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Association of left atrium voltage amplitude and distribution with the risk of atrial fibrillation recurrence and evolution after pulmonary vein isolation: An ultrahigh-density mapping study

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Abstract

Introduction: Ultrahigh-density-voltage mapping (uHD$_V$M) is a new tool that can add new insights into the pathophysiology of atrial fibrillation (AF). The aim of this study was to evaluate the performance of uHD$_V$M in predicting postablation AF recurrence (AFR).

Methods and Results: We included 98 consecutive patients undergoing pulmonary vein isolation for AF (40.8% persistent) using an uHD$_V$M system and followed for 1 year. The left atrium (LA) mean voltage (V_m) and the V_{slope} (slope of the voltage histogram calculated by linear interpolation, with the relative frequency on the vertical axis and the bipolar potential on the horizontal axis) were calculated from 12 567 ± 5486 points per map.

Patients with AFR (N = 29) had lower V_m and higher V_{slope} as compared with patients without AFR (N = 69). Receiver operating characteristic curves identified V_m as the strongest predictor of AFR, with a higher incidence of AFR in patients with V_m 0.758 mV (57.6%) or lower than patients with V_m higher than 0.758 mV (15.4%; $P < .0001$). Among patients with V_m higher than 0.758 mV, patients with V_{slope} 0.637 or higher exhibited higher ($P = .043$) AFR incidence (31.3%) than patients with V_{slope} lower than 0.637 (10.2%). This classification showed incremental predictive value over relevant covariables. V_m values were lower and V_{slope} values were higher in patients that progressed from paroxysmal to persistent AF. Patients with V_{slope} 0.637 or higher had a 14.2% incidence of postablation atypical atrial flutter, whereas patients with V_{slope} lower than 0.637 did not present this outcome.

Gabriel Ballesteros and Susana Ravassa contributed equally to this work.

Conclusions: The risk of AFR, atrial flutter, and progression from paroxysmal to persistent AF can be detected by quantitative analysis of LA uHD$_V$M identifying diverse patterns of atrial substrate alterations.

KEYWORDS
atrial fibrillation ablation, atrial fibrosis, atrial heterogeneity, rhythmia mapping system, ultrahigh-density mapping

1 | INTRODUCTION

The relationship between atrial fibrosis and AF has been demonstrated in histological studies.[1,2] Electroanatomical mapping (EAM) has become the gold standard, an invasive method for the characterization of the so-called atrial cardiomyopathies,[3] as it allows the recording and delimitation of areas of diverse voltages in the atrial wall. There is a general consensus that regions with low-voltage potentials are usually due to atrial fibrosis. These low-voltage areas are more prevalent in patients with AF than in those without[4] and are present in the whole range of patients with this disease, from patients with lone AF[5] to those with persistent forms.[6] In addition, its presence is a predictor of arrhythmic recurrence after ablation.[7]

Most previous studies have focused on quantifying dense scar and areas of severe patchy fibrosis using EAM, reporting the percentage of the total atrial area below a certain empirically determined voltage value as the main parameter.[8-16] Vlachos et al[17] recently described the area below 0.4 mV as a predictor of AF recurrence in high-density voltage atrial maps, with a median number of 2485 points per map. Atrial mean voltage (V_m) measured with uHD$_V$M could represent a more accurate parameter of global fibrosis, detecting not only areas of severe patchy fibrosis but also diffuse interstitial fibrosis. Besides, although tissue heterogeneity is usually considered a key element in the pathophysiology of arrhythmias, to the best of our knowledge, there are no specific markers of it in AF patients. We, therefore, aimed to evaluate the performance of uHD$_V$M to predict the risk of AF recurrence after ablation, assessing not only V_m but also a parameter reflecting tissue heterogeneity (ie, the slope of the voltage histogram or V_{slope}).

2 | METHODS

We prospectively included 98 consecutive patients with paroxysmal or persistent AF for pulmonary vein isolation (PVI) using an uHD$_V$M system in our institution. Patients with previous ablation lines or other surgical scars in the left atrium (LA), except for PVI, were excluded. An independent cohort of patients without previous LA ablation procedures was studied to confirm the main findings of the original group. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. All patients gave their informed consent.

2.1 | Description of the ultrahigh-density mapping and ablation procedure

The strategy for map building and ablation was performed following our standard protocol, which has been previously described in detail.[18,19] Briefly, the day before the procedure, all patients underwent computed tomography (CT) examination and left LA anatomy was characterized by segmentation and three-dimensional reconstruction. If the patient was in AF, electrical cardioversion was performed before starting the procedure. Mapping of the LA was conducted with a uHDM system (Rhythmia; Boston Scientific Corporation, Marlborough, MA) and a 64-electrode basket-type catheter (IntellaMap Orion, Boston Scientific Corporation) during paced atrial rhythm. Bipolar electrogram recordings were filtered at 40 to 400 Hz and were displayed on a commercially available electrophysiological recording system (EP-Tracer V1.0.5.12; Schwarzer Cardiotek, Heilbronn, Germany). The appropriate beats and electrograms were automatically selected by the mapping system and each point acquired was classified according to the peak-to-peak bipolar voltage. Only points located within 2 mm of the external surface of the map were considered for analysis.

After mapping, PVI was performed in all cases following a previously described protocol.[18,19] De novo PVI procedures were performed by standard point-by-point ablation, creating wide ablation circles around the PVs, while redo procedures were performed by the analysis of the activation maps and focal ablation at the reconnection gaps. In all cases, isolation was confirmed with the insertion of an Orion catheter within the PVs and its subsequent expansion. In the event of confirmation of entrance block, the pacing was performed from the equatorial electrodes of the Orion catheter to confirm exit block. In all cases and for each of the isolated veins, an intravenous bolus of adenosine was administered with the Orion catheter inside the vein and a focal ablation was performed in the event of an observed reconnection. Isolation was confirmed in all cases a minimum of 20 minutes after the last radiofrequency application.

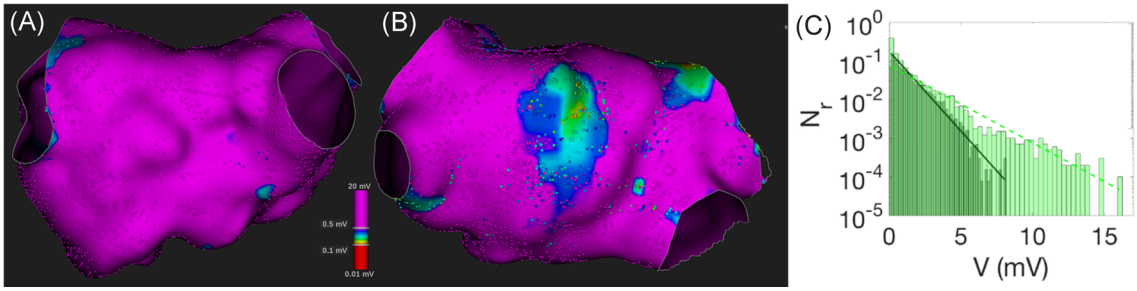

FIGURE 1 Examples of high-density maps with its correspondent voltage histograms. High-density voltage LA maps of two different AF ablation index procedures from a posterior view (A,B) with similar V_m (1.21 and 1.19 mV, respectively) but different V_{slope} (0.46 and 0.95, respectively). C, Voltage histograms with its correspondent slope of A (light green) and B (dark green). LA, left atrium; N_r, relative frequency; mV, millivolts; V, voltage

2.2 | Quantitative map analysis

For each of the patients, one LA uHD$_V$M was acquired before ablation. Then, the pulmonary veins (PV) and the LA appendage were removed from the EAM. In the case of redo procedures, the previous PV encircling ablation lines, defined by the operator based on the interpretation of the activation map as previously described,[19] were removed along with the PV. Subsequently, the map was converted into a format directly readable by MATLAB software (The Mathworks Inc, Natick, MA) for further mathematical analysis. The voltage map is a geometrical surface in three dimensions that is defined by a triangular lattice. The average number of triangle faces was 16 990 ± 4578. In this mesh grid, the average area for the triangle faces was approximately one square millimeter and followed a nearly Gaussian distribution. The value of the bipolar potentials was expressed in millivolts (mV) at each vertex site.

For each map, the following parameters were calculated. (a) The spatial average value of all bipolar potentials on the LA surface (V_m). (b) The slope of the voltage histogram (V_{slope}), where we represent the relative frequency in a logarithmic scale on the vertical axis and the bipolar potential on a linear scale on the horizontal axis. Since the voltage distribution typically follows an exponential distribution, we chose the slope of the scatterplot in these linear-log scales as the simplest way to characterize it. We then verified that the corresponding adjusted R^2 was appropriate and that the 95% confidence interval for the slope estimation was rather narrow. We used the Matlab command "hist(y,M)" for the binning method, with M number of bins set to 50 for all the analyzed data sets. The bin width was set by default and was almost constant on the range of the horizontal variable. From this scatter plot we used linear interpolation to calculate the slope. By measuring the histogram slope we obtained a characteristic voltage decay for each patient (expressed in mV^{-1}) (Figure 1). Because all V_{slope} values were negative, we used the absolute values, therefore, the higher the value, the steeper the decay and the greater the voltage heterogeneity. (c) The relative area below several predefined voltage threshold values: 0.1, 0.4, 0.5, 0.8, and 0.9 mV.

2.3 | Follow-up

Patients were followed-up in the outpatient clinic at 3, 6, and 12 months after discharge with 12-lead ECG and 24-hour Holter ECG. Nonscheduled visits were performed if patients presented with any symptoms suggestive of AF. Episodes of AF or other atrial arrhythmias lasting longer than 30 seconds were considered for analysis. Episodes that occurred after ablation with a blanking period of the first 3 months were considered to indicate arrhythmia recurrence. Antiarrhythmic drugs were usually continued for the first 3 months after ablation and then systematically discontinued.

2.4 | Statistical analysis

Quantitative variables are presented as a mean ± standard deviation or as the median and 25 and 75 percentiles. Categorical variables are presented as a number and a percentage. Normality was demonstrated using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Differences between two groups of subjects were tested using Student *t* test for unpaired data once normality was demonstrated; otherwise, a nonparametric test (Mann-Whitney *U* test) was used. Differences between three groups of subjects were tested by one-way analysis of variance followed by the least significant difference test (Fisher test) once normality had been checked; otherwise, the nonparametric the Kruskal-Wallis test followed by a Mann-Whitney *U* test was used. Baseline characteristics were compared between patients using the χ^2 test or the Fisher exact test for categorical variables. Linear tests for trend were used to assess any tendencies across the different groups.

Receiver operating characteristic (ROC) curves allowed estimation of the strength of association with AF recurrence of the parameters considered. Logistic regression analyses were used to calculate the odds ratios (OR) and their corresponding 95% confidence intervals for the risk of future AF recurrence, adjusting for covariables with $P < .1$ in univariable analyses. Multicollinearity was evaluated by examining the variance inflation factor. Calibration of the logistic models was assessed using the Hosmer-Lemeshow goodness-of-fit test. The additional value of the parameters evaluated for risk prediction of the outcome was

assessed with the Harrell C statistics and the continuous net reclassification index (NRI) estimate by using the STATA commands "somersd" and "incrisk", respectively.

The statistical analysis was performed using version 22 of SPSS software (15.0 version, SPSS Inc, Chicago, IL) Statistics for Windows and STATA version 12.1 (STATA software, version 12.1, Stata Corp, College Station, TX).

3 | RESULTS

A total number of 98 patients underwent PVI guided by uHD$_V$M system. The mean age was 64.5 years, 32.7% were female, with paroxysmal (59.2%) or persistent (40.8%) AF, scheduled for index (58.2%) or redo (41.8%) AF ablation procedure. A preablation LA map was performed in all patients with 12 567 ± 5486 points per map in 17.4 ± 6 minutes, followed by PVI using point-by-point radiofrequency energy.

Tables E1,E2 summarizes the baseline characteristics and main comorbidities according to V_m and V_{slope} tertiles, respectively.

Persistent AF was associated with low V_m (63.6%, 30.3%, and 28.1% of persistent AF in the first, second, and third tertiles of V_m, respectively, $P = .004$) and high V_{slope} (12.5%, 45.5%, and 63.6% of persistent AF in the first, second, and third tertiles of V_{slope}, respectively, $P < .0001$). Both associations were independent of age, sex, and LA volume.

In total, AF recurrence during the first year after the PVI procedure occurred in 29 (29.6%) patients (Table 1). Patients with AF recurrence had lower V_m (0.71 ± 0.4 vs 1.22 ± 0.6 mV, $P < .0001$) and higher V_{slope} (median [interquartile range, IQR]: 0.90 [0.65-1.25] vs 0.57 [0.45-0.79], $P = .0003$) at baseline. Coherently, AF recurrence was more frequent in the first V_m tertile (57.6%) compared with the second (15.2%, $P < .001$), and third (15.2%, $P < 0.001$) tertiles (Figure 2A), and in the third V_{slope} tertile (48.5%) compared with the first tertile (12.5%, $P = .004$) but not with the second tertile (27.3%, $P = .08$) (Figure 2B).

We considered as potentially confounding variables those showing associations ($P < .1$) with AF recurrence in univariate analyses (Table E3). Univariate analyses showed that V_m and V_{slope} were associated with AF recurrence (Table E5). These associations remained significant accounting for the confounding variables: age and sex (model 1), persistent AF and LA volume (model 2), and previous ablation procedure (model 3) (Table E5). The addition of V_m and V_{slope} to relevant variables improved reclassification of patients at risk of AF recurrence (Table 2).

The area under the ROC curve (AUC_{ROC}) of V_m for predicting AF recurrence was 0.757 (95% CI, 0.650-0.864, $P < .0001$) rendering a cutoff value (Youden index) of 0.758 mV with a sensitivity and specificity of 79.7% and 65.5%, respectively ($\chi^2 = 18.7$, $P < .0001$). The AUC_{ROC} of V_m for predicting AF recurrence was significantly greater than the AUC_{ROC} of the LA volume measured by computed tomography (0.611; 95% CI, 0.485-0.737; $P = .049$) (Figure 2C). Interestingly, none of the AUC_{ROC} estimated cutoff values for the other voltage map parameters were significantly greater than the AUC_{ROC} of LA volume, including the percentage of area with voltage below 0.5 mV (Table E4).

TABLE 1 Baseline clinical characteristics in patients classified according to recurrence of AF

	Recurrence of AF		
	No (n = 69)	Yes (n = 29)	*P* value
Age, y	63.4 ± 9	67.2 ± 9.3	.06
Sex, female, n (%)	17 (24.6)	15 (51.7)	.009
BMI, kg/m^2	28.1 ± 4.3	27 ± 3.5	.24
SBP, mm Hg	124 ± 13.6	128 ± 14.9	.12
DBP, mm Hg	77 ± 10.6	78.8 ± 13.8	.49
eGFR, 1.73 m^2, ml/min	81.1 ± 21.4	81.3 ± 10.3	.98
Treatment, n (%)			
Antiarrhythmic	28 (40.6)	14 (48.3)	.48
Calcium antagonists/BB	32 (46.4)	16 (55.2)	.43
Statins	23 (33.3)	13 (44.8)	.25
ACE inhibitor/ARB	37 (53.6)	16 (55.2)	.85
Diuretics	15 (21.7)	7 (24.1)	.75
Comorbidities, n (%)			
Obesity	19 (27.5)	5 (17.2)	.32
Hypertension	39 (56.5)	17 (58.6)	.85
Dyslipidemia	32 (46.4)	17 (58.6)	.27
Diabetes	8 (11.6)	5 (17.2)	.45
Sleep apnea	10 (14.5)	2 (6.9)	.30
CPAP use	7 (10.1)	1 (3.4)	.27
Renal failure	2 (2.9)	1 (3.4)	.99
Medical history, n (%)			
Stroke	2 (2.9)	1 (3.4)	.99
Heart failure	7 (10.1)	2 (6.9)	.61
Peripheral vascular disease	2 (2.9)	0	
Ischemic cardiomyopathy	4 (5.8)	0	
Neoplasia	5 (7.2)	2 (6.9)	.95
Type of AF, n (%)			
Paroxysmal	46 (66.7)	12 (41.4)	.020
Persistent	23 (33.3)	17 (58.6)	
Duration of AF, months	24 (1.0-216)	24 (1.0-120)	.90
Prior flutter ablation, n (%)	5 (7.2)	4 (13.8)	.31
LA computed tomography			
LA diameter, mm	59.9 ± 7.2	63.3 ± 7	.032
LA volume, ml	118 ± 34.4	131 ± 44.4	.20
LA echocardiography			
LVEF, %	60.7 ± 8	63.4 ± 5	.10
LA volume index, ml/m^2	28.5 ± 13.2	36.8 ± 14.5	.008
Reprocedure, n (%)	34 (49.3)	7 (24.1)	.021

Note. Quantitative variables are expressed as mean ± SD or median (interquartile range) and categorical variables as numbers (percentages).
Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II type 1 receptor; BB, beta-blockers; BMI, body mass index; CPAP, positive pressure therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; LA, left atrial; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Among patients without low V_m ($V_m > 0.758$ mV), the V_{slope} was significantly higher in patients with AF recurrence as compared with patients without AF recurrence (0.64 [0.50-0.75] vs 0.51 [0.42-0.62], $P = 0.047$). In fact, among patients with a V_m higher than 0.758 mV, V_{slope} could be used to discriminate the risk of recurrence (AUC, 0.709; 95% CI, 0.529-0.888; $P = .047$) with a

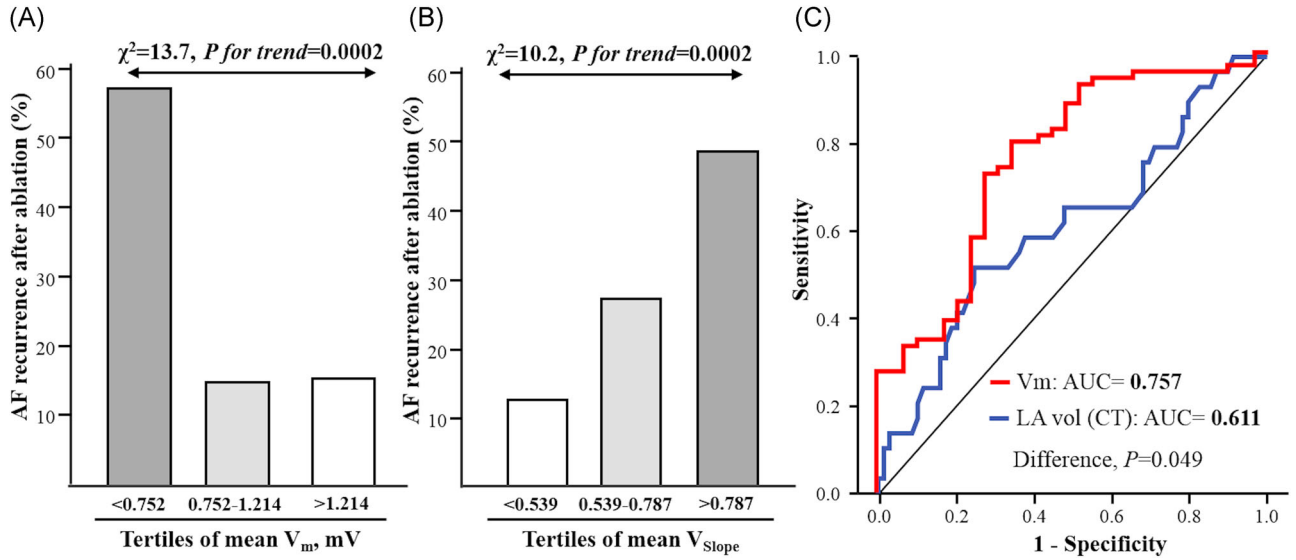

FIGURE 2 Mean voltage (V_m), V_{slope}, and atrial fibrillation (AF) recurrence. Incidence of AF recurrence among study subgroups based on the classification of patients according to tertiles of V_m (A) and V_{slope} (B). C, ROC curves for V_m (red line) and LA volume (blue line), plotted for various cut-off values, for determining AF recurrence. AUC, area under the curve; CT, computed tomography; LA, left atrium; ROC, receiver operating characteristic

cutoff point (Youden index) of 0.637. When combining both parameters, V_{slope} identified a group of patients with intermediate risk: the presence of high V_m (>0.758 mV) and high V_{slope} (≥0.637) was associated with a 31.3% recurrence rate, lower than patients with low V_m (57.6%) but significantly higher than patients with high V_m and low V_{slope} (10.2%, $P = .043$) (Figure 3). The Harrells C and continuous NRI indicated that the addition of the V_m/V_{slope} classification to relevant covariables improved AF recurrence prediction (Table 3).

Twelve patients with paroxysmal AF developed arrhythmia recurrence, nine of them remained paroxysmal and three progressed to persistent AF. Interestingly, V_m values at baseline were lower (0.37 ± 0.25 vs 0.95 ± 0.30 mV, $P = .018$) and V_{slope} values at baseline were higher (median 1.65 [1.29-3.10] vs 0.66 [0.51-0.84], $P = .036$) in patients that progressed from paroxysmal to persistent AF as compared with patients that remained paroxysmal (Figure 4A).

Of the 29 patients with arrhythmia recurrence, postablation atrial flutter occurred in seven. No significant differences were observed in V_m values between these patients and patients with AF recurrence without atrial flutter (0.51 ± 0.36 vs 0.78 ± 0.40 mV, $P = .09$). In contrast, patients with arrhythmia recurrence in the form of atrial flutter did exhibit an increase in V_{slope} values when compared to patients with AF recurrence without atrial flutter (median [IQR]: 1.30 [0.95-2.84] vs 0.73 [0.58-0.97], $P = .003$), and both groups had higher V_{slope} values compared with patients without any arrhythmia recurrence (0.57 [0.45-0.77], $P < .001$) (Figure 4B). Patients with V_{slope} 0.637 or higher had a 14.2% incidence of postablation atypical atrial flutter whereas patients with V_{slope} higher than 0.637 did not present this outcome.

3.1 | Sensitivity analyses

Excluding patients who had undergone prior AF ablation the crude OR of having AF recurrence associated with a V_m 0.758 mV or lower was 15.4 (95% CI, 3.59-66.1; $P < .0001$). This association was independent of age (OR, 15.1; 95% CI, 3.51-65.3; $P < .0001$), sex (OR, 12.5; 95% CI, 2.72-57.7; $P = .001$), persistent AF (OR, 14.2; 95% CI, 3.05-66.3; $P = .001$), and LA volume (OR, 12.7; 95% CI, 2.84-56.5; $P = .001$). The crude OR of having AF recurrence associated with a V_{slope} 0.637 or higher in these patients was 11.5 (95% CI, 3.22-40.9; $P < .001$). This association was also independent of age (OR, 13.3; 95% CI, 3.33-52.8; $P < .001$), sex (OR, 13.4; 95% CI, 3.11-57.3; $P < .001$), persistent AF (OR, 9.29; 95% CI, 2.48-34.9; $P = .001$), and LA volume (OR, 11.0; 95% CI, 2.95-40.9; $P < .001$).

Continuous NRI estimates indicated that the addition of the V_m/V_{slope} classification, as previously defined, to relevant covariables such as age (NRI, 1.09; 95% CI, 0.64-1.51; $P < .0001$), sex (NRI, 1.12; 95% CI, 0.62-1.56; $P < .0001$), persistent AF (NRI, 1.03; 95% CI, 0.67-1.53; $P < .0001$), and LA volume (NRI, 1.20; 95% CI, 0.69-1.58; $P < .0001$) improved AF recurrence prediction in patients without previous AF ablation.

Finally, to confirm the main findings of this study, we conducted a prospective analysis of LA uHD_VM of an independent cohort of 41 patients scheduled for first AF ablation procedure. Using the same cutoff values, we found that patients with V_m lower than 0.758 had an incidence of AF recurrence of 50%, significantly higher than patients with V_m higher than 0.758 (12.1%, $P = .015$). Once again, patients with V_m higher than 0.758 but V_{slope} 0.637 or higher had a 20% incidence of AF recurrence, lower than patients V_m higher than 0.758 (50%) but higher than

TABLE 2 Odds ratio and added the predictive value of V_m and V_{slope} for AF recurrence

Statistic parameter	Value	95% CI[a]	*P* value
Mean voltage (V_m)			
Logistic regression analysis			
Unadjusted analysis	0.32	0.17-0.58	.0002
BM1	0.32	0.17-0.60	.0004
BM2	0.36	0.19-0.67	.001
BM3	0.21	0.10-0.44	<.0001
Added predictive value			
Harrell's C			
BM1	0.674	0.554-0.794	
BM1 + V_m	0.797	0.701-0.894	.044
BM2	0.655	0.529-0.782	
BM2 + V_m	0.765	0.660-0.869	.052
BM3	0.626	0.525-0.726	
BM3 + V_m	0.853	0.766-0.940	<.0001
NRI			
BM1 + V_m	0.79	0.26-1.21	.001
BM2 + V_m	0.76	0.25-1.17	.001
BM3 + V_m	0.95	0.57-1.41	<.0001
Slope of the voltage histogram (V_{slope})			
Logistic regression analysis			
Unadjusted analysis	3.15	1.58-6.28	.001
BM1	3.39	1.66-6.92	.001
BM2	2.69	1.30-5.57	.007
BM3	4.64	2.01-10.	<.0001
Added predictive value			
Harrell's C			
BM1	0.674	0.554-0.794	
BM1 + V_{slope}	0.781	0.678-0.884	.09
BM2	0.655	0.529-0.782	
BM2 + V_{slope}	0.749	0.642-0.856	.08
BM3	0.626	0.525-0.726	
BM3 + V_{slope}	0.796	0.691-0.902	.003
NRI			
BM1 + V_{slope}	0.79	0.29-1.16	.0004
BM2 + V_{slope}	0.76	0.10-1.05	.002
BM3 + V_{slope}	0.83	0.49-1.29	<.0001

Note. Odds ratios were expressed for a doubling of V_m and V_{slope}, and adjusted by baseline model 1 (BM1) (age and sex), BM2 (persistent AF and CT-LA_{Volume}), and BM3 (redo procedure, yes/no).

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CT, computed tomography; LA, left atrial; NRI, net reclassification improvement.

[a]The variance was calculated using bootstrapping (with 1000 resamples) for the NRI estimates and the jack-knife approach for the Harrell C estimates.

patients with V_m higher than 0.758 and V_{slope} lower than 0.637 (8.7%, $P = .015$ for linear association).

4 | DISCUSSION

The main findings of this study, using two complementary parameters to assess the LA electrical activity in AF patients, are the following: First, a low V_m is associated with a very high risk of post-PVI AF recurrence, with a greater association with arrhythmia reappearance than any clinical parameter, atrial size or other voltage map finding. Second, in the absence of low V_m, a high V_{slope} identifies a group of patients with intermediate risk and adds incremental value when combined with clinical and echocardiographic findings. Third, the combination of high V_m and low V_{slope} is associated with a very low risk of post-PVI AF recurrence. Fourth, the clinical progression of the disease, from paroxysmal to persistent AF, seems to be preceded by low V_m and high V_{slope}. Finally, in patients with seemingly low atrial heterogeneity, as assessed as a low V_{slope}, postablation atrial flutter is very infrequent.

Most clinical studies on atrial fibrosis evaluation by EAM have focused on the area below a predetermined voltage value. This approach seems appropriate for detecting replacement fibrosis but not for interstitial fibrosis, since in the latter the limit between normal and abnormal tissue is not well defined. Considering this, we instead studied the V_m variable as an indicator of global fibrosis. Our results show that the reduction of V_m is an independent predictor of AF recurrence and that low V_m values showed a greater association with arrhythmia recurrence than any other finding. Besides, the association between high atrial volume and persistent AF, and AF recurrence is significantly diminished when the "voltage factor" is removed (Figure 5), suggesting that its association with a worse prognosis after PVI could be mainly because this are markers of a higher probability of atrial fibrosis.

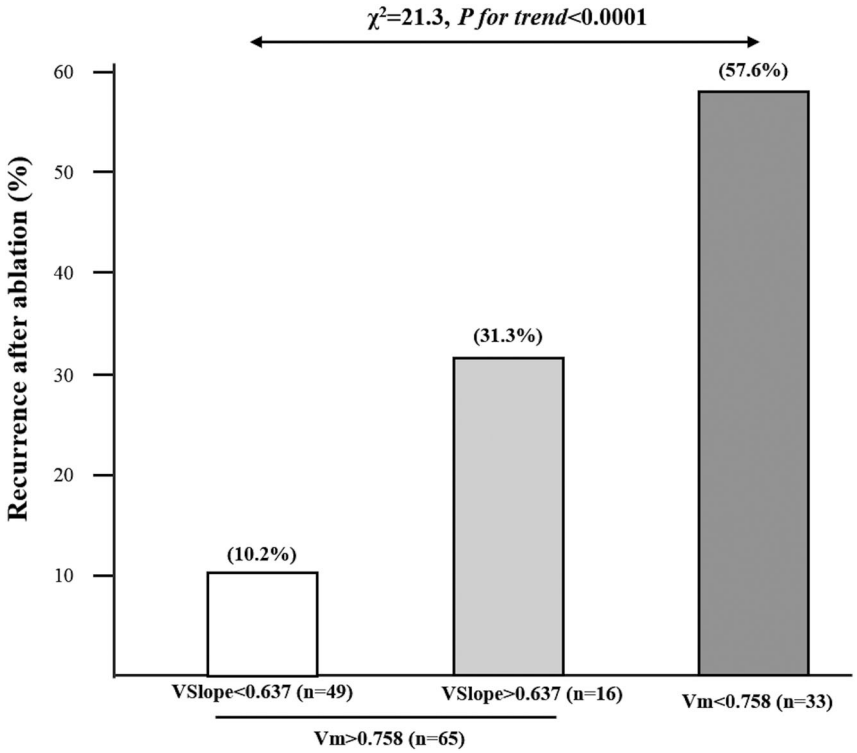

FIGURE 3 Mean voltage (V_m) and slope of the voltage histogram (V_{slope}) combination and association with atrial fibrillation (AF) recurrence. Incidence of AF recurrence among three study subgroups based on the classification of patients according to the presence of high V_m (>0.758 mV) with low V_{slope} (<0.637), high V_m with high V_{slope} (>0.637), and low V_m (<0.758 mV)

While atrial structural heterogeneity is usually considered one of the causes of AF, to the best of our knowledge, there are no specific markers of it. The V_{slope} is the slope of the voltage histogram and, as such, the higher the V_{slope}, the greater the difference between higher voltages and lower voltages. Therefore, although we cannot prove it, we hypothesize that the V_{slope} could reflect atrial heterogeneity. In this cohort, this novel parameter was associated with persistent AF, AF recurrence and postablation atrial flutter. Of note, its utility as a predictor of AF recurrence in patients without extensive fibrosis was confirmed in an independent cohort. These findings should be considered as hypothesis generators and its pathophysiological relevance and potential clinical usefulness must be tested in further studies.

Combining both parameters, the quantitative analysis of the uHD$_V$M data allows for a more precise phenotyping of patients in terms of risk of postablation AF recurrence. In this regard, in routine clinical practice, it is common to find patients who seem difficult to cure with current knowledge and technology. The Marrouche group "Utah Stage IV,"[20] the so-called "strawberry atrium" of Kottkamp et al[10] and our V_m lower than 0.758 probably represent this type of patients, who have severe atrial fibrosis and poor response to current rhythm control strategies. Effective upstream therapies are urgently needed for them. On the other hand, patients with structurally healthy atria, in our study represented by high V_m/low V_{slope} patients, remain free from AF after a single procedure in most cases. The standard approach is sufficient for them and efforts should be directed to achieve a safe and lasting PVI by improving both technique and materials. In our work, a third group of patients emerged: without extensive fibrosis but with seemingly high heterogeneity. Thus, 33 (33.7%) patients were at high risk (low V_m), 16 (16.3%) patients at intermediate risk (high V_m/high V_{slope}), and 49 (50%) patients at low risk (high V_m/low V_{slope}). Having in mind that a high V_{slope} could identify to patients at risk of atypical atrial flutter and progression to persistent AF, low-voltage guided ablation lines or another substrate modification strategy could be used in intermediate risk (high V_m/high V_{slope}) patients. This new ablation therapy approaches should be tested in the context of appropriate controlled clinical trials.

4.1 | Limitations

The lack of contact force-sensing technology may have compromised the quality of some of the analyzed points. However, we carefully created the maps with the guidance of LA three-dimensional CT reconstruction, we evaluated only points located within 2 mm of the shell surface and used a multielectrode-mapping catheter for all patients. Since all patients were similarly subjected to this limitation, an increase in accuracy can only improve our results.

Although only one nonfluoroscopic navigation system was used, the analyzed parameters were calculated from the peak-to-peak voltage values, which are available in all the different systems.

The inclusion of patients undergoing both index and repeated ablation procedures have to be taken into account for the interpretation of the results. We analyzed separately those patients of our cohort

TABLE 3 Odds ratio and added predictive value of V_m/V_{slope} combination for AF recurrence

Statistic parameter	Value	95% CI[a]	*P* value
Logistic regression analysis			
Unadjusted analysis			
Voltage > 0.758 mV-Slope < 0.637	1 (ref)		
Voltage > 0.758 mV-Slope ≥ 0.637	4.00	1.00-16.3	.050
Voltage ≤ 0.758	11.9	3.8-37.9	<.0001
BM1			
Voltage > 0.758 mV-Slope < 0.637	1 (ref)		
Voltage > 0.758 mV-Slope ≥ 0.637	4.82	1.10-21.0	.037
Voltage ≤ 0.758	13.0	3.9-43.9	<.0001
BM2			
Voltage > 0.758 mV-Slope < 0.637	1 (ref)		
Voltage > 0.758 mV-Slope ≥ 0.637	4.57	0.99-20.9	.051
Voltage ≤ 0.758	9.44	2.53-35.2	.001
BM3			
Voltage > 0.758 mV-Slope < 0.637	1 (ref)		
Voltage > 0.758 mV-Slope ≥ 0.637	3.96	0.92-17.2	.056
Voltage ≤ 0.758	23.2	5.78-92.8	<.0001
Added predictive value			
Harrell's C			
BM1	0.674	0.554-0.794	
BM1 + V_m/V_{slope} combination	0.818	0.723-0.912	.017
BM2	0.655	0.529-0.782	
BM2 + V_m/V_{slope} combination	0.800	0.707-0.893	.009
BM3	0.626	0.525-0.726	
BM3 + V_m/V_{slope} combination	0.836	0.747-0.924	<.0001
NRI			
BM1 + V_m/V_{slope} combination	0.93	0.49-1.29	<.0001
BM2 + V_m/V_{slope} combination	0.99	0.64-1.34	<.0001
BM3 + V_m/V_{slope} combination	1.08	0.69-1.38	<.0001

Note. Odds ratios were adjusted by baseline model 1 (BM) (age and sex), BM2 (persistent AF and CT-LA_{Volume}), and BM3 (redo procedure, yes/no).
Abbreviations: AF, atrial fibrillation; CI, confidence interval; CT, computed tomography; LA, left atrial; NRI, net reclassification improvement.
[a]The variance was calculated using bootstrapping (with 1000 resamples) for the NRI estimates and the jack-knife approach for the Harrell C estimates.

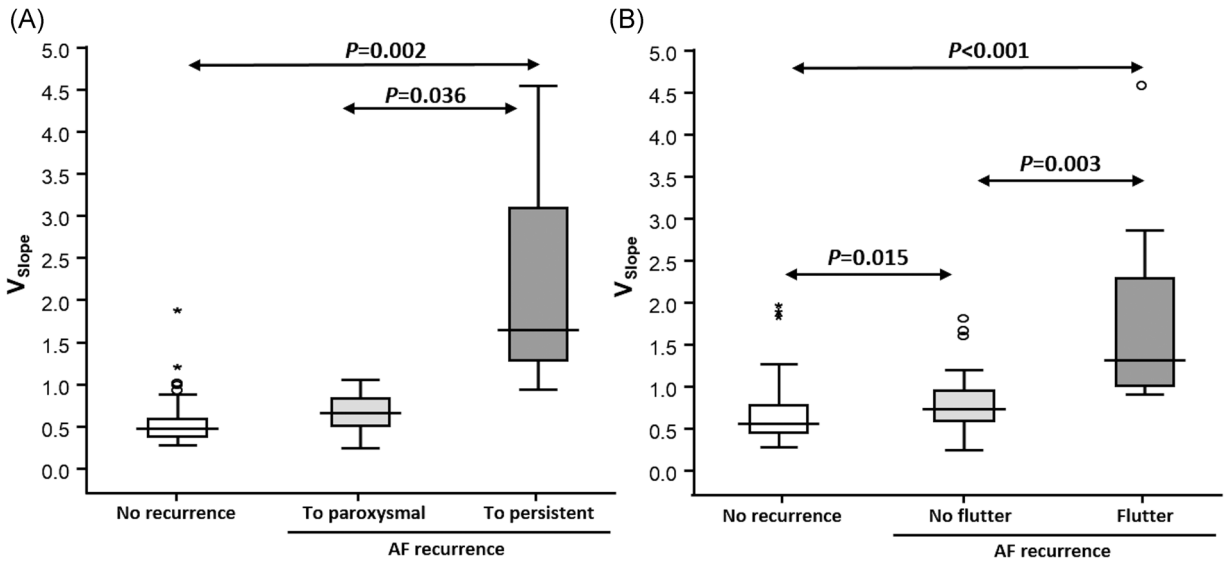

FIGURE 4 Slope of the voltage histogram (V_{slope}) and atrial fibrillation (AF) evolution. A, Distribution of V_{slope} in paroxysmal AF patients classified in three groups according to no arrhythmia recurrence, paroxysmal AF recurrence and persistent AF recurrence. B, Distribution of V_{slope} in patients classified in three groups according to no arrhythmia recurrence, AF recurrence without atrial flutter and postablation atrial flutter

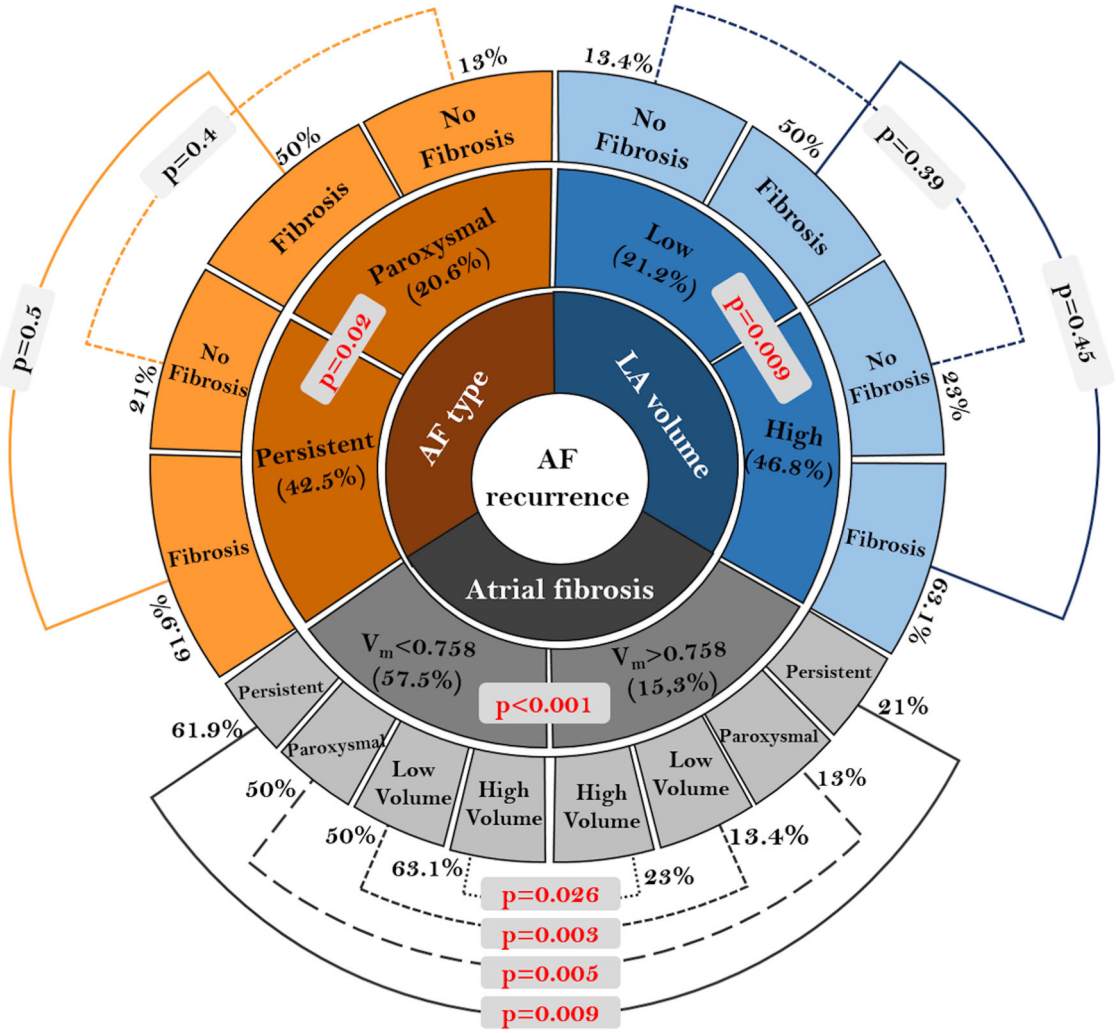

FIGURE 5 Mean voltage (V_m), atrial volume and persistent atrial fibrillation (AF) association with AF recurrence. Persistent AF, dilated LA and low V_m all predict AF recurrence after PVI when they are analyzed individually. This association between high volume (>118 ml) and persistent AF, and AF recurrence is not observed if we remove the "voltage factor" (right and left upper thirds respectively). On the contrary, the differences remain when analyzing the V_m in patients with paroxysmal AF, persistent AF, dilated and undilated LA (lower third). LA, left atrial; PVI, pulmonary vein isolation

without prior ablation and found results consistent with those of the entire cohort. Besides, in an independent cohort of patients scheduled for first ablation procedure, the main results were confirmed. Thus, the utility of the described parameters is independent of the presence of the previous ablation as a confounding factor.

The number of patients included in this study is small for the analysis of low incidence events. Therefore, findings on AF clinical progression and form of recurrence should be considered as hypothesis generators.

There are causes of arrhythmia recurrence that are not directly related to the atrial substrate (for example, the reconnection of the pulmonary veins) and therefore are unexplored in our study.

Finally, since continuous monitoring was not used, short duration episodes of asymptomatic recurrence may not have been detected.

5 | CONCLUSIONS

The findings reported here suggest that the analysis of LA uHD$_V$M based not only on V_m but also on V_{slope} allows the identification of several patterns of atrial substrate alterations that associate with variable risk of AF recurrence and AF progression after ablation. Further studies are required to ascertain whether the combined use of the two electrical biomarkers actually contributes to the development and application of precision medicine to this troublesome arrhythmia.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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