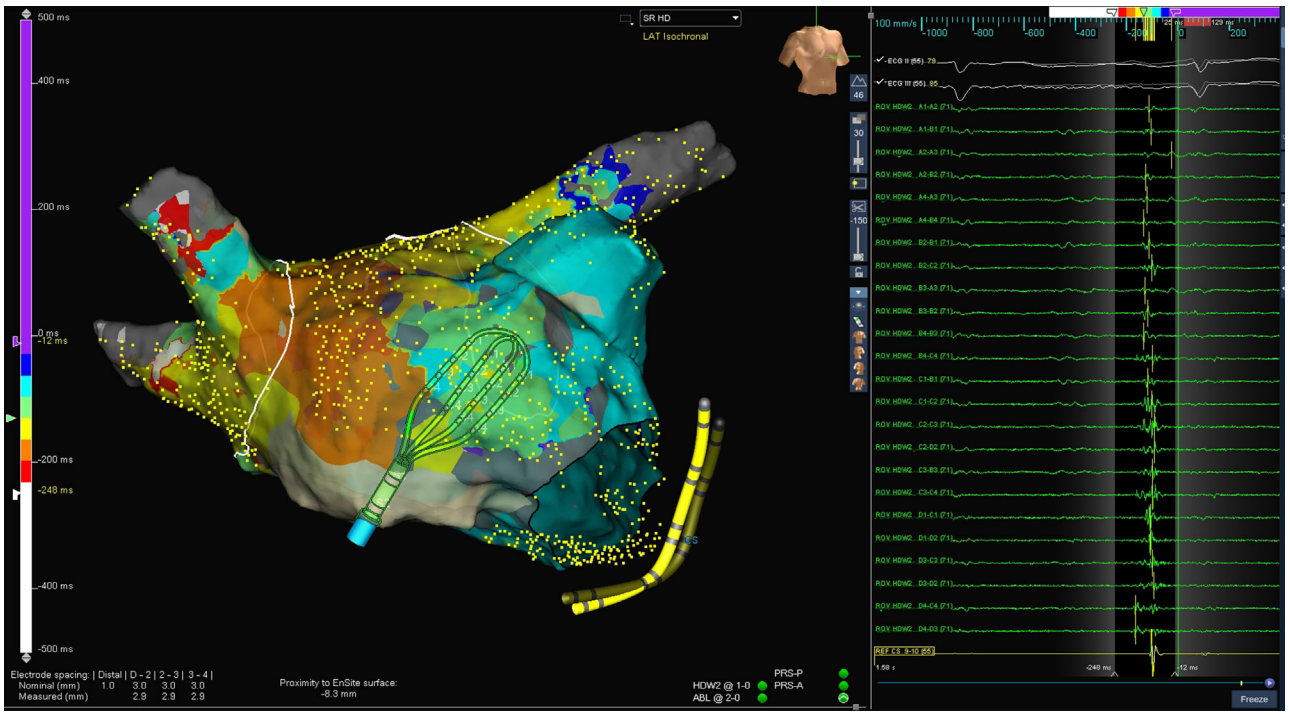

FIGURE 4 Activation map of the left atrium. A line of block is present at the anterior wall of the left atrium [Color figure can be viewed at wileyonlinelibrary.com]

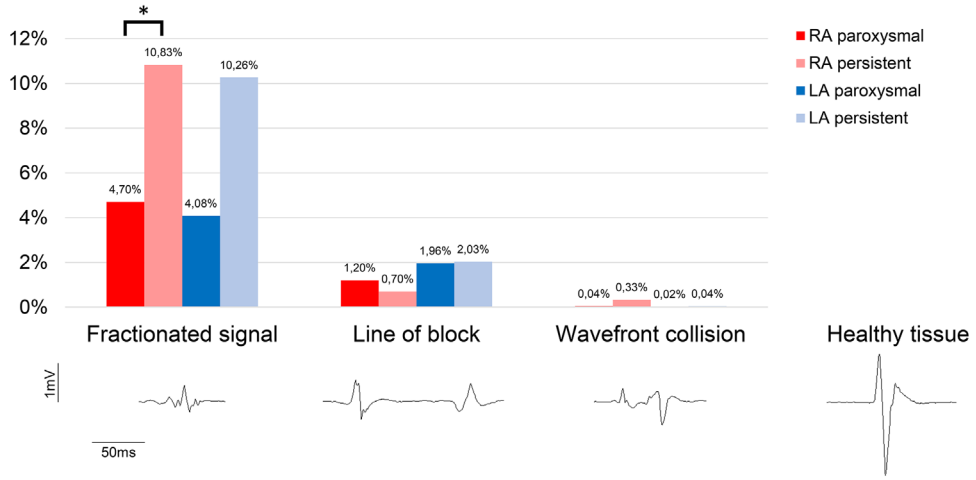

FIGURE 5 Individual EGM signal analysis showed that fractionated signals were more prevalent in both atria of patients with persistent AF. Lines of block were prevalent in the LA of persistent cases [Color figure can be viewed at wileyonlinelibrary.com]

of block may have been unmasked. Furthermore, a low number of EGM signals indicating lines of block were found in most atria.

4.2 | Low voltage area

In the RA, LVA was present in the 60% of paroxysmal patients versus 100% of persistent AF patients. Indeed, LA presented low voltage in 40% patients of paroxysmal AF and two thirds of patients with persistent AF. The relationship of low voltage with slow conduction has already been demonstrated.[17] Wherever signal fractionation occurs, it demonstrate slow amplitude and long duration, and must be assigned as an EGM signature of slow conduction.[22] The authors of the above mentioned manuscript have also demonstrated that EGM amplitude is a function of conduction velocity according to a logarithmic relationship.[24]

4.3 | Mapping both atria or is the LA alone enough?

This research study is the first to characterize the substrate of both atria in patients undergoing AF ablation. This may lead to future studies in which an improved comprehension of the atrial substrate and AF mechanisms can be ascertained by mapping both atria either simultaneously or sequentially. The electrophysiological mechanisms (slow conduction, lines of block, wavefront collision) are at the base of the dynamic and fixed mechanisms of the substrate.[15] Our research demonstrates that the mapping of both atria is feasible, adding only a mean of 12.3±8.1 min to traditional LA only mapping. In this study, a high prevalence of fractionated signals in the RA was significantly associated with persistent AF while in the LA it was not, indicating that mapping of the RA could also add prognostic information. The two atria are connected via specific electrical connections. This has shown in a seminal work by Antz et al.[14] This study also raises the question as to how both atria communicate when there is diffuse fibrosis. We hope that the use of multielectrode multispline mapping tools will further characterize the atrial substrate and resolve this issue.

4.4 | Limitations

While this study is the first of its kind to show the feasibility of high-density mapping of both atria in patients undergoing PVI, a few limitations have to be kept in mind. First, the low sample size may have masked associations that might have become significant otherwise. Second, to keep the procedure time short, no pace-map was performed, which may have revealed rate-dependent electrophysiological phenomena. The absence of mapping during pacing from multiple sites in the atrium may limit accurate delineation of the atrial substrate and EGM characteristics.

Third, the lack of a control group hinders the comparison of electrophysiological phenomena and EGM signal characteristics between patients with paroxysmal AF and healthy patients. This limitation is particularly notable in the era of multielectrode high-density mapping, where bipolar voltage cutoffs for healthy atrial tissue may in fact differ from the standard threshold values of 0.5 mV and 0.05 mV.

5 | CONCLUSIONS

In paroxysmal and persistent AF, there is bi-atrial involvement expressed by slow conduction, lines of block, and low voltage areas.[21] This electrophysiological substrate demonstrates the important interplay with the pulmonary vein triggers to create the electrical substrate required for the persistence of the AF. Further studies should be pursued to elaborate on this key finding and to further clarify the pathophysiology of AF.

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CONFLICT OF INTEREST

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