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LEFT ATRIAL VOLTAGE CHARACTERISTICS IN PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION

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Aim. The aim of the study was to assess the impact of comorbidities and duration of arrhythmic anamnesis on the results of left atrium voltage mapping in patients with persistent atrial fibrillation (AF).

Methods. The study enrolled 50 patients who underwent the first radiofrequency ablation of persistent AF. Left atrium endocardial voltage maps were obtained using a 3D electroanatomical mapping system during AF. The voltage maps consisted of at least 2,000 points, with an average of 2,128±104 points. Low-voltage areas (LVA) were defined as <0.5 mV. The percentage of LVA% and very LVA% were calculated.

Results. We found a statistically significant correlation of LVA% with age ($p<0.001$, $r=0.720$), female sex ($p=0.016$), and the duration of arrhythmic history at the time of the start of persistence ($p<0.001$, $r=0.503$). Based on the data obtained, an original scale was developed to predict LVA%. The scale includes age, female sex, and the duration of arrhythmic history at the start of persistence. A score of 1 point was assigned for an age over 65 years, 1 point for female gender, and 1 point for a duration of arrhythmic history over 4 months; otherwise, 0 points were given. The total score ~~on~~ of the scale showed a high correlation with LVA% ($p<0.001$, $r=0.768$). The scale was named AFD-rhythm (Age, Female Sex, Duration of arrhythmic anamnesis at the Start of Persistence).

Conclusions. Age, female sex, and the duration of arrhythmic anamnesis at the start of persistence are predictors of LVA% of the left atrium in patients with persistent atrial fibrillation. The original AFD-rhythm scale can be used to predict the percentage of left atrium low voltage in patients with persistent AF.

Key words: atrial fibrillation; radiofrequency ablation; high-density mapping; left atrial low voltage

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The identification of pulmonary vein (PV) ectopy as a trigger for atrial fibrillation (AF), first reported by M. Haïssaguerre et al. in 1998, led to the development of PV isolation, which today carries a class I indication for radiofrequency ablation (RFA) of AF [1]. However, it soon became evident that ectopic activity may also originate outside the PVs, and that trigger-induced paroxysmal AF can progress to substrate-dependent persistent or long-standing persistent AF. This was confirmed by J. Seitz et al. (2017), who demonstrated that ablation of AF triggers outside the PVs, without PV isolation, resulted in arrhythmia-free survival in 85% of patients during 18 months of follow-up [2].

At the same time, empirical additional linear ablations and substrate modification, performed with the aim of treating substrate-dependent AF, were investigated in the STAR-AF II trial, which did not show a reduction in AF recurrence compared with standard PV antral isolation [3]. The investigators concluded that patient-specific substrate ablation requires a deeper understanding.

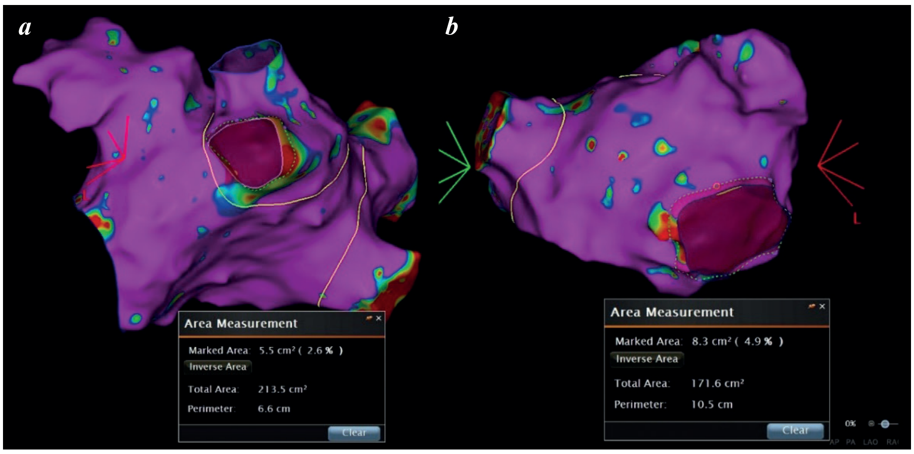

Fig. 1. Left atrial voltage mapping: (a) measurement of the area of the left inferior pulmonary vein ostium; (b) measurement of the mitral valve annulus.

One mechanism of arrhythmia progression is the spread of left atrial (LA) fibrosis and its arrhythmogenic effect. The gold standard for visualising myocardial fibrosis is late gadolinium enhancement magnetic resonance imaging (MRI), which allows indirect assessment of the extent of LA fibrosis [4]. However, this method has several limitations, including cost, contraindications, and poor reproducibility across centres [5]. R. S. Oakes et al. (2009) demonstrated a correlation between the extent of late gadolinium enhancement and low-voltage areas on electroanatomical mapping [6]. Subsequently, it was shown that the extent of low-voltage areas directly correlates with AF recurrence rates [7].

A large number of scoring systems have been proposed to predict the proportion of low-voltage areas in the LA. However, in studies supporting the utility of such scores, electroanatomical mapping was usually performed in sinus rhythm after cardioversion in patients with persistent AF, which may have influenced mapping results. At the same time, little attention has been paid to the assessment of factors influencing atrial signal amplitude during ongoing AF.

Aim: to evaluate the influence of comorbidities and arrhythmia history on LA voltage mapping outcomes in patients with persistent AF.

METHODS

The study included 50 patients with persistent AF referred for first-time RFA. The mean age was 67.10 ± 9.49 years; 36 were men (72%) and 14 women (28%). In all patients, AF was clinically significant, manifesting as persistent or intermittent palpitations and/or reduced exercise tolerance. The presence of AF was documented by both standard electrocardiography and Holter monitoring.

For each patient, the total duration of arrhythmic history, duration of persistent AF, and duration of arrhythmic history prior to the onset of persistence were recorded. The mean duration of arrhythmic history was 50.38 ± 10.00 months, with persistence lasting 17.03 ± 3.76 months, and arrhythmic history prior to persistence amounting to 32.5 ± 8.21 months.

Voltage mapping of the LA was performed using the CARTO 3 navigation system (Biosense Webster, USA). Mapping was carried out with a multielectrode PentaRay catheter (Biosense Webster, USA) using the tissue proximity function, with mapping points located ≤5 mm from the atrial anatomical shell, and the confidense module configured with the following parameters: catheter stability 6 mm, electroanatomical point density 1 mm. All voltage maps comprised a minimum of 2000 points, with a mean of 2128 ± 104. Voltage maps were analysed to identify low-voltage areas and calculate the percentage of low-voltage area.

Regions with a bipolar signal amplitude >0.5 mV were defined as normal voltage, 0.1-0.5 mV as low voltage, and <0.1 mV as very low voltage. These thresholds were chosen based on prior studies, many of which proposed 0.5 mV as the cut-off for low voltage [8-10], a value now widely adopted in the literature. In the study by Y. Lin et al. (2014), voltages <0.1 mV were defined as "dense scar" [11].

For each map, the percentage of low voltage (LVA%) and very low voltage (VLVA%) was calculated. LVA% was computed relative to the total LA surface area. The area measurement tool was used to calculate the total surface area of the LA map, subtracting the area of the mitral annulus and PV ostia. Measurement of the mitral annulus and PV ostia areas is illustrated in Figure 1. The surface area of low-voltage regions was then determined using the same area measurement tool (Fig. 2). Based on the reconstructed anatomical model of the LA, excluding the PVs, LA volume was also calculated, including the LA appendage.

A correlation analysis was performed to assess the relationship of LVA% and VLVA% with sex, age, duration of arrhythmic history, duration of persistence, duration of arrhythmic history at the onset of persistence, comorbidities (coronary artery atherosclerosis, interventricular septal thickness [as a marker of LV hypertrophy], diabetes mellitus, body mass index, estimated glomerular filtration rate [eGFR]), LA anteroposterior diameter (as measured by echocardiography), LA size index, LV ejection fraction,

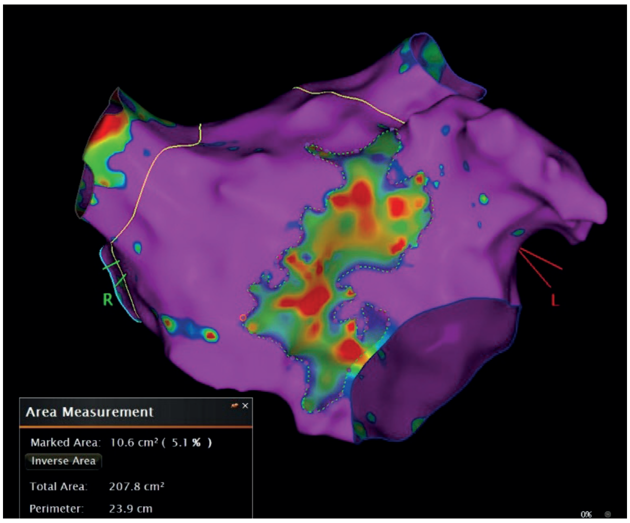

Fig. 2. Measurement of the low-voltage area.

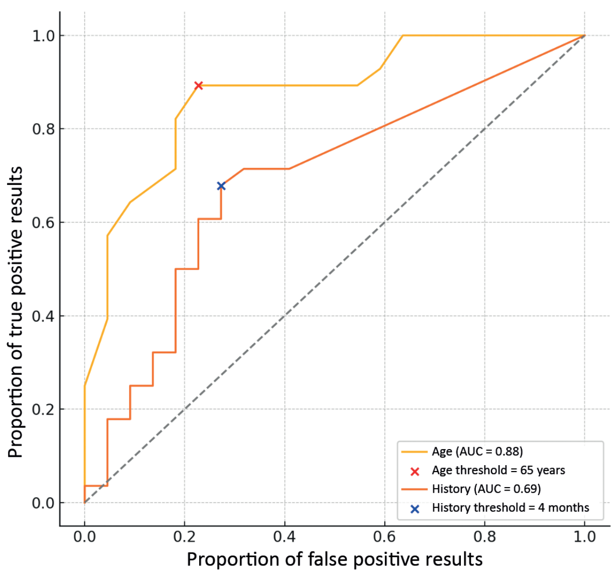

Fig. 3. ROC curves for determining the cut-off points for age and arrhythmic history duration at the onset of persistence in relation to LV% (low-voltage percentage).

left atrial appendage emptying velocity (by preoperative transoesophageal echocardiography), and LA volume as determined from the reconstructed LA model.

Statistical analysis

Statistical analysis was performed using StatTech v.4.6.3 (StatTech LLC, Russia). Quantitative variables were tested for normality using the Shapiro-Wilk test (for sample sizes <50) or the Kolmogorov-Smirnov test (for sample sizes >50). Variables with a normal distribution were described as means (M) with standard deviations (SD) and 95% confidence intervals (95% CI). Non-normally distributed data were described as medians (Me) with interquartile ranges (Q1-Q3).

Comparisons between two groups for non-normally distributed quantitative variables were performed using the Mann-Whitney U test. The strength and direction of correlations between two quantitative variables were assessed using Pearson's correlation coefficient (for normally distributed variables) or Spearman's rank correlation coefficient (for non-normally distributed variables).

A prognostic model describing the dependence of a quantitative variable on selected factors was developed using linear regression analysis. A two-tailed p-value <0.05 was considered statistically significant.

Table 1.

Values at the optimal threshold of sensitivity, specificity, and Youden's index

Parameter	Sensitivity	Specificity	Youden's Index
Age ≥65 years	0.89	0.77	0.67
Anamnesis ≥4 months	0.68	0.73	0.41

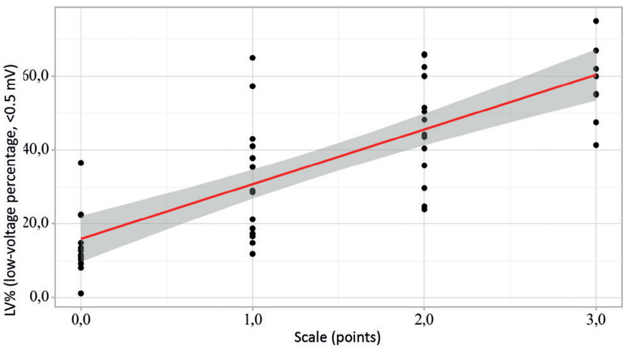

Fig. 4. Regression function graph illustrating the relationship between LV% (low-voltage percentage) and the score on the original scale.

Table 2.

Results of correlation analysis of the relationship between the factors included in the scale, the scale score, and LV% (low-voltage percentage)

Indicator	ρ	p
Age	0.720	<0.001
Female sex		0.016
Duration of arrhythmia history*	0.503	<0.001
Total score on the scale	0.778	<0.001

Note: * - at the onset of persistent atrial fibrillation.

RESULTS

We identified a statistically significant strong correlation between LVA% and age (p<0.001, r=0.720), female sex (p=0.016), and a moderate correlation with the duration of arrhythmic history at the onset of persistence (p<0.001, r=0.503). A statistically significant but weak association was also observed between LVA% and eGFR (p=0.002, r=−0.336), left atrial (LA) volume measured on electroanatomical mapping (p=0.019, r=0.330), LA size index (p<0.001, r=0.432), and LA appendage (LAA) emptying velocity (p=0.023, r=−0.335).

No correlation was found between LVA% and the duration of persistence (p=0.728), interventricular septal thickness (p=0.976), body mass index (p=0.814), presence of coronary atherosclerosis (p=0.058), diabetes mellitus (p=0.192), left ventricular ejection fraction (p=0.125), or anteroposterior LA diameter (p=0.213).

For VLVA%, we observed a statistically significant correlation with age (p<0.001, r=0.656) and female sex (p=0.039), a weak association with eGFR (p=0.013, r=−0.357) and arrhythmic history duration at the onset of persistence (p<0.003, r=0.410), and a very weak correlation with LA size index (p=0.048, r=−0.276). No correlation was found between VLVA% and the duration of persistence (p=0.567), interventricular septal thickness (p=0.876), body mass index (p=0.900), coronary atherosclerosis (p=0.055), diabetes mellitus (p=0.098), left ventricular ejection fraction (p=0.300), anteroposterior LA diameter (p=0.481), LA volume (p=0.618), or LAA emptying velocity (p=0.371).

Thus, the variables showing the strongest correlations with LVA% and VLVA% were age, female sex, arrhythmic history duration at the onset of persistence, and eGFR. Based on these findings, we developed an original predictive score for LVZ%, incorporating age, sex, and arrhythmic history duration at the onset of persistence.

To determine threshold values for age and arrhythmic history duration, ROC analysis was performed for each variable. The area under the ROC curve (AUC) was used to evaluate discriminatory ability, and optimal cut-offs were identified using Youden's index (J = sensitivity + specificity − 1). The point with the maximum Youden index was considered the optimal diagnostic threshold. For dichotomization, LVA%=35% was chosen as the reference threshold, since the median LVA% was 35.57% and the 35% cut-off corresponds to the boundary of advanced fibrosis in the Utah classification. The optimal Youden index for age was achieved at a threshold of 65 years, and for arrhythmic history duration at the onset of persistence at 4 months. ROC curves are shown in Fig. 3, and the sensitivity, specificity, and Youden index values are provided in Table 1.

Patients aged >65 years were assigned 1 point, female sex 1 point, and arrhythmic history duration >4 months at the onset of persistence 1 point; otherwise, 0 points were assigned. The total score demonstrated a strong correlation with LVA% (p<0.001, r=0.778). This scoring system was named the "AGD-rhythm" scale (Age, Gender, Duration of arrhythmic history at persistence onset).

A regression analysis of the relationship between the score and LVA% is shown in Fig. 4, while Table 2 presents the correlation analysis results for the individual factors included in the score and the overall score in relation to LVA%. The score also showed a moderate correlation with VLVA% (p<0.001, r=0.597).

DISCUSSION

Various scoring systems have been developed to predict the percentage of low-voltage areas in the left atrium, incorporating different clinical and echocardiographic factors. The DR-FLASH score, which includes diabetes mellitus, renal dysfunction, persistent atrial fibrillation, a left atrial anteroposterior diameter greater than 45 mm, age over 65 years, female sex, and arterial hypertension, has demonstrated high effectiveness in predicting the presence of low-voltage areas [12-14].

To predict AF recurrence after RF ablation in patients undergoing primary and repeat procedures, the APPLE score was developed. This included: age >65 years, persistent AF, reduced eGFR <60 ml/min/1.73m², anteroposterior LA diameter >42 mm, and left ventricular ejection fraction (LVEF) <50%. This score provided a means of predicting the extent of low-voltage areas [12]. Table 3 summarises scoring systems reported in the literature for predicting the distribution of low-voltage areas.

A critical methodological issue is that in most studies validating these scores, electroanatomical mapping was performed during sinus rhythm. Patients with persistent or long-standing persistent AF first underwent cardioversion, followed by voltage mapping during sinus rhythm or atrial pacing. However, A. Lahuerta et al. (2022) demonstrated that voltage mapping results obtained during AF and sinus rhythm in the same patient differ substantially [15]. Similarly, N.A. Qureshi et al. (2019) reported that the correlation between low-voltage areas identified by endocardial mapping and areas of fibrosis detected by late gadolinium enhancement MRI was significantly stronger when mapping was performed during AF compared with sinus rhythm [16]. In addition, J. Chen et al. (2019) showed that most arrhythmogenic regions of the LA (areas of spatiotemporal dispersion and prolonged activity) overlapped with low-voltage zones identified during AF mapping, underscoring the importance of studying low-voltage areas independently of atrial fibrosis [15].

Another methodological concern is that patients with unsuccessful cardioversion or immediate AF recurrence after rhythm restoration were excluded from analysis. In one study, this group comprised 12.9% of patients [17]. Excluding such patients—those with more advanced disease—may bias results. Electrical cardioversion itself, and the fact that mapping is performed immediately afterwards, is an important factor influencing mapping outcomes.

As noted, results of voltage mapping during AF and sinus rhythm in the same patient differ markedly, and it remains unclear which rhythm better reflects the true extent of LA fibrosis. In our view, given these limitations, including mapping immediately after cardioversion and exclusion of patients with unsuccessful cardioversion, voltage mapping during AF in patients with persistent AF appears more rational.

In our study, high-density mapping included >2000 analysed electrograms per LA map, whereas earlier studies typically used ~200 points, which does not meet current definitions of high-density mapping and may have affected their results [18-20]. Moreover, some studies used different

Table 3.

Scales for predicting the extent of low-voltage areas in the left atrium

Scale	Parameters	Number of Mapping Points in LA	Mapping Catheter
DR-FLASH [12, 13]	DM, CKD, PersAF, LA > 45 mm, age > 65 years, female sex, HTN	>1000; 144±76	SmartTouch (Biosense Webster), TactiCath (Abbott), multielectrode circular catheter
APPLE [11, 18]	Age > 65, PersAF, GFR < 60 ml/min/1.73 m², LA > 43 mm, LVEF < 50%	>1000; >200	Age > 65, PersAF, GFR < 60 ml/min/1.73 m², LA > 43 mm, LVEF < 50%
(m)APPLE [19]	Age > 65, PersAF, GFR < 60 ml/min/1.73 m², LAVI ≥ 39 ml/m², LAEF < 31%	>1000	SmartTouch (Biosense Webster), TactiCath (Abbott), multielectrode circular catheter
SPEED [21]	Female sex, PersAF, age > 70 years, proBNP > 400 pg/ml, DM	≥100 (3.5-mm ablation catheter), ≥1000 (multielectrode catheter)	3.5-mm ablation or multielectrode catheter (Biosense Webster/Boston Scientific/Abbott)
ZAQ [20]	Age > 65 years, female sex, LAVI 57 ml/m²	>200	TactiCath (Abbot), ThermoCool SmartTouch (Biosense Webster)
ANP [43]	Age > 65 years, NT-proBNP ≥ 17 ng/ml, PersAF	>1000	Reflexion Spiral (Abbot), Lasso (Biosense Webster)
ATLAS [45]	Age > 60 years, female sex, PersAF, smoking, LAVI (1 point per 10 ml/m²)	2876 ± 1058	PentaRay (Biosense Webster)

Note: LA – left atrium; DM – diabetes mellitus; CKD – chronic kidney disease; PersAF – persistent atrial fibrillation; HTN – arterial hypertension; GFR – glomerular filtration rate; LVEF – left ventricular ejection fraction; LAVI – left atrial volume index.

electrode types (3.5 mm ablation vs. multielectrode catheters) [12, 13, 18, 19, 21]. E. Anter et al. (2015) demonstrated that in areas of preserved voltage, bipolar signal amplitudes were consistent across catheter types, whereas in low-voltage zones, the total area with voltages <0.5 mV measured using multielectrode catheters with 1 mm electrodes was smaller than when measured using a 3.5 mm ablation catheter [9, 22].

One of the most debated issues remains the discrepancy between mapping during sinus rhythm and AF. As highlighted in the aforementioned studies, sequential mapping during both rhythms in the same patient revealed substantial differences when low-voltage thresholds of 0.5 and 0.3 mV were applied [14, 16]. This highlights the need for rhythm-specific voltage thresholds.

Numerous attempts have been made to define a suitable threshold for AF mapping, proposing values from 0.24 to 0.35 mV, which may correspond to the 0.5 mV threshold used during sinus rhythm [16, 23, 24]. However, no consensus has yet been reached. D. Nairn et al. (2023) noted that even with adjusted thresholds, concordance between sinus rhythm and AF maps remains only moderate, with greater detection of low-voltage areas during AF mapping [24].

In our opinion, given the fundamental differences in activation direction and conduction velocity between sinus rhythm and AF, it is unlikely that a single threshold can harmonise voltage maps across both rhythms. Therefore, predictors of low-voltage areas should probably be determined separately for sinus rhythm and AF mapping.

Based on prior studies adopting a 0.5 mV threshold and the findings of N.A. Qureshi et al. (2019) showing higher concordance between AF mapping and late gadolinium enhancement MRI, we applied 0.5 mV and 0.1 mV thresholds to identify predictors of low voltage [16]. Importantly, no significant differences were observed in the results of correlation analysis when comparing the thresholds for low and very low voltage.

Left atrial voltage reduction and age

Atrial fibrillation (AF) is the most common age-associated arrhythmia, and ageing is generally linked to an increased risk of AF [25]. This association has been reported in both animal experiments and small-scale clinical studies, which described age-related alterations in the electrophysiological properties of atrial myocytes and conduction abnormalities [25, 26].

The relationship between LA fibrosis and age has been demonstrated in histological analyses of tissue samples obtained at autopsy and during open-heart surgery. Atrial tissue analysis revealed a correlation between atrial fibrosis and a history of AF. Importantly, the authors reported no significant fibrosis in age-matched control patients without a history of AF [27, 28].

However, findings regarding the correlation between LA fibrosis and age remain inconsistent. In an autopsy-based study, P.G. Platonov et al. (2011) found no association between age and the extent of LA fibrosis [28]. Conversely, in a clinical study by H. Cochet et al. (2015), age was identified as a predictor of fibrosis diagnosed using late gadolinium enhancement MRI [29].

In our study, age demonstrated the strongest correlation with the percentage of low-voltage areas in the LA.

Left atrial voltage reduction and sex

The EORP-AF study demonstrated sex-related differences in the epidemiology, clinical management, and treatment of AF [30]. Women with AF were shown to have a 1.3-2.0-fold higher risk of AF recurrence following RFA [31-33]. The FIRE and ICE trial reported that female sex was associated with an almost 40% increase in atrial arrhythmia recurrences after pulmonary vein isolation [34]. Other studies indicated that although women had higher recurrence rates after RFA, repeat procedures revealed less frequent pulmonary vein reconnections in women compared with men [35, 36]. This finding may be explained by a greater prevalence of non-pulmonary vein AF triggers, which could be related to areas of low voltage.

Previous investigations have identified female sex as an independent predictor of LA fibrosis [37-39]. This observation is believed to be linked to a direct sex-specific effect, driven by differences in the influence of sex hormones on adverse LA remodelling and fibrosis.

In our study, female sex correlated with a higher percentage of low-voltage areas in the LA.

Left atrial voltage reduction and duration of arrhythmic history

An interesting observation was the association between the duration of arrhythmic history at the onset of persistence and the percentage of low voltage (LV%). Patients with a history of paroxysmal AF prior to transition to the persistent form demonstrated a higher LV% compared with those whose first manifestation of AF was persistence. On the one hand, this may indicate distinct mechanisms underlying AF persistence; on the other, it underscores the potential need for earlier intervention to maintain sinus rhythm and to minimise the spread of low-voltage areas, which adversely affect the prognosis and the efficacy of interventional treatment.

Our findings also suggest that the extent of low-voltage areas is primarily driven by preceding paroxysmal AF episodes rather than by the duration of persistence itself. The absence of an association between AF persistence duration and LV% in our cohort is consistent with previous reports [40]. To our knowledge, no prior studies have examined the correlation between the duration of arrhythmic history at the onset of persistence and LV%. The present study is the first to highlight the influence of the duration of preceding paroxysmal AF on the prevalence of low-voltage areas.

Left atrial voltage reduction and associated comorbidities

according to our data, comorbidities did not influence the percentage of very low-voltage areas (VLVA%). This finding is consistent with some studies that failed to demonstrate an association between comorbid conditions and atrial voltage reduction in patients with persistent AF [40]. At the same time, studies evaluating previously proposed scoring systems have shown their utility in predicting the extent of low-voltage areas in the left atrium [12]. Experimental animal models have demonstrated a link between arterial hypertension and atrial fibrosis [41]. Furthermore, obesity has been shown to promote the development of atrial fibrosis in experimental settings, with regression of fibrosis observed following weight reduction [42].

Renal dysfunction merits particular attention, as estimated glomerular filtration rate (eGFR) exhibited a statistically significant moderate correlation with both LVA% and VLVA%. Evidence regarding the association between eGFR and the extent of low-voltage areas is conflicting, with some studies reporting a relationship and others not [43, 44]. It is likely that the lack of a strong correlation in our cohort is related to the fact that only patients with mild-to-moderate renal impairment were included (mean eGFR 61.8 mL/min/1.73m²), while none had stage IV or V chronic kidney disease.

We developed an original scoring system, the AFD-Rhythm score (Age, Female, Duration of arrhythmic history), to predict the extent of low-voltage areas in patients with persistent AF. This score is designed to estimate the percentage of low-voltage burden in patients undergoing mapping during arrhythmia. As noted earlier, previous studies have demonstrated a correlation between the extent of low-voltage areas and AF recurrence following RFA [7]. Based on this, it can be hypothesised that our score may also predict the efficacy of AF ablation. However, this assumption requires validation in future studies.

CONCLUSION

Age, female sex, and the duration of arrhythmic history at the onset of persistence are independent predictors of low-voltage burden in the left atrium among patients with persistent atrial fibrillation. The proposed original AFD-Rhythm score may be employed to predict the extent of low-voltage burden in this patient population.

REFERENCES

1. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10): 659-66. https://doi.org/10.1056/NEJM199809033391003.
2. Seitz J, Bars C, Théodore G, et al. AF Ablation Guided by Spatiotemporal Electrogram Dispersion Without Pulmonary Vein Isolation: A Wholly Patient-Tailored Approach. J Am Coll Cardiol. 2017;69(3): 303-21. https://doi.org/10.1016/j.jacc.2016.10.065.
3. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015;372(19): 1812-22. https://doi.org/10.1056/NEJMoa1408288.
4. Marrouche NF, Naccarelli GV, Akoum Y, et al. Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation: The DECAAF Study. JAMA. 2014;312(17): 1805-14. https://doi.org/10.1001/jama.2014.3.
5. Sramko M, Peichl P, Wichterle D, et al. Clinical value of assessment of left atrial late gadolinium enhancement in patients undergoing ablation of atrial fibrillation. Int J Cardiol. 2015;179: 351-7. https://doi.org/10.1016/j.ijcard.2014.11.072.
6. Oakes RS, Badger TJ, Kholmovski EG, et al. Detection and quantification of left atrial structural remodeling with delayed-enhancement magnetic resonance imaging in patients with atrial fibrillation. Circulation. 2009;119(13): 1758-67. https://doi.org/10.1161/CIRCULATIONAHA.108.811877.
7. Yamaguchi T, Tsuchiya T, Nagamoto Y, et al. Long-term results of pulmonary vein antrum isolation in patients with atrial fibrillation: an analysis in regard to substrates and pulmonary vein reconnections. Europace. 2014;16(5): 511-20. https://doi.org/10.1093/europace/eut265.
8. Sanders P, Morton JB, Kistler PM, et al. Electrophysiological and electroanatomic characterization of the atria in sinus node disease: Evidence of diffuse atrial remodeling. Circulation. 2004;109(11): 1514-22. https://doi.org/10.1161/01.CIR.0000121734.47409.AA.
9. Anter E, Tschabrunn CM, Josephson ME. High-resolution mapping of scar-related atrial arrhythmias using smaller electrodes with closer interelectrode spacing. Circ Arrhythm Electrophysiol. 2015;8(3): 537-45. https://doi.org/10.1161/CIRCEP.114.002737.
10. Saghy L, Callans DJ, Garcia F, et al. Is there a relationship between complex fractionated atrial electrograms recorded during atrial fibrillation and sinus rhythm fractionation? Heart Rhythm. 2012;9(2): 181-8. https://doi.org/10.1016/j.hrthm.2011.09.062.
11. Lin Y, Yang B, Garcia FC, et al. Comparison of left atrial electrophysiologic abnormalities during sinus rhythm in patients with different type of atrial fibrillation. J Interv Card Electrophysiol. 2014;39(1): 57-67. https://doi.org/10.1007/s10840-013-9838-y.
12. Kornej J, Schumacher K, Dinov B, et al. Prediction of electro-anatomical substrate and arrhythmia recurrences using APPLE, DR-FLASH and MB-LATER scores in patients with atrial fibrillation undergoing catheter ablation. Sci Rep. 2018;8(1): 12686. https://doi.org/10.1038/s41598-018-31133-x.
13. Kosiuk J, Dinov B, Kornej J, et al. Prospective, multicenter validation of a clinical risk score for left atrial arrhythmogenic substrate based on voltage analysis: DR-FLASH score. Heart Rhythm. 2015;12(9): 2207-12. https://doi.org/10.1016/j.hrthm.2015.07.003.
14. Andrés Lahuerta A, Roberto C, Saiz FJ, et al. Atrial low voltage areas: A comparison between atrial fibrillation and sinus rhythm. Cardiol J. 2022;29(2): 252-62. https://doi.org/10.5603/CJ.a2021.0125.
15. Chen J, Arentz T, Cochet H, et al. Extent and spatial distribution of left atrial arrhythmogenic sites, late gadolinium enhancement at magnetic resonance imaging, and low-voltage areas in patients with persistent atrial fibrillation: comparison of imaging vs. electrical parameters of fibrosis and arrhythmogenesis. Europace. 2019;21(10): 1484-93. https://doi.org/10.1093/europace/euz159.
16. Qureshi NA, Kim SJ, Cantwell CD, et al. Voltage during atrial fibrillation is superior to voltage during sinus rhythm in localizing areas of delayed enhancement on magnetic resonance imaging: An assessment of the posterior left atrium in patients with persistent atrial fibrillation. Heart Rhythm. 2019;16(9): 1357-67. https://doi.org/10.1016/j.hrthm.2019.05.032.
17. Kiedrowicz RM, Wielusinski M, Wojtarowicz A, et al. Predictors of the voltage derived left atrial fibrosis in patients with long-standing persistent atrial fibrillation. Cardiol J. 2022;29(4): 660-9. https://doi.org/10.5603/CJ.a2020.0069.

18. Kornej J, Büttner P, Sommer P, et al. Prediction of electro-anatomical substrate using APPLE score and biomarkers. Europace. 2019;21(1): 54-9. https://doi.org/10.1093/europace/euy120.
19. Seewöster T, Kosich F, Sommer P, et al. Prediction of low-voltage areas using modified APPLE score. Europace. 2021;23(4): 575-80. https://doi.org/10.1093/europace/euaa311.
20. D'Ambrosio G, Romano S, Alothman O, et al. Computed tomography-derived left atrial volume index, sex, and age to predict the presence and the extent of left atrial low-voltage zones in patients with atrial fibrillation: The ZAQ score. J Cardiovasc Electrophysiol. 2020;31(4): 895-902. https://doi.org/10.1111/jce.14391.
21. Matsuda Y, Masuda M, Asai M, et al. A new clinical risk score for predicting the prevalence of low-voltage areas in patients undergoing atrial fibrillation ablation. J Cardiovasc Electrophysiol. 2020;31(12): 3150-8. https://doi.org/10.1111/jce.14761.
22. Gasimova NZ, Shabanov VV, Safonov NV, et al. Multipolar mapping in the management of different arrhythmias. Journal of Arrhythmology. 2024;31(1): 110-122. https://doi.org/10.35336/VA-1297.
23. Rodríguez-Mañero M, Valderrábano M, Baluja A, et al. Validating Left Atrial Low Voltage Areas During Atrial Fibrillation and Atrial Flutter Using Multielectrode Automated Electroanatomic Mapping. JACC Clin Electrophysiol. 2018;4(12): 1541-52. https://doi.org/10.1016/j.jacep.2018.08.015.
24. Nairn D, Eichenlaub M, Lehrmann H, et al. Spatial correlation of left atrial low voltage substrate in sinus rhythm versus atrial fibrillation: The rhythm specificity of atrial low voltage substrate. J Cardiovasc Electrophysiol. 2023;34(8): 1613-21. https://doi.org/10.1111/jce.15984.
25. Anyukhovsky EP, Sosunov EA, Plotnikov A, et al. Cellular electrophysiologic properties of old canine atria provide a substrate for arrhythmogenesis. Cardiovasc Res. 2002;54: 462-9. https://doi.org/10.1016/S0008-6363(02)00271-7.
26. Gramley F, Lorenzen J, Knackstedt C, et al. Age-related atrial fibrosis. Age. 2009;31: 27-38. https://doi.org/10.1007/s11357-008-9077-9.
27. Kainuma S, Masai T, Yoshitatsu M, et al. Advanced left-atrial fibrosis is associated with unsuccessful maze operation for valvular atrial fibrillation. Eur J Cardiothorac Surg. 2011;40(1): 61-9. https://doi.org/10.1016/j.ejcts.2010.11.008.
28. Platonov PG, Mitrofanova LB, Orshanskaya V, et al. Structural abnormalities in atrial walls are associated with presence and persistency of atrial fibrillation but not with age. J Am Coll Cardiol. 2011;58(21): 2225-32. https://doi.org/10.1016/j.jacc.2011.05.061.
29. Cochet H, Mouries A, Nivet H, et al. Age, atrial fibrillation, and structural heart disease are the main determinants of left atrial fibrosis detected by delayed-enhanced magnetic resonance imaging in a general cardiology population. J Cardiovasc Electrophysiol. 2015;26: 484-92. https://doi.org/10.1111/jce.12651.
30. Lip GY, Laroche C, Boriani G, et al. Sex-related differences in presentation, treatment, and outcome of patients with atrial fibrillation in Europe: a report from the Euro Observational Research Programme Pilot survey on Atrial Fibrillation. Europace. 2015;17: 24-31. https://doi.org/10.1093/europace/euu155.
31. Xiaocheng C, Qiongwen H, Lei G, et al. Sex-related differences in catheter ablation of atrial fibrillation: a systematic review and meta-analysis. Europace. 2019;21(10): 1509-18. https://doi.org/10.1093/europace/euz179.
32. Wong GR, Nalliah CJ, Lee G, et al. Sex-related differences in atrial remodeling in patients with atrial fibrillation: relationship to ablation outcomes. Circ Arrhythm Electrophysiol. 2022;15(1). https://doi.org/10.1161/CIRCEP.121.009925.
33. Kerr CR, Humphries K. Gender-related differences in atrial fibrillation. J Am Coll Cardiol. 2005;46: 1307-8. https://doi.org/10.1016/j.jacc.2005.07.007.
34. Kuck KH, Brugada J, Schlüter M, et al. The FIRE AND ICE Trial: What We Know, What We Can Still Learn, and What We Need to Address in the Future. J Am Heart Assoc. 2018;7(24). https://doi.org/10.1161/JAHA.118.010777.
35. Tanaka N, Inoue K, Kobori A, et al. Sex differences in atrial fibrillation ablation outcomes: insights from a large-scale multicentre registry. Europace. 2020;22(9): 1345-57. https://doi.org/10.1093/europace/euaa104.
36. Sugumar H, Nanayakkara S, Chieng D, et al. Arrhythmia recurrence is more common in females undergoing multiple catheter ablation procedures for persistent atrial fibrillation: Time to close the gender gap. Heart Rhythm. 2020;17(5 Pt A):692-98. https://doi.org/10.1016/j.hrthm.2019.12.013.
37. Akoum N, Mahnkopf C, Kholmovski EG, et al. Age and sex differences in atrial fibrosis among patients with atrial fibrillation. Europace. 2018;20(7): 1086-92. https://doi.org/10.1093/europace/eux260.
38. Huo Y, Gaspar T, Pohl M, et al. Prevalence and predictors of low voltage zones in the left atrium in patients with atrial fibrillation. Europace. 2018;20(6): 956-62. https://doi.org/10.1093/europace/eux082.
39. Wu N, Liu W, Yang G, et al. Sex difference in atrial scar prevalence: What can we learn from the STABLE-SR-III trial? Heart Rhythm. 2024;21(7): 1001-07. https://doi.org/10.1016/j.hrthm.2024.02.020.
40. Ammar-Busch S, Buiatti A, Tatzber A, et al. Predictors of low voltage areas in persistent atrial fibrillation: is it really a matter of time? J Interv Card Electrophysiol. 2020;57: 345-52. https://doi.org/10.1007/s10840-018-0471-7.
41. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. Eur Heart J. 2013;34(35): 2746-51. https://doi.org/10.1093/eurheartj/eht280.
42. Mahajan R, Lau DH, Brooks AG, et al. Electrophysiological, Electroanatomical, and Structural Remodeling of the Atria as Consequences of Sustained Obesity. J Am Coll Cardiol. 2015;66: 1-11. https://doi.org/10.1016/j.jacc.2015.04.058.
43. Matsuda Y, Masuda M, Asai M, et al. Impact of Renal Dysfunction on Left Atrial Low-Voltage Areas in Patients With Atrial Fibrillation. Circ J. 2019;83(5): 985-90. https://doi.org/10.1253/circj.CJ-18-1277.
44. Seewöster T, Büttner P, Zeynalova S, et al. Are the atrial natriuretic peptides a missing link predicting low-voltage areas in atrial fibrillation? Introducing the novel bio-

marker-based atrial fibrillation substrate prediction (ANP) score. Clin Cardiol. 2020;43(7): 762-68. https://doi.org/10.1002/clc.23378.
45. Kiedrowicz RM, Wielusiński M, Wojtarowicz A, et al. Atrial fibrillation risk scores to evaluate left atrial substrate based on voltage analysis in long-standing persistent type of arrhythmia. Kardiol Pol. 2021;79(5): 525-30. https://doi.org/10.33963/kp.15902.