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The impact of the presence of left atrial low voltage areas on outcomes from pulmonary vein isolation

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Abstract

Background: AF ablation (AFA) with pulmonary vein isolation (PVI) is highly successful for paroxysmal atrial fibrillation (PAF). However, success rates for persistent AF (PsAF) are significantly lower. In this study we evaluate the impact of left atrial (LA) low voltage areas (LVA) on response to AFA.

Methods: Consecutive patients undergoing first-time radiofrequency AFA were included (n = 160, 53% PAF). PVI was performed followed by LA voltage mapping during sinus rhythm. Patients were categorized as having LVA based on the presence of LVA (0.2-0.5 mV) in the LA assessed visually by the operator intra-procedurally. Further adjunctive LA ablation was performed at the operators' discretion. The endpoint was recurrence of any sustained atrial arrhythmia (atrial fibrillation/tachycardia/flutter) during 12 months follow-up.

Results: All patients had PVI and 23 (14%) had adjunctive LA ablation. LVA were found in 49 (31%) patients and were an independent predictor of arrhythmia recurrence. Patients with LVA compared to those without had significantly lower 12-month arrhythmia-free survival in both PAF (38% vs 76%; $P = 0.002$) and PsAF (27% vs 61%; $P = 0.015$). PsAF patients without LVA (93% had PVI alone) had similar arrhythmia-free survival to patients with PAF (61% vs 67%, respectively; $P = 0.42$). Recurrence in patients with LVA compared to those without was more likely to be an organized atrial arrhythmia rather than AF (16/30 recurrences vs 2/26, $P < 0.001$).

Conclusions: The presence of LVA predicts AFA success as well as the type of arrhythmia recurrence. The absence of LVA identifies PsAF patients that respond well to a PVI-based ablation strategy.

KEYWORDS

atrial fibrillation, catheter ablation, left atrial scar, low voltage areas, pulmonary vein isolation

1 | INTRODUCTION

Catheter ablation is a highly successful treatment for patients with symptomatic paroxysmal atrial fibrillation (PAF). In these patients the cornerstone of ablation is elimination of AF triggers by isolation of the pulmonary veins (PVI), and the degree of procedural success directly correlates with the longevity of PVI.[1] However, success rates for catheter ablation in patients with persistent AF (PsAF) are significantly lower. In an attempt to improve outcomes in PsAF, additional ablation beyond PVI is often performed. To date, results have been disappointing for these adjunctive ablation strategies and there is currently no consensus concerning which, if any, are more effective than PVI alone.[2]

An additional question is whether some patients with PsAF respond to PVI alone, and if so how best to identify them.[3] The burden of left atrial (LA) scar quantified by late gadolinium cardiovascular magnetic resonance (LGE-CMR) has been shown to predict response to AF ablation (AFA) in a number of prospective studies.[4] However, LA scar quantification using CMR is highly operator-dependent and not available in most ablation centers.[5] An alternative and more accessible approach to assessing the LA substrate is to perform an intra-procedural voltage map using electro-anatomic mapping (EAM), which enables the real-time identification of the presence of LA low voltage areas (LVA).[6] In this study we evaluate the impact of the real-time assessment of LVA using voltage mapping on outcomes from AFA, and specifically the response to PVI alone.

2 | METHODS

2.1 | Patient population

We included consecutive patients undergoing first-time radiofrequency (RF) AFA at King's College Hospital, a tertiary cardiothoracic centre, between January 2014 and September 2016. Patients were excluded from the study if they had a previous AFA or did not have an LA voltage map performed. Patients that had a previous ablation for another non-AF arrhythmia were included.

PAF and PsAF were defined according to the 2012 HRS/EHRA/ECAS consensus report.[1] Each patient had a preprocedural transthoracic echocardiogram to quantify their LA dimensions and left ventricular function. Routine preprocedural blood tests including renal profile, full blood count, and coagulation screen were performed in all patients.

All patients had been on oral anticoagulation (OAC) for at least 4 weeks preprocedure. Patients on warfarin continued it for the procedure. For patients on a direct oral anticoagulant (DOAC), the medication was held on the evening before and morning of the procedure. Antiarrhythmic drugs, other than amiodarone, were typically stopped at least 48 hours preprocedure.

2.2 | General procedure set-up

All procedures were performed under general anesthesia. Transoesophageal echocardiography was performed preprocedurally to exclude the presence of left atrial thrombus. Vascular access was via the right and/or left femoral veins using two transseptal long sheaths (SL0, St. Jude Medical Inc., St Paul, MN, USA). Transseptal access was performed using a Brockenbrough needle (St. Jude Medical Inc.). After gaining LA access, unfractionated heparin was given to achieve an activated clotting time of greater than 300 seconds.

Mapping and ablation were performed using an electro-anatomic mapping system (CARTO-3 system, Biosense Webster, Diamond Bar, CA, USA; EnSite Velocity, St. Jude Medical, St Paul, MN, USA; Rhythmia mapping system, Boston Scientific, Marlborough, MA, USA). Multipolar mapping catheters were used in all cases (Lasso or PentaRay, Biosense Webster; Inquiry Optima, St. Jude Medical; IntellaMap Orion, Boston).

Ablation was performed with 3-4 millimetre irrigated-tip catheters (Thermocool SmartTouch or Thermocool, Biosense Webster; TactiCath or Flexability, St. Jude Medical; Blazer, Boston Scientific). Power settings of 25-30 watts (w) were used in all areas other than for a cavotricuspid isthmus (CTI) line, where up to 40 w was used, and for a mitral isthmus line, where up to 35 w was used. No specific guidance concerning contact force settings was given.

2.3 | Ablation protocol and voltage mapping

At the start of the case, a detailed LA geometry was created using a multipolar catheter. Wide area circumferential ablation (WACA) was then performed in all patients to achieve PVI. Patients in AF were electrically cardioverted (DCC) either before or after PVI at the operator's discretion.

Following PVI, a voltage map of the LA was created using a multipolar mapping catheter during coronary sinus pacing to confirm PVI and evaluate the LA substrate for LVA (Figure 1). Maps were created using peak-to-peak bipolar voltages and an interpolation threshold for surface color projection was set at 7 for both CARTO (Biosense Webster) and EnSite Velocity (St. Jude Medical). All colour gaps in the map were filled and areas of apparent low voltage were confirmed using an ablator, with the aid of contact force sensing if available.

We used peak-to-peak bipolar voltage cut-offs of 0.2-0.5 millivolts (mV) to define a low-voltage point based on previous studies, which also defined scar tissue as <0.2 mV, disease substrate as 0.2-0.5 mV and normal tissue as >0.5 mV.[7] This real-time assessment was performed visually by the operator during the procedure. No attempt to further classify the degree or pattern of LVA was made. This intra-procedural LVA categorization was used to guide the ablation strategy and forms the basis of the present analysis.

For patients without any spontaneously occurring organized atrial tachyarrhythmia (comprising atrial tachycardia or flutter, OAT), PVI alone was performed. Empiric adjunctive LA ablation was not performed. However, further tailored adjunctive ablation was performed after voltage mapping in 3 situations:

1. To treat an OAT occurring spontaneously after PVI.
2. If DCC failed to restore SR after PVI.
3. To isolate/homogenize LVA seen on the voltage map.

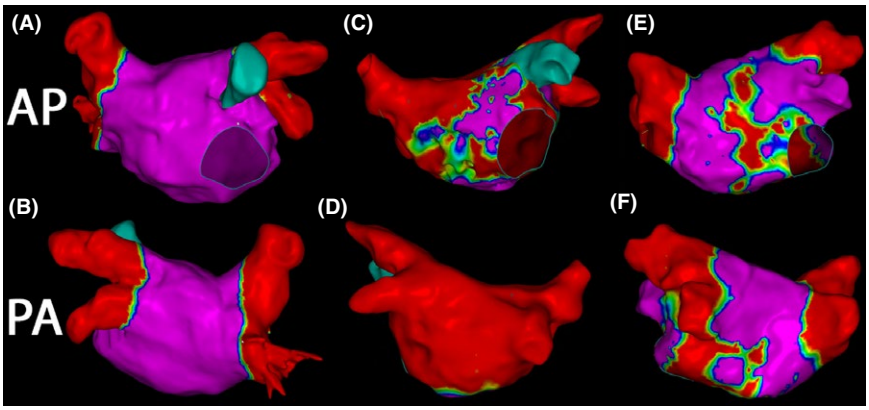

FIGURE 1 LA voltage maps from 3 patients generated using the CARTO mapping system. Voltage maps were performed following PVI with coronary sinus pacing. Bipolar peak-to-peak voltage cut-offs of 0.2-0.5 mV were used to define scar tissue (<0.2 mV – red on the map) and normal tissue (>0.5 mV – purple on the map). The top images (A, C, and E) are in the anteroposterior (AP) projection and the lower images (B, D, and F) in the posteroanterior (PA) projection. Patient 1 (images A/B) has no significant LVA outside of the isolated PVs. Patient 2 (images C/D) has widespread LVA across the posterior wall, septum and roof. Patient 3 (images E/F) has LVA in the inferior and anterior LA

The exact adjunctive LA ablation strategy was at the operator's discretion but included linear lesions (mitral and/or roof lines), posterior wall isolation, box isolation of LVA, and homogenization of LVA. CTI ablation was performed at the operator's discretion.

The end-point for PVI was entrance block of all PVs assessed using the LA voltage map as well as the placement of a multipolar mapping catheter inside individual PVs. PVI was reassessed following a 20 minutes (min) wait for each vein and confirmed with adenosine, given at a dose to induce transient heart block (typically 10-20 mg).

The end-point for linear lesions was bidirectional block. The end-point for posterior wall isolation was an absence of electrograms on the posterior wall, confirmed with voltage mapping and placement of a multipolar mapping catheter within the posterior box. The end-point for box isolation was an absence of signals inside the box and a loss of capture while stimulating with the ablation catheter at a high output (10 V; 2 ms). The end-point for LVA homogenization was a significant reduction in local electrogram size and a loss of capture while stimulating with the ablation catheter at a high output (10 V; 2 ms).

All patients were kept in overnight, and if well, discharged home the following day. Patients on warfarin took their normal dose on the evening of the procedure. Patients on a DOAC restarted it at least 4 hours after the procedure once hemostasis had been achieved.

2.4 | Follow-up

Patients were routinely followed up at 3, 6, and 12 months post-procedure. If they were symptom-free at 12 months, they were subsequently discharged back to their referring doctor. At each outpatient visit they had a 12-lead ECG and clinical assessment. Routine 24-hour Holter monitoring was performed in all patients every 3-6 months until 12 months postprocedure. Patients with ongoing symptoms had more intensive monitoring dictated by their symptom frequency.

OAC was continued until outpatient clinical review and then re-assessed based on the CHA_2DS_2VASc score. Antiarrhythmic drugs (AADs) were stopped at 3 months in patients without evidence of recurrence.

The study end-point was the recurrence of any sustained atrial arrhythmias (atrial fibrillation, atrial tachycardia, or atrial flutter) lasting more than 30 seconds on or off AADs during 12 months of follow-up. Given the difficulty in determining the exact timing of arrhythmia recurrence in a retrospective study, no blanking period was employed in our analysis.

2.5 | Statistical analysis

The SPSS 24.0 software package was used to conduct the statistical analysis. Categorical variables are expressed as numbers (percentages) and compared using the Chi-squared test. Normally distributed continuous variables are expressed as mean ± standard deviation (SD) and compared using Student *t* test.

The association between clinical, laboratory, echocardiographic and scar variables, and arrhythmia-free survival was assessed in univariable Cox proportional hazard analyses. Variables demonstrating a significant association with the end-point ($P < 0.1$) were included in a multivariable model performed using forward stepwise logistic regression analysis. The proportional hazards assumption was checked by plotting the Schoenfeld residuals against rank time and fitting a smooth curve with 95% confidence bands as well as plotting log[log(survival probability)] against time for different variables to ensure that the curves were parallel.

Given the possibility that adjunctive LA ablation in patients with LVA may have worsened outcomes, we also explored the association of LVA and outcomes in an univariable analysis excluding patients with adjunctive LA ablation. However, this variable was not inserted into the multivariable model.

Kaplan-Meier survival curves were created for the end-point of arrhythmia-free survival. Patients were grouped by type of AF (PAF

vs PsAF) as well as the presence or absence of LVA. Arrhythmia-free survival was then compared between groups using the log-rank test.

Any differences were considered significant with a $P < 0.05$.

3 | RESULTS

3.1 | Patient population

During the 2-year study period 190 patients had a first-time RF AFA. Of these, 160 had an LA voltage map performed and were included in our analysis (Table 1). The mean age was 60 ± 10 years, 67% (n = 108) were male, and 53% (n = 85) had PAF.

3.2 | Procedural details

The mean procedure duration was 193 ± 50 minutes and mean fluoroscopy time 22 ± 10 minutes. All cases used an electro-anatomic mapping system and the majority a force-sensing catheter (94%). Full procedural details are given in Table 2.

TABLE 1 Clinical characteristics of all patients with first-time RF AFA included in the analysis

Characteristics	Total population (n = 160)
Age, y	60 ± 10
Sex (Males)	108 (67)
Paroxysmal AF	85 (53)
LA diameter (cm)	4.5 ± 0.5
LVEF (%)	52 ± 5
Creatinine (μmol/L)	82 ± 20
eGFR (mL/min/1.73 m^2)	76 ± 13
Heart failure	20 (13)
Hypertension	75 (47)
Previous stroke	6 (4)
Diabetes (Type 1 or 2)	15 (9)
Known CAD	21 (13)
CHA_2DS_2VASc score	1.6 ± 1.3
Previous cardioversion	82 (51)
Previous non-AF ablation	13 (8)
AADs on admission	
Class 1	41 (26)
Class 2	85 (53)
Class 3	66 (41)
Class 4	11 (69)
Class 5	9 (6)
Previously tried ≥ 2 AAD	66 (41)

Data are presented as mean ± SD or n (%).
RF AFA, radiofrequency atrial fibrillation ablation; LA, left atrium; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; AAD, antiarrhythmic drugs.

PVI was performed in all patients and 28% (n = 44) required DCC back to SR to enable voltage mapping. LVA were found in 31% of patients (n = 49) and were more frequently seen in patients with PsAF (n = 32/75, 43%) than PAF (n = 17/85, 20%) ($P < 0.001$).

3.3 | Adjunctive ablation

Overall the vast majority of patients were treated with PVI alone (n = 137, 86%). A small number (n = 23, 14%) had adjunctive substrate modification performed after voltage mapping, 18 of these had LVA. The documented indications for adjunctive LA ablation were:

1. To treat a spontaneous OAT occurring after PVI – 10 patients.
2. Failure of DCC to restore SR after PVI – 5 patients.
3. To isolate/homogenize LVA present on the voltage map – 8 patients.

For patients with PAF (n = 85), seven had adjunctive LA ablation performed, of which five had LVA (Figure 2). Three patients had an intra-procedural OAT following PVI mapped and then treated with linear ablation, 3 patients had LVA treated with posterior wall isolation (n = 1) or LVA homogenization (n = 2), and 1 patient failed to cardiovert following DCC and had linear ablation performed with subsequent successful cardioversion.

For patients with PsAF (n = 75), 16 had adjunctive LA ablation performed, of which 13 had LVA (Figure 2). Six had an intra-procedural OAT following PVI mapped and then treated with linear ablation (n = 5) or posterior wall isolation (n = 1). One patient had a previous diagnosis of an OAT that was treated with linear ablation. Five patients had LVA treated with posterior wall isolation (n = 1), LVA homogenization (n = 2) or linear ablation (n = 2). Four patients failed to cardiovert with DCC and had posterior wall isolation performed, with subsequent successful cardioversion.

Four (2.5%) patients experienced major procedural complications comprising of a mitral valve injury because of the multipolar mapping catheter entrapment (n = 1), pericardial effusion requiring percutaneous drainage (n = 2), and a right leg pseudoaneurysm (n = 1).

3.4 | Outcomes

Fifty-six patients (35%) had arrhythmia recurrence during follow-up. This was AF in 38 patients and an OAT in 18 patients. In the total population, 12-month arrhythmia-free survival was 57% and significantly higher for patients with PAF than PsAF (67% vs 44%, P = 0.008) (Figure 3).

3.5 | Predictors of recurrence

In univariable analyses, variables significantly associated with arrhythmia recurrence were LA size ($P < 0.001$), the presence of LVA ($P < 0.001$), a history of hypertension ($P = 0.004$), and type of AF (PAF vs PsAF) ($P = 0.01$) (Table 3). In multivariable analysis LA size ($P = 0.03$), the presence of LVA ($P = 0.002$) and a history of

TABLE 2 Procedural data of all patients according to type of AF

Variables	PAF (n = 85)	PsAF (n = 75)	Total (n = 160)
Procedural time	191 ± 50	195 ± 50	193 ± 50
Fluoroscopy time	20 ± 13	23 ± 15	22 ± 10
Presented to Lab in AF	17 (20)	55 (73)	72 (45)
DCCV after PVI	15 (18)	29 (39)	44 (28)
Mapping system used			
Carto	47 (55)	43 (57)	90 (56)
NavX	31 (36)	29 (39)	60 (38)
Rhythmia	7 (8)	3 (4)	10 (6)
Contact force-sensing catheter used	79 (93)	71 (95)	150 (94)
LVA present on voltage map	17 (20)	32 (43)	49 (31)
CTI line performed	16 (19)	9 (12)	25 (16)
PVI performed	85 (100)	75 (100)	160 (100)
Adjunctive LA ablation	7 (8)	16 (21)	23 (14)
Linear lesions	4 (5)	8 (11)	12 (8)
Posterior wall isolation	1 (1)	6 (8)	7 (4)
LVA Homogenization/Isolation	2 (2)	2 (3)	4 (3)
Indications for adjunctive LA ablation			
Spontaneous OAT	3 (4)	7 (9)	10 (6)
To treat LVA	3 (4)	5 (7)	8 (5)
Unable to DCC after PVI	1 (1)	4 (5)	5 (3)

Data are presented as mean ± SD or n (%).
AF, atrial fibrillation; PAF, paroxysmal AF; PsAF, persistent AF; DCC, direct current cardioversion; PVI, pulmonary vein isolation; LVA, low voltage areas; CTI, cavotricuspid isthmus; LA, left atrium; OAT, organized atrial tachyarrhythmia.

hypertension ($P = 0.03$) remained significantly associated with recurrence, whereas type of AF did not ($P = 0.09$).

3.6 | AFA and heart failure

Twenty patients had a clinical diagnosis of heart failure prior to AFA (Baseline left ventricular ejection fraction (LVEF), 41% ± 9). Compared to patients without heart failure, the presence of heart failure was not significantly associated with arrhythmia recurrence following AFA ($P = 0.24$). Independent factors associated with reduced 12-month arrhythmia-free survival in the heart failure patients were the presence of LVA (found in 10/20 patients, $P = 0.01$), a preprocedural LVEF ≤ 35% (6/20, $P = 0.04$) and a moderate to severely dilated LA (8/20, $P = 0.007$).[8] There was no difference in arrhythmia-free survival between PAF and PsAF (6/20 PAF, $P = 0.12$).

3.7 | Relationship between LVA and outcomes

In the total population (n = 160), patients with LVA had significantly lower 12-month arrhythmia-free survival compared to patients without LVA (32% vs 70%, $P < 0.001$) (Figure 3). This finding remained consistent in the subgroups of patients with PAF (38% vs 76%, $P = 0.002$) and PsAF (27% vs 61%, $P = 0.015$).

There was a strong association between LVA status and response to PVI alone. The absence of LVA identified patients that responded well to PVI alone, with 12-month arrhythmia-free survival of 76% in PAF (n = 66) and 60% in PsAF (n = 40) (Figure 2). In contrast, success rates for PVI only in patients with LVA were much lower, with 12-month success rates of 46% in PAF (n = 12) and 37% in PsAF (n = 19). Furthermore, patients with PsAF but without LVA (n = 43) had similar arrhythmia-free survival rates compared to patients with PAF (61% vs 67%, respectively, $P = 0.42$). This was also valid when compared independently with both, PAF patients with LVA ($P = 0.17$) and without LVA ($P = 0.09$).

In our study we used four multipolar mapping catheters across the 160 cases. The incidence of LVA for each mapping catheter was 31% for Lasso (32/103 patients), 29% for PentaRay (10/34 patients), 31% for Optima (4/13 patients), and 30% for Orion (3/10 patients). There was no difference in LVA incidence across these groups ($P = 0.99$) suggesting that catheter type may not have a major impact on LVA identification.

3.8 | Outcomes without adjunctive ablation

The association between the presence of LVA remained significant even when patients that had adjunctive LA ablation were excluded from the analysis (n = 23). For patients treated with PVI alone, 12-month success

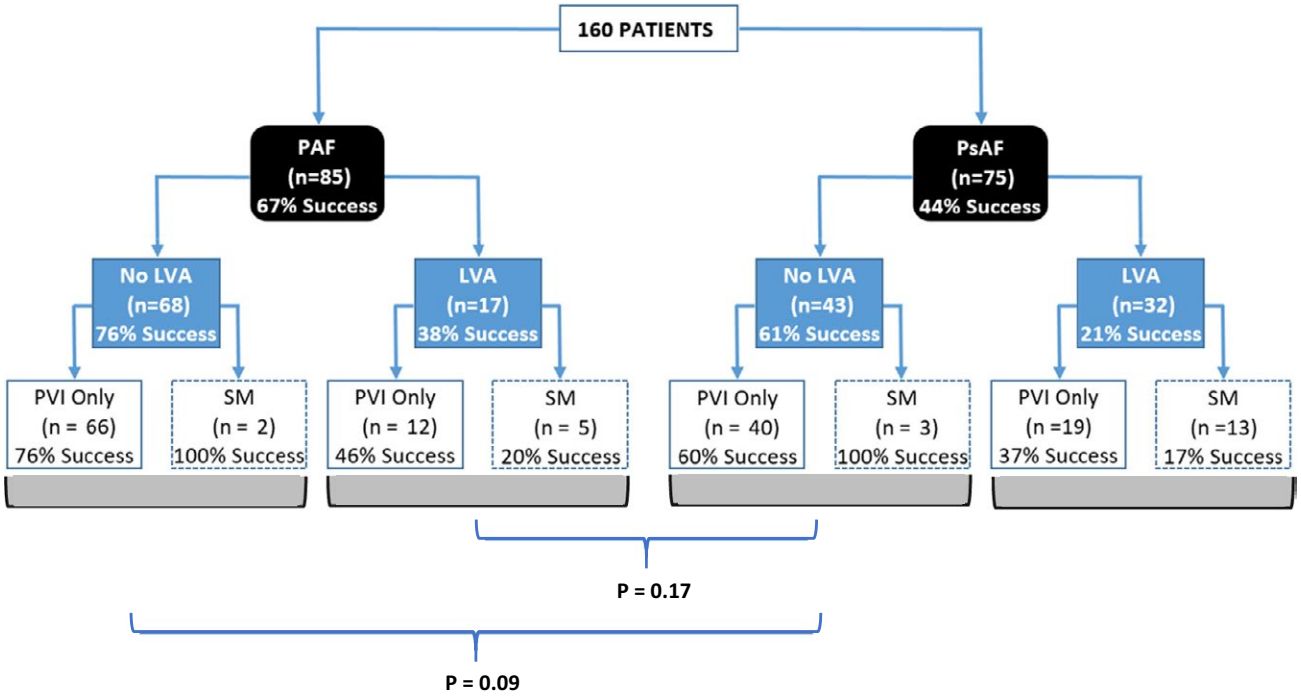

FIGURE 2 12-month arrhythmia-free survival rates (%) according to a type of AF, presence of LVA, and type of AFA performed. All patients had PVI and some had additional LA substrate modification. PAF, Paroxysmal Atrial Fibrillation; PsAF, Persistent atrial fibrillation; LVA, low voltage areas; PVI, pulmonary vein isolation; SM, substrate modification

rates were much lower for patients with LVA compared to without (n = 137, $P = 0.003$). Adjunctive LA ablation was not associated with improved outcomes in patients with LVA and 12-month arrhythmia-free survival was similar in patients with LVA whether adjunctive LA ablation was or was not performed (18% vs 41%, respectively, $P = 0.19$).

3.9 | Relationship between LVA and type of arrhythmia recurrence

There was a significant relationship between the presence of LVA and the type of arrhythmia recurrence post-AFA. In the 111 patients without LVA 26 experienced a recurrent atrial arrhythmia, 24 with AF, and 2 with an OAT. The two OATs comprised of one CTI-dependent atrial flutter and one arrhythmia of undetermined mechanism (redo procedure not performed). In the 49 patients with LVA 30 experienced a recurrent arrhythmia, 14 with AF and 16 with an OAT ($P < 0.001$). The 16 OATs comprised of one focal LA atrial tachycardia, five LA macro-reentrant atrial flutters, two CTI-dependent atrial flutters and eight arrhythmias of undetermined mechanism (redo procedures were not performed, or the arrhythmia terminated/degenerated prior to mapping).

The association between LVA and type of recurrence remained irrespective of whether adjunctive ablation was performed or not. In the 31 patients with LVA but without adjunctive LA ablation 6/16 recurrences were because of an OAT ($P = 0.04$ vs patients without LVA). Furthermore, none of these 6 patients had an identifiable OAT on initial AFA. In the 18 patients with LVA and adjunctive LA ablation 10/14 recurrences were because of an OAT ($P < 0.001$).

There was also no association between preexisting OAT and recurrence. Out of the 18 OAT recurrences in patients with and without LVA, only 6/18 were documented as having an OAT following PVI in the first AFA and therefore treated. However, 12/18 recurrences of OAT were new and 10/12 of these patients had LVA.

4 | DISCUSSION

4.1 | Main findings

There are three main findings of our study. First, in both PAF and PsAF the presence of LVA, assessed in real-time intra-procedurally by the operator, are a strong and independent predictor of arrhythmia recurrence following AFA. Second, the presence of LVA predicts the type of arrhythmia recurrence, with patients having LVA more likely to present with an OAT (rather than AF) compared to patients without LVA. Importantly, both these associations remained irrespective of whether adjunctive LA ablation was performed or not. Third, patients with PsAF but no LVA have similar 12-month arrhythmia-free survival rates compared to patients with PAF (61% vs 67%, respectively) and respond well to PVI alone.

4.2 | LVA predict AFA success

Our finding, that the presence of LVA predict outcomes following AFA, is consistent with previous studies using both MRI and EAM to quantify LA scar. The DECAAF study evaluated the relationship

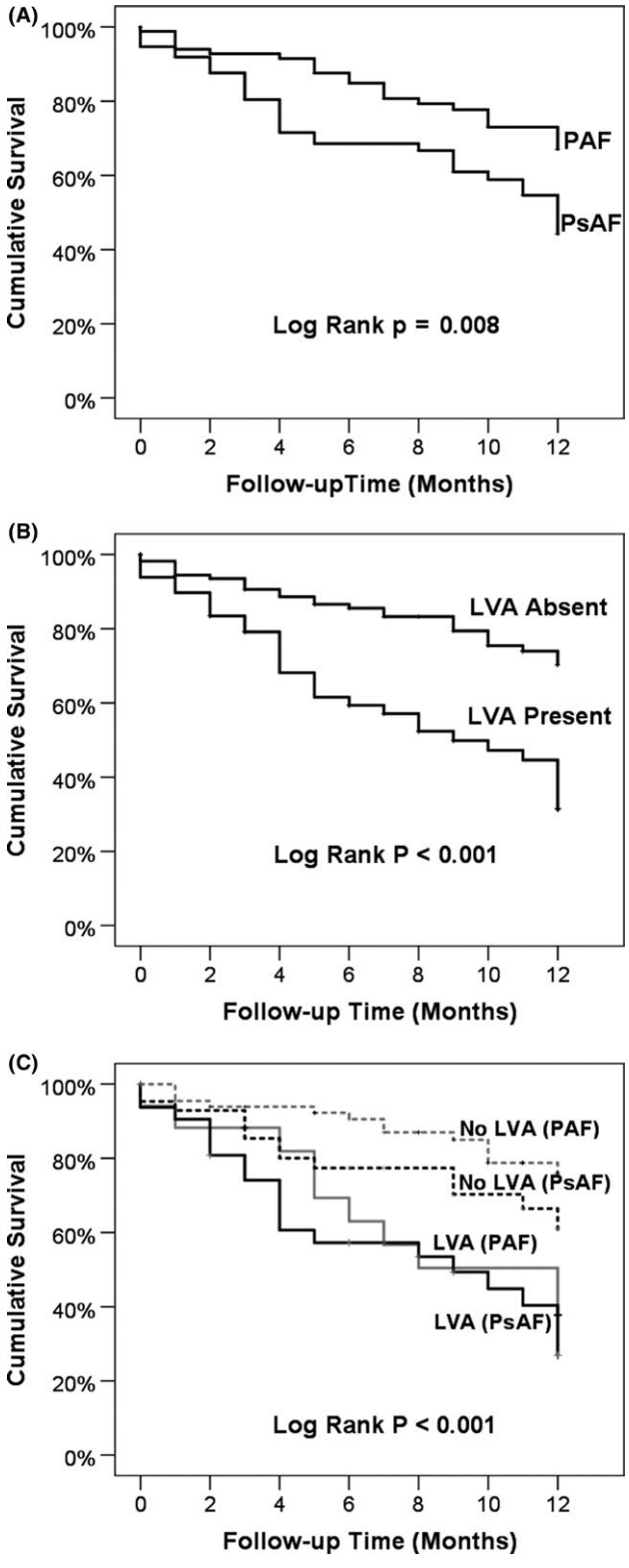

FIGURE 3 Kaplan-Meier survival curves demonstrating arrhythmia-free survival over 12 months. Patient groups are stratified by (A) type of AF (PsAF vs PAF), (B) the presence/absence of LVA and (C) both type of AF and presence of LVA

between LA fibrosis, quantified by LGE-MRI, and outcomes in a prospective, multicenter study of 272 patients undergoing AFA.[4] The percent atrial fibrosis was a strong and independent predictor of arrhythmia recurrence, with a hazard ratio of 1.06 (95% CI, 1.03-1.09; $P < 0.001$) per 1% increase in atrial fibrosis. However, the assessment of LA scar using MRI is not widely available in clinical practice and has limitations.[9] Even in experienced centers a proportion of scans are not suitable for assessment—in DECAAF 17% of the scans were excluded because of the poor quality.[4] Furthermore, although many studies suggest a strong relationship between MRI-defined LA scar burden and outcomes after AFA, not all investigators have been able to reproduce these findings and most data in this area has come from a small number of specialist centers.[5]

The presence of left atrial LVA generated using EAM correlates well with the amount of LGE on MRI.[10] Additionally, the presence of LVA also predict arrhythmia recurrence following AFA. In an early study looking at the prognostic importance of LVA, Verma et al studied 700 consecutive AF patients (61% persistent) undergoing first-time PVI.[11] Six per cent of patients had widespread left atrial scarring and these patients had a higher rate of arrhythmia recurrence compared to patients without scar (57% vs 19%, $P = 0.003$). These findings have been confirmed more recently by other investigators.[6,12,13] In a single-center prospective observational study, Masuda et al evaluated the impact of the presence of LVA on outcomes in 152 consecutive patients (46% persistent) undergoing first-time AFA.[13] LVA were identified in 41% of the patients. During a mean follow-up of 9 months, 22% of the patients had recurrent atrial arrhythmias, and after adjustment for the type of AF the presence of LVA was a strong predictor ($P = 0.013$) of arrhythmia recurrence.

4.3 | LVA and outcomes in PAF

In our study we found that LVA predicted outcomes in both PsAF and PAF, irrespective of whether adjunctive LA ablation was performed. Most previous studies have focussed on patients with PsAF, because of their lower AFA success rates. However, success rates with PVI alone in contemporary studies of PAF are still limited, with 1-year success rate of around 65%, irrespective of the technology used.[14] The finding that LVA are present in some patients with PAF, and that these patients have higher recurrence rates, may explain why some PAF patients do not respond to a PVI-alone strategy. Similar findings have also been observed more recently by other investigators.[15,16]

4.4 | LVA predict type of arrhythmia recurrence

In our cohort we found that the presence of LVA did not just predict arrhythmia recurrence post-AFA, but also the type of arrhythmia. Patients with LVA were more likely to experience the spontaneous occurrence of an OAT both in the lab and during follow-up, irrespective of whether or not they had adjunctive LA ablation or a preexisting OAT. In patients with LVA over half of the recurrences were because of an OAT, compared to only a small minority in patients without LVA.

TABLE 3 Cox proportional hazards analyses demonstrating the association of clinical, laboratory, echocardiographic, and procedural variables and 12-month arrhythmia-free survival

	Univariable analysis		Multivariable analysis	
	P	HR (95% CI)	*P*	HR (95% CI)
Age (per year)	0.11	1.02 (1.00-1.05)		
Male gender (vs female)	0.24	0.73 (0.43-1.24)		
Hypertension	0.004	2.23 (1.29-3.85)	0.03	1.85 (1.06-3.22)
Heart failure	0.25	1.52 (0.74-3.09)		
Vascular disease	0.84	0.92 (0.39-2.14)		
Diabetes	0.22	1.70 (0.73-3.98)		
CAD history	0.80	0.90 (0.39-2.10)		
Creatinine (per 1 μmol/L)	0.88	0.99 (0.99-1.01)		
LA size (per cm increase)	<0.001	1.66 (1.27-2.16)	0.03	1.37 (1.04-1.79)
LVEF	0.21	1.23 (0.89-1.23)		
PsAF (vs PAF)	0.01	2.00 (1.17-3.42)	0.09	NS
LVA present	<0.001	3.01 (1.78-5.09)	0.002	2.38 (1.37-4.13)
LVA present (excluding patients with adjunctive LA ablation)	0.004	2.51 (1.35-4.69)		

Abbreviations as in Tables 1 and 2.

4.5 | LVA to guide AF ablation strategy

Our results show success rates for PsAF patients identified without LVA, treated with PVI alone, and were very similar to patients with PAF, with 12-month success rates of 60%. These findings are consistent with other studies that have used LVA to guide ablation. In a study of 41 patients undergoing AFA by Kottkamp et al, 13 PsAF patients treated with PVI only had little or no LVA. After 12 months follow-up 69% remained in SR.[17] These findings have been reproduced by others with typical single-procedure success rates in PsAF patients, without LVA, treated by PVI alone ranging from 60%-75%.[6,18]

Over the last decade research has focused on developing adjunctive ablation strategies that can be employed in addition to PVI in unselected PsAF patients. While early observational and randomised studies showed encouraging results, more recent larger RCTs have proven negative and suggest that when AFA in concerned, less may be more. The STAR AF II study evaluated three ablation strategies in a prospective, multicenterd, randomized trial of 589 patients with PsAF.[19] After 18 months, there was no improvement in freedom from AF for patients who had PVI plus linear ablation (46%) or complex fractionated atrial electrogram (CFAE) ablation (49%), when compared to PVI alone (59%) ($P = 0.15$). The CHASE-AF study was a prospective, single-center, randomized trial of 205 patients with PsAF. It found no additional benefit in arrhythmia-free survival when a stepwise ablation approach, consisting of PVI followed by biatrial ablation of CFAEs and linear ablation lines, was compared with PVI alone, in patients where AF did not terminate after PVI ($P = 0.468$).[20]

A number of centers have published recent series using voltage mapping to guide individualized substrate-based ablation.[6,13,17,18] This has typically involved linear lesions to prevent macro-reentrant LA flutter, or isolation/homogenization of LVA. These studies have reported significantly higher success rates with this approach compared to historical controls. In our center, although this individualized substrate-based ablation approach was performed in some cases, during the majority of the study period there was little data to support it and most operators opted for PVI alone for the majority of patients with PsAF that cardioverted successfully in the lab without a spontaneous OAT. Furthermore, in our series adjunctive LA ablation in patients with LVA did not improve outcomes compared to PVI alone. However, the numbers were small and there may have been significant selection bias as patients with adjunctive LA ablation were likely to have a more diseased substrate. Given the lack of randomized data, the benefit of such tailored ablation approaches remains uncertain.

It is not clear whether LVA are mechanistically important in the pathophysiology of atrial arrhythmias, or purely associated with their occurrence. Two pieces of data support their mechanistic involvement. First, some authors have found that ablation sites that result in AF termination frequently coexist with LVA. In a study of 85 patients undergoing ablation for PsAF, high density voltage mapping was performed following PVI if AF persisted. Ablation was then performed during AF in areas of low voltage that demonstrated fractionated activity, which led to AF termination in 73% of the patients. When voltage mapping was then performed in sinus rhythm,

the termination sites were colocated with LVA in 80% of the time.[18] Second, as described above, a number of studies have used LVA as targets for ablation and reported improved arrhythmia-free survival in comparison to PVI alone.[6,17]

4.6 | Real-time assessment of LVA

In our study, the presence or absence of LVA was assessed visually by the operator during the procedure rather than off-line. The rationale for this was that the study aimed to evaluate whether a voltage map, generated and interpreted intra-procedurally in real-time by the operator, could be used to guide both ablation strategy and future management decisions. It is possible that if the scar maps were evaluated off-line in more detail, there may be some reclassification of patients in terms of the presence or absence of LVA. However, there is currently no rapid, automated tool available to detect and quantify LVA, and therefore for the purposes of decision-making during the procedure visual assessment of the presence of LVA is the most pragmatic approach. Furthermore, despite our approach the incidence of patients defined as having LVA in our study (20% in PAF, 43% in PsAF) was similar to other single-center observational studies, which have reported an LVA prevalence of 15%-34% for PAF and 35%-50% for PsAF.[6,7,13,21]

4.7 | Study limitations

Our study has a number of limitations that should be considered when interpreting our results. First, it is a small, retrospective, single-center observational study, and at risk of all the limitations inherent in such a study design.

Second, at 12 months the follow-up was relatively short. This is based on clinical practice in the United Kingdom (UK), where most patients are discharged back to primary care or their referring hospital if they are symptom-free at 12 months. It is possible that a longer follow-up would have altered the results. Furthermore, we did not include a postprocedural blanking period in our analysis. The reason for this is that in a retrospective analysis it is difficult to determine accurately when an arrhythmia recurred, and more specifically whether it recurred within the blanking period. However, since this issue is likely to have affected all patients equally, it should not have significantly impacted on the nature of the results only the absolute success rates, which are likely to be lower.

Third, while our results show no difference in the incidence of LVA having used different multipolar mapping catheters, this may still have affected the true value. The voltage maps were also generated after PVI so that they could be used to confirm PVI. However, by this approach it is possible that LVA within the WACA may have been missed or the WACA itself could have influenced LVA distribution. In addition, as described above, voltage maps were interpreted by the operator during the case, rather than analyzed off-line. This may have led to some inaccuracies in terms of classification of the presence of LVA.

Lastly, the voltage cut-offs used to define LVA (0.2 and 0.5 mV) were based on previous studies.[7] However, these cut-offs are relatively arbitrary and precise cut-offs of what defines diseased substrate remains unclear. These cut-offs have also not been evaluated in all mapping systems.

5 | CONCLUSION

The presence of LVA predicts success as well as the type of arrhythmia recurrence following AFA. The absence of LVA identifies a group of PsAF patients that respond reasonably well to a PVI-based ablation strategy, with similar arrhythmia-free survival to patients with PAF.

CONFLICT OF INTEREST

The authors declare no conflict of interests for this article.

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