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Low voltage-guided ablation of posterior wall improves 5-year arrhythmia-free survival in persistent atrial fibrillation

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Abstract

Introduction: The posterior wall (PW) has been proposed as a standard target for ablation beyond pulmonary vein antral isolation (PVI) in patients with persistent atrial fibrillation (AF). However, studies have shown inconsistent outcomes with the addition of PW ablation. The presence or absence of low voltage on the PW may explain these inconsistencies. We evaluated whether PW ablation based on the presence or absence of low voltage improves long-term arrhythmia-free outcomes.

Methods: We retrospectively reviewed 5-year follow-up in 152 consecutive patients who received either standard ablation (SA) with PVI alone or PVI + PW ablation (PWA) based on physician discretion ($n = 77$) or voltage-guided ablation (VGA) with PVI and addition of PWA only if low voltage was present on the PW ($n = 75$).

Results: The two groups were well matched for baseline characteristics. At 5-year follow-up, 64% of patients receiving VGA were atrial tachyarrhythmia (AT)/AF free compared to 34% receiving SA (HR 0.358 $p < .005$). PWA had similar AF recurrence in SA and VGA groups (0.30 vs. 0.27 $p = .96$) but higher AT recurrence when comparing SA and VGA groups (0.39 vs. 0.15 $p = .03$). In multivariate analysis, both VGA and PWA predicted AF arrhythmia-free survival (HR 0.33, $p = .001$ and HR 0.20, $p = .008$, respectively). For AT, VGA predicted arrhythmia-free survival (HR 0.22, $p = .028$), while PWA predicted AT recurrence (HR 4.704, $p = .0219$).

Conclusion: VGA of the posterior wall ablation beyond PVI in persistent AF significantly improves long-term arrhythmia-free survival when compared with non-voltage-guided ablation. PW ablation without voltage-guidance reduced AF recurrence but at the cost of a higher incidence of AT.

KEYWORDS

catheter ablation, low voltage, persistent atrial fibrillation, posterior wall

[Correction added on 26 October 2022, after first online publication: Revised manuscript is republished.]

Drs. Michael J. Cutler and Prasongchai Sattayaprasert contributed equally to this study.

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1 | INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia to date that carries significant morbidity and mortality.¹ As the annual incidence of AF continues to rise, the management of AF presents an increasing societal burden. Catheter ablation has become an important component of the management of both paroxysmal and persistent AF yet, recurrence of AF following catheter ablation in patients with persistent AF remains high when compared to patients with paroxysmal AF.^{2,3}

Furthermore, the current consensus on the location and extent of ablation beyond pulmonary vein antral isolation (PVI) for persistent AF remains uncertain.²⁻⁴ Nonpulmonary vein triggers in persistent AF have been identified in the posterior wall of the left atrium, left atrial appendage, and coronary sinus, and ablation targeting these regions have shown improved AF-free survival in persistent atrial fibrillation.^{5,6} Although these triggers can be seen spontaneously or provoked pharmacologically, they are not always present during the ablation procedure. The posterior wall which shares its embryological origins with the pulmonary vein sleeves has been proposed as the standard target for ablation beyond the pulmonary veins in patients with persistent AF.⁷ However, persistent AF ablation studies for left atrial posterior wall ablation in addition to PVI have shown inconsistent outcomes and recent data have raised some doubt as to the benefits of this additional ablation.⁸

The presence of low amplitude of left atrial electrograms in sinus rhythm and in atrial fibrillation, referred to as low voltage, has been correlated with atrial fibrosis and may be a target for catheter ablation in patients with persistent AF.^{9,10} Previously, we reported that 1-year arrhythmia-free survival was improved using a voltage-guided ablation (VGA) strategy to guide ablation of the posterior wall in addition to PVI in persistent AF patients. Specifically, VGA of the posterior wall reduced recurrence of atrial fibrillation compared to both PVI alone or PVI with the posterior wall in this study. We now present long-term (5-year) follow-up in these patients with a detailed analysis of recurrence type that gives further insight into the previously reported inconsistencies in posterior wall ablation outcomes.

2 | MATERIALS AND METHODS

We present 5-year data on a single-center retrospective clinical study of two AF ablation strategy techniques: (1) standard ablation (SA) versus (2) VGA. Consecutive patients presenting for ablation of persistent AF from 2010 to 2014 were included in the study. This study only included patients with persistent AF. Patients with longstanding persistent AF, paroxysmal AF, or prior AF ablation were excluded.

2.1 | Ablation strategy

PVI was performed in all patients. With SA, ablation of the left atrial (LA) posterior wall beyond PVI was performed at the discretion of the operator, but importantly the decision was not guided by the presence or absence of low voltage. With VGA, additional ablation of the LA posterior wall was performed only if the voltage mapping of this region in sinus rhythm showed low voltage (LA voltage < 0.5 mV at >0.5 × 0.5 cm). Six total operators performed these procedures. Three of our operators only used the standard approach, while the other three adapted the voltage-guided approach. This investigation was performed with the approval of the MetroHealth Institutional Review Board. Figure 1 shows a schematic of the study design.

2.2 | Ablation and mapping techniques

All procedures were performed with uninterrupted anticoagulation and off antiarrhythmic drugs for at least 3 days before the ablation. Amiodarone was stopped 1 month before ablation. An irrigated tip catheter for all procedures with energy delivered from 25 to 40 W. With the standard approach, PVI is followed by LA posterior wall ablation at the discretion of the operator based on factors such as the presence of complex fractionated electrograms, the size of the left atrium, the persistence of AF following PVI, and observation of nonpulmonary vein triggers arising from the posterior wall spontaneously or with isoproterenol infusion. Once the operator

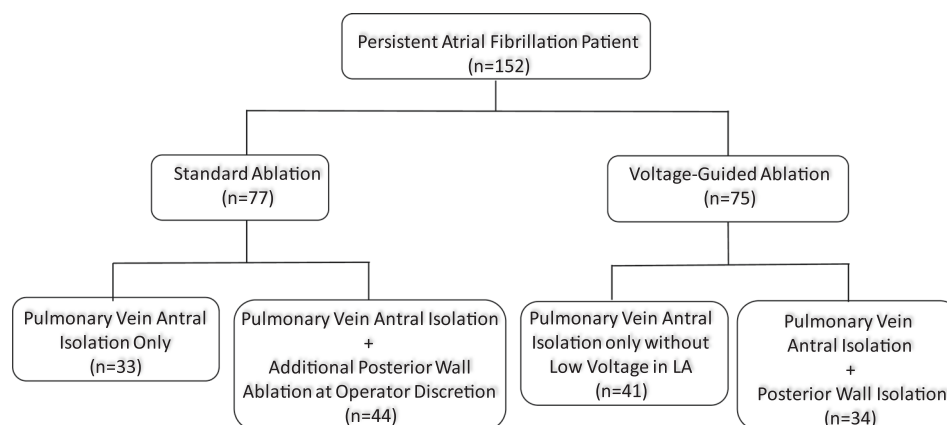


FIGURE 1 Study Design. Breakdown of 152 consecutive patients with persistent atrial fibrillation presenting for catheter ablation with 77 receiving standard ablation strategy and 75 receiving a voltage-guided strategy.

completed all planned ablation, if AF persisted, the patient is cardioverted.

In the VGA group, cardioversion is performed after pulmonary vein isolation was achieved if AF persisted. Subsequently, posterior wall voltage mapping is performed using a 3-D electroanatomical mapping system (Biosense Webster) during sinus rhythm. Based on previous publications, we defined the presence of a scar as a region on the posterior wall with a voltage less than 0.5 mV. We used the presence of a stable near-field bipolar electrogram and beat-to-beat catheter tip stability on fluoroscopic inspection to demonstrate adequate contact during the mapping of each point. Contact force ablation catheters were not available at our institution during the time period of this study. The presence of low voltage was defined as a voltage of <0.5 mV reproducibly measured within an area of at least $0.5 \times 0.5 \text{ cm}^2$ within the posterior wall. Points, where the voltage was <0.5 mV but were within 5 mm from radiofrequency (RF) lesions delivered for PVI, were excluded. With VGA, operators were encouraged to take as many points on the posterior wall as possible, but at least 10 points to cover the entirety of the posterior wall. We defined the anatomical limits of the posterior wall superiorly by a line connecting the superior most aspect of the left and right superior veins and inferiorly by a line connecting the most inferior aspect of the left and right inferior veins. Typically, once low voltage was found, high-density point-by-point mapping was performed in the region to fully delineate the border of the low-voltage region. With VGA, additional ablation on the LA posterior wall was performed only if voltage mapping of this region in sinus rhythm showed areas of low voltage. If no low voltage was seen, no further LA ablation was performed. If low voltage of posterior wall was found, posterior wall ablation was completed. In the SA group, a left atrial voltage map was not obtained. In this study, only the posterior wall was mapped in the VGA group. In patients with low voltage found on the posterior wall, the extent of low voltage on the posterior wall was analyzed retrospectively by two blinded electrophysiologists and categorized as covering >50% of the posterior wall, 25%–50% of the posterior wall, or less than 25% of the posterior wall.

With posterior wall isolation in both SA and VGA groups, our operators most frequently performed a posterior roof line (connecting the superior border for the left superior pulmonary vein and right superior pulmonary vein antra) and a floor line connecting the inferior border of the left inferior pulmonary vein and right inferior pulmonary vein antra) completing a posterior wall “box.” Importantly, the borders of the box were intended to encompass the area of low voltage. However, posterior wall isolation could also be accomplished by sequential targeting of posterior wall electrograms. All operators were encouraged to demonstrate posterior wall exit block, by either dissociated capture of the posterior wall or non-capture of the posterior wall with pacing from the ablation catheter at a 10 mA output, as an immediate endpoint when posterior wall ablation was performed. In both groups, at the operator's discretion, a region of the posterior wall could be left unablated if clinically indicated, such as with esophageal temperature concerns.

Finally, our protocol during this time period was to encourage superior vena cava (SVC) isolation in all patients coming for PVI and to challenge with isoproterenol at $20 \mu\text{g}/\text{min}$ for 10 min. Additional

ablation in the LA was performed in both SA and VGA when reconnection of the pulmonary veins and posterior wall (when performed) was observed during isoproterenol infusion. At the time, we were not using adenosine challenge. With SA, additional ablation for nonpulmonary vein triggers was performed at the operator's discretion. However, during the first ablation for AF, the SA operators generally avoided ablation beyond pulmonary veins, posterior wall, and SVC. With VGA, additional ablation of the nonpulmonary vein triggers based on isoproterenol infusion was not performed.

2.3 | Patient follow-up

All patients underwent our institution's protocol for follow-up postablation. Patients are seen 1, 3, 6, 9, and 12 months postablation with ECG at each visit. Event monitor is provided for 3 months postablation with weekly asymptomatic transmissions as well as transmissions for symptoms. A 2-week Holter is obtained at 6 months postablation. Operators were encouraged to use antiarrhythmic medications initially postprocedure with amiodarone stopped 2-month postablation and all other antiarrhythmic medication stopped 3 months postablation.

Atrial tachyarrhythmia or atrial fibrillation (AT/AF)-free endpoint was defined as no sustained (greater than 30 s) or symptomatic AT/AF seen off antiarrhythmic medication after a 2-month postablation blanking period. Re-initiation of antiarrhythmic medication was assumed to be a result of recurrence of atrial arrhythmias and therefore was treated as a recurrence event. Atrial tachyarrhythmias were defined as any atrial flutter or atrial tachycardia.

Beyond 12-month postablation patients were followed clinically in our system by internists, cardiologists, or electrophysiologists. Rhythm documentation was performed on an “as needed” basis with ECG's, events, and Holter monitors after 12 months.

2.4 | Statistical analysis

All continuous variables were analyzed with a Student *t*-test. Categorical variables were compared with a χ^2 test. Arrhythmia-free survival was analyzed with a Kaplan–Meier method. We constructed a Cox proportional hazards model for AF and AT recurrences that included procedural variables (VGA strategy, posterior wall ablation, posterior box technique, and posterior wall exit block), patient characteristics, and the two baseline variables that represented structural heart disease (LA volume index and LVEF). Statistical significance was set as two-sided $p < .05$ for all tests.

3 | RESULTS

3.1 | Clinical characteristics

One hundred and fifty-two consecutive patients with persistent AF presenting for initial PVI from 2010 to 2014 were included, with 77

patients in the SA group and 75 patients in the VGA group. Table 1 shows the baseline clinical characteristics of these patients and demonstrates that the groups were well matched at baseline. The majority of patients in both groups were male with a high prevalence of congestive heart failure and hypertension. Both patient groups demonstrated mild to moderate left atrial enlargement. Moderate to severe LA enlargement was present in both groups with 23% of SA patients having an LA diameter of >4.7 cm, compared to 33% of VGA patients ($p = .19$). No significant difference was found in the mean left atrial volume index of the two groups (Table 1). A large proportion of patients in both groups were on antiarrhythmic medications before ablation, primarily on class III agents

TABLE 1 Baseline patient characteristics

	Standard ablation (n = 77)	Baseline characteristics Voltage-guided (n = 75)	p Value
Age	61 ± 9	62 ± 13	.527
Male	61%	73%	.150
Diabetes mellitus	19%	26%	.414
Hypertension	67%	72%	.634
Congestive heart failure	46%	60%	.164
Coronary artery disease	31%	24%	.391
LV ejection fraction	51 ± 12	47 ± 15	.301
Left atrial diameter	4.3 ± 0.6	4.4 ± 0.8	.121
Left atrial volume index	38 ± 12	41 ± 17	.294
Antiarrhythmic use	92%	96%	.518
Class I	12%	5%	.177
Class III	56%	57%	.983
Amiodarone	23%	32%	.314
Time since AF diagnosis (months)	35 ± 24	26 ± 24	.066

Abbreviation: AF, atrial fibrillation.

TABLE 2 Procedure characteristics

	Standard ablation (n = 77)	Protocol characteristics Voltage-guided (n = 75)	p Value
Posterior wall ablation	57%	47%	.295
Posterior wall ablation using box technique	22%	36%	.06
Posterior wall isolation	20%	32%	.181
SVC isolation	95%	89%	.349
Isoproterenol use	90%	81%	.223
Adherence to protocol			
Complete all monitor	72%	77%	.601
D/C antiarrhythmic drug	93%	91%	.83

Abbreviation: SVC, superior vena cava.

and amiodarone, with no significant difference in antiarrhythmic use between groups. The patients were well matched for time since AF was initially diagnosed.

In the VGA group, 47% of patients were found to have low voltage on the posterior wall and underwent ablation of the posterior wall beyond PVI. Of these patients, 43% had a region of low voltage that covered greater than 50% of the posterior wall, while 31% had a region categorized as covering 25%–50% of the posterior wall and 26% had a region of low voltage covering less than 25% of the posterior wall. Interestingly, there were similar rates of attempted posterior wall ablation, achievement of posterior wall isolation, SVC isolation, and isoproterenol use between the two groups (Table 2). Furthermore, adherence to the protocol of discontinuing antiarrhythmic medications and postablation monitoring was similar in the two groups.

3.1.1 | VGA improved arrhythmia-free survival

At 5 years of follow-up, 64% of patients in the VGA group were AT/AF free compared to 34% in the SA group. The AT/AF Kaplan–Meier arrhythmia-free survival (Figure 2A) shows that the VGA group had a significant improvement in the AT/AF free survival compared to the SA group that started within the first year and was maintained at 5 years postablation (HR 0.358 $p < .005$). Figure 2B shows the survival curves of each subgroup within the SA and VGA group with and without posterior wall ablation. At 5 years of follow-up, VGA demonstrated a significant reduction in AF/AT in both patients receiving posterior wall ablation (HR 0.16 $p = .002$) and those receiving PVI alone (HR 0.33, $p = .002$) compared to SA PVI alone. Though there was a trend for improved arrhythmia-free survival in the SA group with PVI + posterior wall ablation compared to PVI alone, at 5 years post ablation there was no significant difference (HR 0.79 $p = .38$). Furthermore, no significant differences in arrhythmia-free survival were seen in the VGA group between PVI alone and PVI + posterior wall ablation. These data support the fact that posterior wall ablation was not the primary driver of improved arrhythmia-free survival in the VGA compared to SA groups.

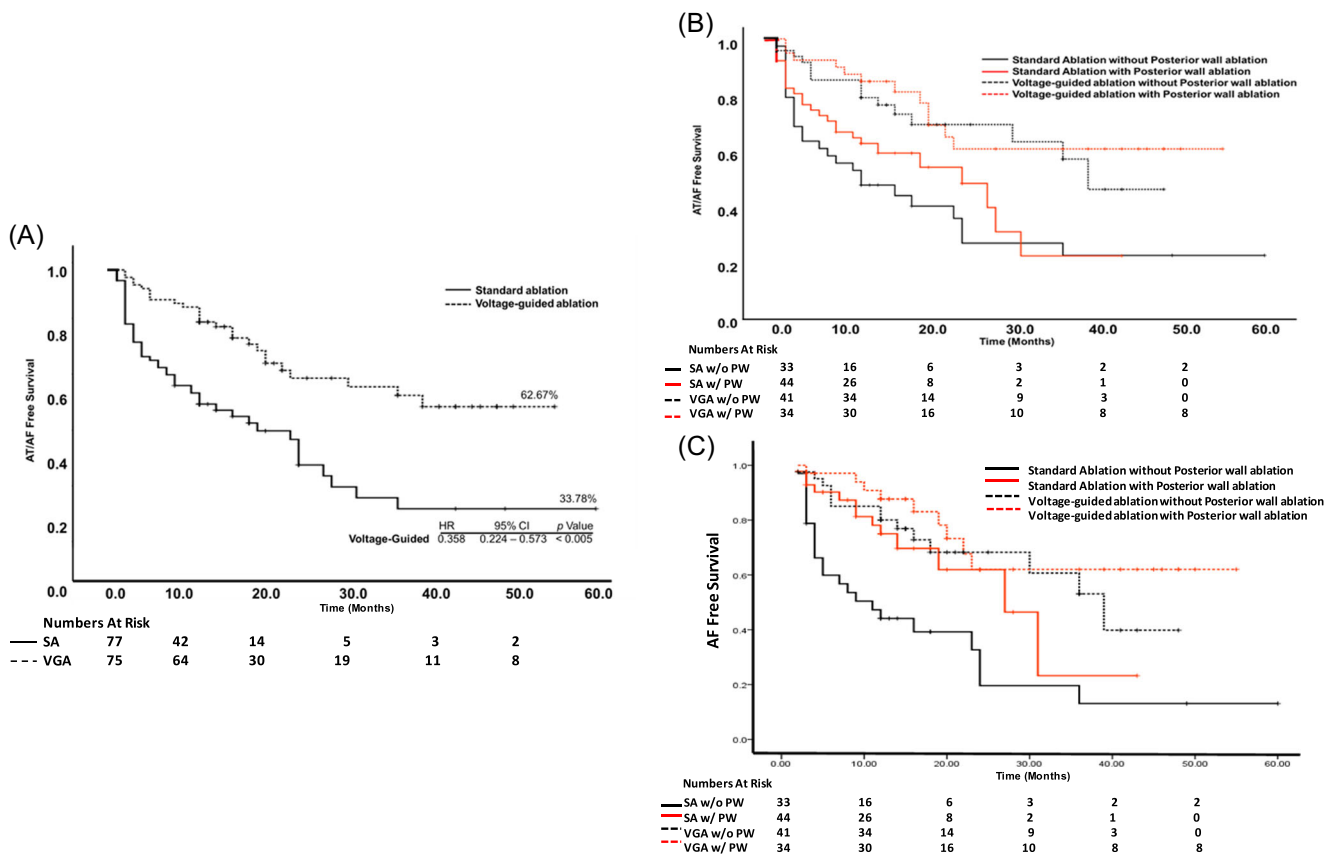


FIGURE 2 (Central illustration): Voltage-guided ablation effect on AT/AF free survival over 5 years. (A, left): Primary outcome AT/AF free survival in SA and VGA groups showing VGA group with significant improvement in 5-year AT/AF free survival. (B, right, top): Primary outcome AT/AF free survival in VGA and SA groups further divided into PVI + posterior wall and PVI alone subgroups. (C, right, bottom): AF-only arrhythmia-free survival in VGA and SA groups further divided into PVI + posterior wall and PVI alone subgroups. AF, atrial fibrillation; AT, atrial tachyarrhythmia; PVI, pulmonary vein antral isolation; SA, standard ablation; VGA, voltage-guided ablation.

3.1.2 | VGA impact on recurrence phenotype

We evaluated differences in the type of arrhythmia recurrence (AT or AF) within the four subgroups. As demonstrated, PVI alone in the VGA group resulted in decreased AF and AT recurrence compared to PVI alone in the SA group (Figure 3A). In contrast, there was no significant difference in AF recurrence with PVI + posterior wall ablation between the VGA and SA groups (Figure 3B). However, PVI + posterior wall ablation resulted in an increase in AT in the SA group (Figure 3B).

Given these results, we postulated that if we analyzed our data using AF recurrences only as the endpoint, we would see improved outcomes in the SA subgroup receiving posterior wall ablation compared to the SA subgroup receiving PVI alone. This analysis is shown in Figure 2C, in which the four subgroups (SA PVI alone, SA PVI + posterior wall, VGA PVI alone, and VGA PVI + posterior wall) were analyzed for AF-only arrhythmia-free survival. Indeed, PVI + posterior wall ablation in SA showed a significantly improved arrhythmia-free survival compared to SA with PVI alone (HR 0.45 $p = .018$). Both VGA with PVI alone and VGA with posterior wall ablation also show significantly improved AF free survival with HR 0.36 ($p = .002$) and HR 0.23 ($p = .0003$), respectively.

3.1.3 | Effect of posterior wall ablation on arrhythmia-free survival

To further investigate the effect of posterior wall ablation beyond PVI in the entire cohort, we compared AT/AF recurrence rates in all patients (SA and VGA groups) receiving PVI alone versus PVI with posterior wall ablation. As shown in Figure 4A, there was no difference in AF/AT survival in the PVI alone compared to PVI + posterior wall ablation from the entire cohort (43% vs. 53%, respectively HR 0.727, $p = .159$). When comparing only AF recurrence in the entire cohort (Figure 4B), PVI + posterior wall significantly reduced arrhythmia recurrence compared to PVI alone (HR 0.494, $p = .009$). Conversely, when comparing only AT recurrence in the entire cohort (Figure 4C), PVI + posterior wall showed no improvement in recurrence rates compared to PVI alone (HR 0.858, $p = .621$).

3.1.4 | Multivariate analysis

Multivariate predictors of AF-free survival and AT-free survival are both shown in Tables 3a,b. For AF recurrence both voltage-guided ablation

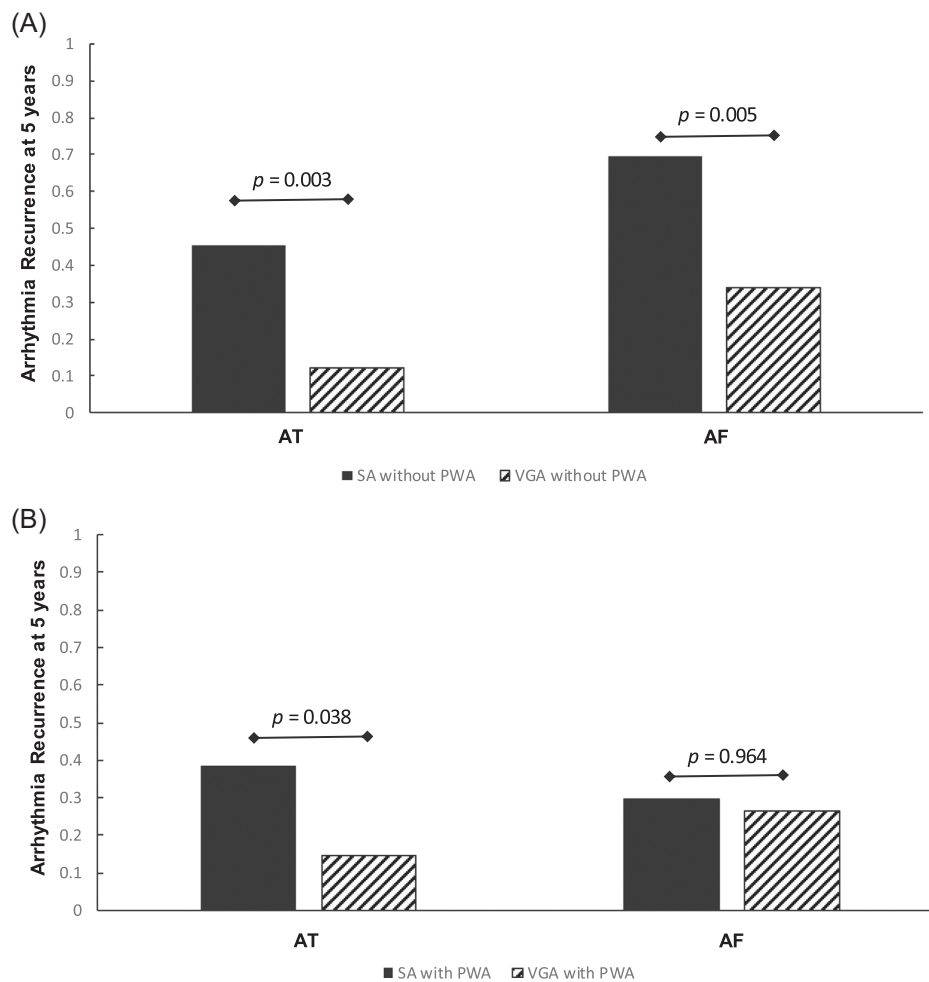


FIGURE 3 VGA impact on recurrence phenotype. (A, top): Incidence of arrhythmia recurrence, AT (left) and AF (right), in SA and VGA groups in patients that did not receive posterior wall ablation. (B, bottom): Incidence of arrhythmia recurrence, AT (left) and AF (right), in SA and VGA groups in patients that received posterior wall ablation. AF, atrial fibrillation; AT, atrial tachyarrhythmia; SA, standard ablation; VGA, voltage-guided ablation.

and ablation of the posterior wall were independent procedure-related predictors of arrhythmia-free survival. VGA demonstrated a hazard ratio of 0.33 (95% confident interval (CI) 0.19–0.96, $p = .001$) while posterior wall ablation demonstrated a hazard ratio of 0.20 (95% CI: 0.08–0.51, $p = .008$). Interestingly, none of the other procedure-related variables in the model, including posterior wall “box” ablation or demonstration of exit block, predicted AF-free survival. As expected, a severely enlarged left atrium (left atrial volume index >48 ml/m²) was a significant predictor of AF recurrence with a hazard ratio of 1.75 (95% CI: 1.01–3.06, $p = .041$). Age >65 was also a significant predictor of AF recurrence (HR 2.057 95% CI 1.076–3.933, $p = .029$).

For AT recurrence, no baseline characteristic was predictive. VGA was a significant predictor of AT-free survival (HR 0.22, 95% CI 0.059–0.848, $p = .028$), while posterior wall ablation was a significant predictor of AT recurrence (HR 4.704, 95% CI 1.252–17.672, $p = .0219$). This data further supports that VGA of the posterior wall reduces both AT and AF recurrences, while posterior wall ablation without voltage guidance reduces AF recurrences but at the cost of increased AT recurrences.

4 | DISCUSSION

We and others have previously demonstrated improved arrhythmia-free survival at 12 months using a voltage-guided ablation strategy to guide ablation beyond PVI in persistent atrial fibrillation.^{11,12} The present study extends these findings to show that voltage-guided ablation in persistent atrial fibrillation improves arrhythmia-free to 5 years postablation when compared to non-voltage-guided ablation. Additional key findings of this investigation include (1) voltage-guided ablation in persistent atrial fibrillation improves arrhythmia-free survival when PVI alone is performed, (2) Utilizing the presence or absence of low voltage to guide posterior wall ablation beyond PVI in persistent AF significantly improves long-term AT/AF free survival when compared with non-voltage-guided ablation, and (3) posterior wall ablation without regard for the presence of low voltage may reduce AF recurrence yet, at the expense of increased AT recurrence.

These results are consistent with our initial study which demonstrated an improvement in arrhythmia-free survival when posterior wall ablation is added to PVI only when low voltage is present compared to

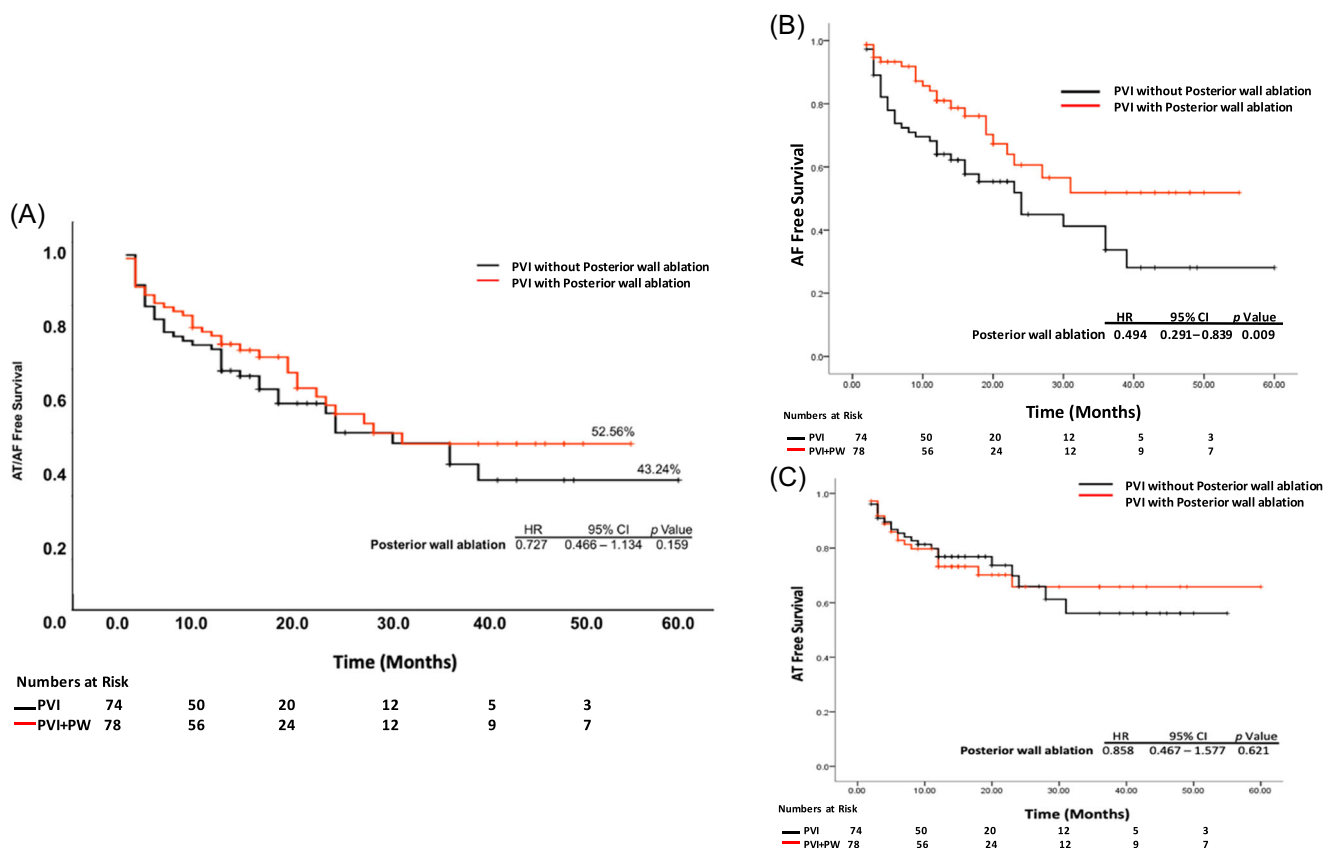


FIGURE 4 Posterior wall ablation effect on AT/AF free survival over 5 years. (A, left): Reanalyzed data of the entire cohort showing no significant difference between PVI + posterior wall and PVI alone. (B, right, top): Reanalyzed data of the entire cohort comparing AF recurrence only, showing PVI + posterior wall significantly reduced AF recurrence compared to PVI alone. (C, right, bottom): Reanalyzed data of the entire cohort comparing AT recurrence only, showing no significant difference in AT recurrence between PVI + posterior wall and PVI alone. AF, atrial fibrillation; AT, atrial tachyarrhythmia; PVI, pulmonary vein antral isolation.

an ablation strategy that is not guided by voltage mapping. At 1-year post ablation, 80% of patients in the VGA group remained in sinus rhythm compared with 57% in the SA group.¹³ At 5 years post ablation 63% of patients in the VGA group remained in sinus rhythm compared with 34% in the SA group. The reduction in AT/AF survival over the additional years of follow-up in both groups has been reported in other AF ablation studies and likely results from ongoing underlying comorbid conditions that continue to drive AF triggers/substrate, such as hypertension, sleep apnea, and heart failure.

Interestingly, at 5 years postablation, voltage-guided ablation improved arrhythmia-free survival in the PVI alone patients when compared to PVI alone in the SA group. These data suggest that using a voltage-guided ablation strategy may help to risk stratify those patients in which PVI alone is sufficient. More specifically, this finding suggests that in the absence of significant low voltage, PVI alone is sufficient in patients with persistent atrial fibrillation. This is consistent with the finding of Marrouche et al. showing that atrial scar burden predicts the likelihood of arrhythmia-free survival following catheter ablation for atrial fibrillation.¹⁴ We suspect that PVI alone in the SA group included patients both low voltage and normal voltage patients and we would estimate that 40% of the PVI alone patients in the SA group had low voltage based on the prevalence of low voltage in the VGA group. As

such, we postulate that in some of the patients in which PVI alone was performed in the SA group, significant regions of low voltage may have been present increasing the likelihood of AF/AT recurrence.

Additionally, these findings highlight potential limitations of a dichotomous stratification of atrial fibrillation into paroxysmal and persistent for the purpose of guiding catheter ablation. For example, it is generally accepted that PVI alone is sufficient in most patients with paroxysmal atrial fibrillation yet, there remains significant debate regarding the best ablation strategy in persistent atrial fibrillation. The results of STAR AF II suggest that ablation beyond PVI in persistent atrial fibrillation does not improve outcomes.¹⁵ In contrast, the recent findings of the hybrid ablation trial CONVERGE suggest that PVI plus left atrial posterior isolation improves arrhythmia-free survival in persistent atrial fibrillation.¹⁶ Interestingly, in the current study when PVI alone was compared to PVI plus posterior wall isolation in the entire cohort, regardless of ablation strategy (SA vs. VGA), there were no differences in arrhythmia-free survival. This highlights the value of a voltage mapping to help stratify patients for ablation beyond PVI. Atrial fibrosis has been implicated in both generating AF triggers through alteration in calcium handling,¹⁷ and maintaining AF through conduction velocity slowing.¹⁸ Indeed, the presence of fibrosis has been correlated with poor outcomes with

TABLE 3a Multivariate analysis for AF recurrence only

	Multivariate analysis for AF recurrence		
	Hazard ratio	95% confident interval	p Value
Voltage-guided ablation	0.331	0.187–0.586	.0001
Posterior wall ablation	0.202	0.080–0.513	.0008
Posterior wall ablation using box technique	2.262	0.493–13.979	.258
Posterior wall isolation	1.039	0.214–5.048	.962
SVC isolation	2.196	0.662–7.277	.198
Isoproterenol use	0.876	0.376–2.049	.759
Age >65-year old	2.057	1.076–3.933	.029
Diabetes	0.799	0.402–1.589	.522
Hypertension	0.660	0.376–1.161	.149
Coronary artery disease	1.141	0.629–2.070	.664
Congestive heart failure	0.648	0.354–1.184	.158
Ejection fraction <35%	1.703	0.663–4.373	.269
LA volume index >48 ml/m ²	1.754	1.007–3.056	.047
Duration since diagnosis of atrial fibrillation	1.003	0.993–1.013	.536

Abbreviations: AF, atrial fibrillation; LA, left atrial; SVC, superior vena cava.

TABLE 3b Multivariate analysis for AT recurrence only

	Multivariate analysis for AT recurrence		
	Hazard ratio	95% confident interval	p Value
Voltage-guided ablation	0.224	0.059–0.848	.028
Posterior wall ablation	4.704	1.252–17.671	.022
Posterior wall ablation using box technique	1.576	0.150–16.524	.705
Posterior wall isolation	0.235	0.018–3.098	.271
SVC isolation	0.452	0.071–2.896	.402
Isoproterenol use	0.940	0.196–4.511	.938
Age >65-year old	0.688	0.218–2.169	.523
Diabetes	0.732	0.193–2.782	.648
Hypertension	0.576	0.210–1.582	.285
Coronary artery disease	1.417	0.465–4.320	.540
Congestive heart failure	1.547	0.483–4.952	.462
Ejection fraction <35%	0.983	0.217–4.454	0.982
LA volume index >48 ml/m ²	1.468	0.512–4.207	0.475
Duration since diagnosis of atrial fibrillation	0.998	0.981–1.016	0.846

Abbreviations: AT, atrial tachyarrhythmia; SVC, superior vena cava.

PVI alone. As a result, a number of groups have begun to target fibrosis with ablation, mostly with the use of either bipolar electrogram voltage or late-gadolinium enhancement on MRI to identify fibrosis.^{13,19,20} The current study corroborates these earlier studies and adds to this literature by demonstrating that improved arrhythmia-free survival is still seen in long-term follow-up. Furthermore, it provides a potential explanation for the inconsistent outcomes reported with adjunct posterior wall isolation in persistent AF patients. Further research is needed to clarify the value of atrial voltage-mapping to help stratify patients for ablation beyond PVI in persistent atrial fibrillation.

We found that catheter ablation of the left atrial posterior wall decreased AF recurrence in both the VGA and SA groups however, posterior wall ablation in the SA group resulted in an increase in recurrent AT compared to the VGA group. Further, LA volume index, an independent predictor of AF recurrence,²¹ was associated with AF but not with AT recurrence in the entire cohort. We suspect the increase in AT with posterior wall ablation without voltage guidance is in part related to the healthy posterior wall posing a challenge for operators to consistently achieve durable isolation when balancing adequate energy delivery with the potential for esophageal injury. This concept is supported by the fact that of the 15 patients who returned for repeat ablation of AT after receiving posterior wall ablation without voltage guidance, 9 had left atrial tachycardia dependent on the posterior wall, while 5 had mitral annulus flutter and 1 had a typical flutter. We believe that the presence of low voltage allows for more consistent durable posterior wall isolation without the risk of collateral damage. This postulate is partially supported by the findings of the CONVERGE trial showing improved arrhythmia-free survival with hybrid (endo/epi) left atrial posterior wall ablation compared to endocardial PVI plus roof line ablation.

Multiple approaches have been attempted to improve ablation outcomes with persistent AF.^{22–28} yet, posterior wall isolation as adjunctive ablation to PVI has recently gained traction in the field as a possible ablation target to improve outcomes. The utility of posterior wall isolation beyond in all patients with persistent atrial fibrillation has remained controversial. While some groups have reported excellent results,^{29–32} other groups have raised concerns about the lack of efficacy in all patients and the possibility of pro-arrhythmic effects of posterior wall ablation.^{33–35} We postulate that ablation without regard to the presence or absence of atrial fibrosis as delineated by low voltage may explain some of the outcomes differences in these studies. For example, a population with a higher incidence of low voltage on the posterior wall would do well with posterior wall ablation with fewer AT recurrences, and simultaneously in this same population the PVI alone would have a higher recurrence of AT and AF. Conversely, in a population where there is little posterior wall low voltage, posterior wall ablation outcomes would be hindered by an increase in AT and PVI alone would be adequate, similar to the VGA group in the current study that received PVI alone. Further investigation is warranted to fully understand the interplay between the AF ablation success rates, low voltage, and posterior wall ablation.

5 | STUDY LIMITATIONS

Our study used voltage guidance based on the amplitude of bipolar electrograms during sinus rhythm. Bipolar electrogram amplitude may be affected not only by atrial tissue characteristics but also by a number of sampling variables including the vector of activation, contact force, and electrode size.³⁶ Despite these limitations Yagishita et al.³⁷ showed that low voltage in the left atrium could be identified regardless of the rhythm (SR vs. AF) by adjusting the upper limit of voltage cutoff in atrial fibrillation from normal controls. Several investigators have supported voltage assessment during AF or assessment of delay in activation to guide AF ablation.³⁸ Understanding of the mechanistic relationship between voltage and atrial arrhythmias would improve our understanding of the appropriate target. If conduction delay and facilitation of functional reentry is the key mechanism of fibrosis, assessment of the dynamics of conduction delay may be more fruitful compared to the static voltage assessment in sinus rhythm. In contrast, if atrial ectopy is a key component of the mechanism of AF related to atrial fibrosis,³⁹ a static assessment of the fibrosis region may be adequate. We believe that while voltage in sinus rhythm may have limitations, it is easily reproducible and given the currently available technology can improve AF ablation outcomes.

Voltage mapping, in this study, was used to guide the decision to ablate the posterior wall since at the time of the study this was a common target for ablation beyond PVI at our facility. We did not measure voltage or target ablation based on low voltage in areas beyond the posterior wall. Scar presence may be equally important for AF triggers or substrate in other locations in the left atrium. Indeed, other groups have shown improvement in efficacy when voltage-guided ablation is applied to other locations in the left atrium.⁴⁰ Further investigation would be warranted to look at the differential contribution to arrhythmia recurrence of the left atrial roof, atrial septum, and the inferior wall. In addition, we used a voltage of 0.5 mV empirically based on previous descriptions of voltage in the LA. Yagishita et al.⁴¹ recently investigated LA regional and global voltage distribution in normal controls (pts without AF) in sinus rhythm and found that 95% of LA voltage points were >1.1 mV. The cut-off of 0.5 mV to define low voltage in the atria has not been fully validated. It is unclear whether targeting voltages of less than 1 mV based on the Yagishita data would lead to improved results. The extent and nature of low voltage that should be targeted for catheter ablation need further investigation. Furthermore, the study is limited by the lack of a group that underwent voltage mapping without further ablation. Such a group would have added insight to the mechanism of low voltage on the posterior wall and AT/AF recurrence.

It is important to note that while the use of the isoproterenol challenge was widespread in this study, we avoided targeting potential triggers outside of the pulmonary veins, posterior wall, and SVC. Targeting nonpulmonary vein triggers beyond the posterior wall and SVC may be more important in patients with more advanced disease that may be associated with larger LA diameter. These patients were likely not well represented in our study, and therefore this potentially useful technique was not addressed in our study. Finally, our study was not a randomized trial. We attempted to account for major confounders yet, the VGA approach itself remained

an independent predictor of improved outcomes. Although these data strongly suggest that a voltage-guided approach would improve ablation outcomes in patients with persistent AF, this study needs to be reproduced in a prospective randomized fashion.

6 | CONCLUSIONS

In patients with persistent atrial fibrillation, the use of voltage mapping to guide whether to ablate or not to ablate the posterior wall in addition to PVI improves long-term arrhythmia-free survival when compared to a nonvoltage-guided ablation strategy. A prospective randomized trial is currently underway to study this technique of ablation for persistent atrial fibrillation (NCT03355456).

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