Received: 16 February 2022 | Revised: 25 March 2022 | Accepted: 21 April 2022

DOI: 10.1002/joa3.12727

ORIGINAL ARTICLE

Journal of Arrhythmia Open Access WILEY

Pulmonary vein isolation alone versus pulmonary vein isolation with additional extensive ablation for paroxysmal and persistent atrial fibrillation

Joey Junarta MBBS[1] | Sean J. Dikdan MD, MPH[2] | Naman Upadhyay MD[1] | Andrea Molin MD[1] | Sairamya Bodempudi MD[1] | Eric Warner MD[1] | Daniel Joffe BS[3] | Zachary Pang BS[3] | Daniel R. Frisch MD, FACC[2]

[1]Department of Medicine, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA

[2]Jefferson Heart Institute, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA

[3]Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania, USA

Correspondence
Daniel R. Frisch, Jefferson Heart Institute, Thomas Jefferson University Hospital, 925 Chestnut Street, Mezzanine level, Philadelphia, PA 19107, USA.
Email: daniel.frisch@jefferson.edu

Funding information
The authors have no sources of funding for this research to declare.

Abstract

Background: The value of additional ablation beyond pulmonary vein isolation for atrial fibrillation (AF) ablation is unclear, especially for persistent AF. It is uncertain whether substrate modification with additional extensive ablation improves outcomes. We reviewed our experience to determine whether pulmonary vein isolation with additional extensive ablation (PVIEA) improves outcomes compared to pulmonary vein isolation alone (PVIA) for AF ablation.

Methods: Consecutive cases of patients with PVIA versus PVIEA were compared between September 9, 2013 and December 12, 2020. Procedural data collected include radiofrequency ablation delivery time (RADT) and arrhythmia inducibility. Clinical data collected include sinus rhythm maintenance post-procedure.

Results: A total of 235 patients were studied (67 PVIA and 168 PVIEA). RADT was shorter when comparing ablation with PVIA versus PVIEA (32 vs. 40 min; $p = .04$). More arrhythmias were inducible with PVIEA ($p < .01$). There was no difference in sinus rhythm maintenance by Kaplan–Meier survival analysis (log-rank test $p = .75$), after 3 or 12 months between groups overall, and when stratified by AF type (paroxysmal and persistent), left atrial volume, CHA_2DS_2-VASc score, left ventricular ejection fraction, or catheter ablation setting (high-power short-duration, standard-power standard-duration, temperature-controlled non-contact-force).

Conclusion: AF ablation with PVIA or PVIEA produces similar sinus rhythm maintenance overall and when stratified by catheter setting and AF type. PVIA reduced procedure times and less arrhythmias were inducible post-ablation.

KEYWORDS
atrial fibrillation, catheter ablation, electrophysiology, persistent atrial fibrillation, substrate modification

1 | INTRODUCTION

Paroxysmal atrial fibrillation (AF) is largely triggered by ectopic foci originating from the pulmonary veins (PV), and the foundation of AF ablation is based on the formation of an electrical barrier at the level of the PV antra to isolate the PVs from the left atrium.[1,2] While effective for paroxysmal AF, the success rate of PV isolation (PVI) alone for long-term rhythm control in persistent AF is poor.[3,4] Hence, adjunctive ablation strategies targeting areas of the atria thought to maintain and perpetuate AF have been pursued.[5] This substrate modification approach includes ablation of complex fractionated atrial electrograms (CFAEs), isolation of the left atrial appendage, and forming linear lesions in the left atrium.[5,6]

It is uncertain whether substrate modification with additional extensive ablation actually improves sinus rhythm maintenance. The recent STAR-AF II study showed no improvement in ablation efficacy comparing PVI alone versus PVI plus linear lesions.[7] The CHASE-AF study also did not demonstrate improved outcomes with additional linear lesions and defragmentation of PVI compared to PVI alone.[8]

The value of additional ablation beyond PVI for AF remains unclear, especially for persistent AF. The optimal lesion set required beyond PVI is controversial, including whether lines and CFAE have a remaining role. The objective of this study is to report our experience on whether PVI with additional extensive ablation (PVIEA) improves outcomes compared to PVI alone (PVIA) for AF ablation.

2 | METHODS

2.1 | Study population and design

This consecutive case series included patients with paroxysmal or persistent AF presenting for their first AF ablation between September 9, 2013 and December 12, 2020. The ablation strategy was left up to the interventionalist and not randomized prior to the procedure. Patients were eligible if they were undergoing radiofrequency (RF) ablation. Patients were excluded if they underwent ablation for any other arrhythmia, if they presented for repeat ablation for AF, or if an ablation modality other than RF was used. Data on procedural and clinical characteristics were collected from our institution's electronic health record and stored in a secure password-protected database. The study was approved by our institutional review board.

2.2 | Catheter ablation procedure

In accordance with institutional policy, all patients provided informed consent for catheter ablation. Antiarrhythmic drugs other than amiodarone were stopped 3 days before the procedure. Our ablation protocol is as follows: we obtain femoral venous access and place a multipolar catheter in the coronary sinus. Then, we introduce a diagnostic intracardiac ultrasound catheter (5.5–10 MHz, AcuNav, Biosense Webster, or ViewFlex™, Abbott Medical) into the right atrium. Access to the left atrium is obtained from two separate interatrial transseptal punctures allowing for the introduction of an ablation catheter as well as a mapping catheter (Spiral or Advisor™ HD Grid, Abbott Medical). Three-dimensional electroanatomic mapping is performed using the St. Jude EnSite™ Velocity™ system (Abbott Medical), which is capable of recording the lesion site index (LSI) during ablation.

Pulmonary veins are routinely isolated as a pair. Ablation is performed in the carina between ipsilateral veins if isolation cannot be achieved with wide area encirclement. For PVIEA, additional ablation targets included the anterior left atrial wall, posterior left atrial wall, left atrial roof, anterior mitral isthmus, posterior mitral isthmus, interatrial septum, cavotricuspid isthmus, and/or coronary sinus. The degree of extensive ablation was determined on a case-by-case basis dictated by what was found on electroanatomic mapping to limit overtreatment, thereby reducing the risk of iatrogenic post-ablation atrial arrhythmia, unnecessarily increased procedure duration, and x-ray exposure. If durable PVI was noted, extensive ablation was usually pursued. Generally, anterior ablation is performed if there is evidence of a re-entrant circuit or focal tachycardia originating from the anterior left atrial wall. With posterior wall ablation, either a circuit is identified on the posterior wall or high-frequency, low amplitude signals are identified and targeted. Typically, the intention is complete posterior wall isolation when the posterior wall is targeted.

RF ablation with standard-power standard-duration (SPSD) and high-power short-duration (HPSD) settings is delivered with a 3.5-mm open-irrigated contact-force (CF) sensing catheter (TactiCath 65,75, DF SE or FJ SE, Abbott Medical). Prior to the availability of CF catheters, RF ablation for temperature-controlled non-contact-force (TCNC) settings was delivered with a non-CF open irrigated thermocool ablation catheter (Biosense Webster). Our TCNC protocol involved administering RF at 20–40 W to lesions for 30–60 s to achieve a decrease in impedance of at least 5–10 Ohms at the ablation site. Our SPSD protocol involves ablating with a flow of 17 cc/min for 30–60 s, with a power of 20–25 W, at a goal of 10–40 g per lesion, and a goal of 400–500 g seconds per site, with a LSI of 4.5–5.5. Our HPSD protocol involves administering RF ablation with a flow of 30 cc/min for up to 15 s, with a power of 50 W, at a goal of 8–40 g per lesion, guided by a LSI of 6 on the anterior surface of the PV and an LSI of 5 on the posterior aspect. In all cases, esophageal temperature monitoring is arranged and lesions are aborted if the temperature rises by 0.2°C or more.

Successful PVI is defined by the loss of all PV potentials (entrance block) and failure to capture the left atrium when pacing from sequential bipoles of the mapping catheter placed at the ostium of each PV (exit block; 10 mV were delivered with a 2-ms pulse width with each pacing stimulus). Verification for block across all linear lesions was always conducted. Attempts at reinduction with burst pacing are performed. If spontaneous ectopic foci that triggered AF or atrial tachycardia were observed, subsequent mapping and ablation were applied.

2.3 | Follow-up

In this study, patients were routinely followed up at 1, 3, 6, and 12 months to assess clinical outcomes. At each follow-up visit, patients' reports of symptoms were evaluated to determine AF status. We also recorded a 12-lead electrocardiogram to inform further management of the patient's AF status. If clinically indicated, mobile cardiac outpatient telemetry monitors were utilized if patients had signs or symptoms concerning for recurrence of their AF, including if they were intermittently symptomatic with chest pain, shortness of breath, palpitations, near syncope, or syncope. Additionally, patients were encouraged to report symptoms via telephone, email, or electronic medical record messaging.

2.4 | Study endpoints

Procedural endpoints include RF ablation delivery time (RADT) and the inducibility of arrhythmias after ablation. RADT is the total time that RF ablation was delivered and not the time in between lesions. Clinical endpoints included the recurrence of AF in the first 3 and 12 months after ablation as well as the probability of AF recurrence over 12 months by Kaplan–Meier survival analysis. Recurrence of AF was defined as ≥30 s of asymptomatic or symptomatic AF.

2.5 | Statistical analyses

The Student's *t*-test was used to analyze the means of continuous variables. The median of variables was compared using the nonparametric Wilcoxon–Mann–Whitney test. A chi-squared test was used to analyze categorical variables. Kaplan–Meier curves and the log-rank test were used to compare AF recurrence. A two-sided *p*-value of <.05 was used to determine statistical significance. Analyses were performed using STATA/SE 16.1.

3 | RESULTS

3.1 | Baseline characteristics

Table 1 shows the baseline characteristics of all included patients. Table 2 shows baseline characteristics stratified by atrial fibrillation type, be it paroxysmal or persistent. In both cases, there was no difference in age, gender, AF type, CHA_2DS_2-VASc score, antiarrhythmic drug use, oral anticoagulation use, left atrial volume, or left ventricular ejection fraction (LVEF) between groups. Both left atrial volume and LVEF were measured by echocardiogram. There was no difference in the use of antiarrhythmic drugs at 3 or 12 months after ablation between groups.

3.2 | Procedural outcomes

Figure 1 compares the procedural times between groups. RADT was shorter for PVIA versus PVIEA (32 ± 25 min vs. 40 ± 36 min; $p = .04$). RADT was shorter when comparing HPSD versus SPSD versus TCNC settings (24 ± 12 min vs. 35 ± 17 min vs. 74 ± 29 min; $p < .01$). Non-PV sources for PVIEA that were targeted included the following: cavotricuspid isthmus (149 patients), left atrial roof line (35 patients), mitral isthmus line (27 patients), posterior left atrial wall (10 patients), left atrial floor line (7 patients), anterior left atrial wall (4 patients), interatrial septum (4 patients), and coronary sinus (3 patients). There was a difference in the ability to reinduce arrhythmias between ablation strategies (Table 3). More atrial tachyarrhythmias were inducible with PVIEA compared to PVIA. Non-inducibility was not associated with sinus rhythm maintenance at 12 months in the PVIA ($p = .06$) or PVIEA group ($p = .16$).

TABLE 1 Overall baseline clinical characteristics

	Pulmonary vein isolation alone (*N* = 67)	Pulmonary vein isolation with additional extensive ablation (*N* = 168)	*p*-value
Age in years, mean (SD)	60.9 (9.7)	63.1 (9.6)	.11
Male gender, no. (%)	51 (76.1%)	111 (66.1%)	.13
Paroxysmal atrial fibrillation, no. (%)	26 (38.8%)	81 (49.1%)	.15
CHA_2DS_2-VASc score, median (IQR)	2 (1–3)	2 (1–3)	.21
Antiarrhythmic drug use, no. (%)	34 (50.8%)	100 (59.5%)	.22
Antiarrhythmic drug use at 3 months, no. (%)	47 (70.0%)	115 (68.5%)	.83
Antiarrhythmic drug use at 12 months, no. (%)	33 (49.2%)	89 (53.0%)	.21
Anticoagulant use, no. (%)	53 (79.1%)	128 (76.2%)	.63
Left atrial volume ml, mean (SD)	132.6 (50.8)	136.3 (54.5)	.64
Left ventricular ejection fraction %, mean (SD)	57.9 (13.7)	56.7 (12.8)	.54

Abbreviations: IQR, inter-quartile range; ml, milliliters; *N*, number of participants; no., number; SD, standard deviation.

TABLE 2 Baseline clinical characteristics stratified by atrial fibrillation type

	Paroxysmal atrial fibrillation (*N* = 108)			Persistent atrial fibrillation (*N* = 127)		
	PVI alone	PVI with additional extensive ablation	*p*-value	PVI alone	PVI with additional extensive ablation	*p*-value
Age in years, mean (SD)	59.6 (8.1)	61.8 (10.6)	.32	61.5 (10.5)	64.3 (8.3)	.11
Male gender, no. (%)	17 (65.4%)	55 (65.5%)	.99	35 (83.3%)	60 (68.9%)	.05
CHA_2DS_2-VASc score, median (IQR)	2 (1–2)	2 (0–3)	.78	2 (1–3)	2 (1–3)	.22
Antiarrhythmic drug use, no. (%)	12 (46.2%)	48 (57.1%)	.33	23 (54.8%)	52 (59.8%)	.59
Anticoagulant use, no. (%)	21 (80.8%)	61 (72.6%)	.40	33 (78.6%)	69 (79.3%)	.92
Left atrial volume ml, mean (SD)	118.2 (47.5)	113.3 (45.6)	.64	140.4 (51.8)	154.0 (55.5)	.20
Left ventricular ejection fraction %, mean (SD)	63.3 (7.0)	60.3 (9.4)	.13	54.1 (15.7)	53.3 (14.4)	.77

Abbreviations: IQR, inter-quartile range; ml, milliliters; *N*, number of participants; no., number; PVI, pulmonary vein isolation; SD, standard deviation.

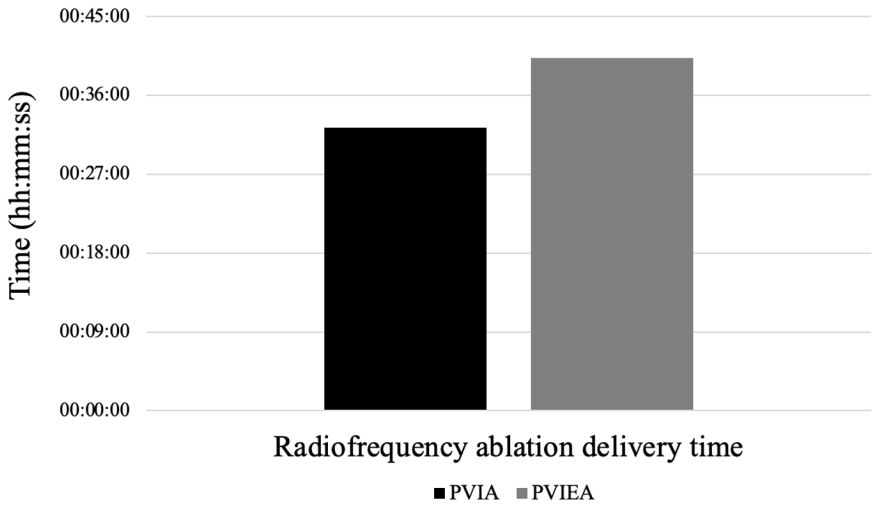

FIGURE 1 Procedural time by ablation strategy. PVIA, pulmonary vein isolation alone; PVIEA, pulmonary vein isolation with additional extensive ablation

TABLE 3 Arrhythmia inducibility by ablation strategy

	Pulmonary vein isolation alone (*N* = 58)	Pulmonary vein isolation with additional extensive ablation (*N* = 153)	*p*-value
Non-inducible, no. (%)	42 (72.4%)	65 (42.5%)	<.01
Atrial fibrillation, no. (%)	5 (8.6%)	31 (20.3%)	
Atrial flutter, no. (%)	2 (3.4%)	34 (22.2%)	
Atrial tachycardia no. (%)	5 (8.6%)	4 (2.6%)	
Atrioventricular nodal reentry tachycardia, no. (%)	1 (1.7%)	10 (6.5%)	
Atrioventricular reentrant tachycardia, no. (%)	3 (5.2%)	9 (5.8%)	

Abbreviations: *N*, number of participants, no., number.

3.3 | Clinical outcomes

The recurrence of AF was assessed at 3 and 12 months after ablation. There was no difference in the overall percentage of patients in sinus rhythm between groups at 3 months (Table 4) or 12 months (Table 5). There was no difference in AF recurrence when patients were stratified by AF type, left atrial volume, CHA_2DS_2-VASc score, left ventricular ejection fraction, or

TABLE 4 Patients in sinus rhythm after 3 months overall and stratified based on clinical characteristics

		Pulmonary vein isolation alone (*N* = 67)	Pulmonary vein isolation with additional extensive ablation (*N* = 166)	*p*-value
Overall patients in sinus rhythm, no. (%)		52 (77.6%)	129 (77.7%)	.67
Type of atrial fibrillation, no.	Paroxysmal	18	64	.07
	Persistent	34	63	
Left atrial volume ml, no.	≥150	16	44	.46
	<150	35	74	
CHA_2DS_2-VASc score, no.	≥2	25	74	.26
	<2	27	55	
Left ventricular ejection fraction %, no.	≥55	41	94	.40
	<55	11	35	
Catheter setting	HPSD	19	66	.13
	SPSD	20	44	
	TCNC	13	19	

Abbreviations: HPSD, high-power short-duration; ml, milliliters; *N* number of participants; no., number; SPSD, standard-power standard-duration; TCNC, temperature-controlled non-contact-force.

TABLE 5 Patients in sinus rhythm after 12 months overall and stratified based on clinical characteristics

		Pulmonary vein isolation alone (*N* = 67)	Pulmonary vein isolation with additional extensive ablation (*N* = 166)	*p*-value
Overall patients in sinus rhythm, no. (%)		51 (76.1%)	127 (76.5%)	.78
Type of atrial fibrillation, no.	Paroxysmal	18	62	.08
	Persistent	33	63	
Left atrial volume ml, no.	≥150	16	42	.58
	<150	34	73	
CHA_2DS_2-VASc score, no.	≥2	23	72	.16
	<2	28	55	
Left ventricular ejection fraction %, no.	≥55	41	89	.16
	<55	10	38	
Catheter setting	HPSD	19	66	.07
	SPSD	18	43	
	TCNC	14	18	

Abbreviations: HPSD, high-power short-duration; ml, milliliters; *N*, number of participants; no., number; SPSD, standard-power standard-duration; TCNC, temperature-controlled non-contact-force.

catheter setting at 3 or 12 months. The time to first AF recurrence for each patient was assessed. There was no difference between groups over 12 months by Kaplan–Meier survival analysis (log-rank test $p = .75$) (Figure 2).

3.4 | Adverse events

There was no difference in the number of adverse events between groups ($p = .30$). All adverse events were pericardial effusions with or without the need for pericardiocentesis, which occurred in 1 of 67 patients in the PVIA group and in 7 of 168 patients in the PVIEA group. No esophageal injuries, phrenic nerve injuries, bleeding requiring transfusion, strokes, or deaths occurred in any group.

4 | DISCUSSION

Our study demonstrated no difference in sinus rhythm maintenance comparing PVIA versus PVIEA for AF ablation. There was no difference in sinus rhythm maintenance even when patients were stratified by AF type, left atrial volume, CHA_2DS_2-VASc score, left ventricular ejection fraction, or catheter setting. Importantly, PVIEA induced more atrial tachyarrhythmias after ablation, while PVIA produced shorter procedure times.

4.1 | Substrate modification by ablating CFAEs and lines

PVI is the cornerstone of AF ablation irrespective of AF type. In paroxysmal AF, the PVs are important trigger sites and their electric

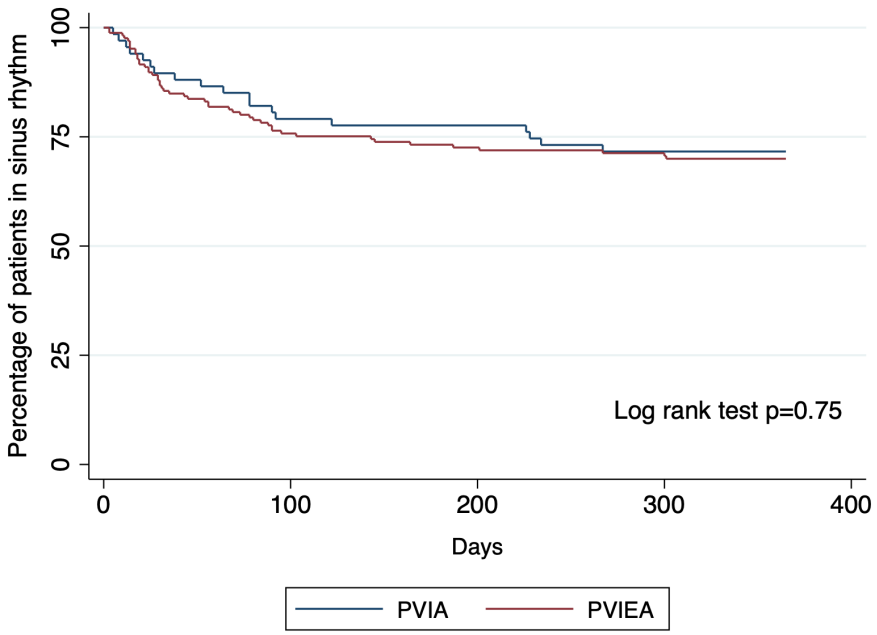

FIGURE 2 Kaplan–Meier survival analysis for atrial fibrillation recurrence. PVIA, pulmonary vein isolation alone; PVIEA, pulmonary vein isolation with additional extensive ablation

isolation allows a high degree of sinus rhythm maintenance. In contrast, ensuring AF freedom after ablation in non-paroxysmal AF has posed a significant challenge. In non-paroxysmal AF, additional arrhythmogenic atrial sites are thought to be responsible for AF maintenance and perpetuation. Thus, more extensive ablation strategies have been attempted to target non-PV areas of the atria perceived to harbor these sites. This includes approaches ablating CFAEs and linear lesions in addition to PVI. However, randomized controlled trials (RCTs) have not shown that extensive ablation strategies translate to improved outcomes.

STAR-AF II randomized 589 patients with persistent AF in a 1:4:4 ratio to ablation with PVI alone, PVI plus ablation of CFAE, or PVI plus additional linear ablation across the left atrial roof and mitral valve isthmus.[7] After 18 months of follow-up, no reduction in the rate of recurrent AF was found between groups ($p = .15$). In CHASE-AF, 205 patients with persistent AF were randomized to PVI alone or a stepwise ablation approach which consisted of PVI, ablation of CFAE, and additional linear ablation lines in the setting of atrial tachycardias. Arrhythmia-free survival did not differ between groups ($p = .47$).[8] SMAN-PAF trial was a multicenter RCT that compared PVI alone versus PVI plus ablation of lines, which included left atrial, mitral isthmus, and tricuspid isthmus lines.[9] A total of 122 patients with persistent AF or sustained paroxysmal (>12 h) AF were included and followed up for 12 months. No difference in atrial tachyarrhythmia recurrence was found between groups overall ($p = .50$), in those with persistent AF ($p = .45$), or in those with sustained paroxysmal AF ($p = .86$). In all three trials, procedure time was shorter with PVI alone, allowing for the reduction in fluoroscopy time and RF duration. Indeed, we also showed no difference in sinus rhythm maintenance comparing PVIA versus PVIEA for AF ablation. However, PVIA produced shorter procedure times.

4.2 | Issues with substrate modification by ablating CFAEs and lines

There are several issues with how substrate modification has been performed that can explain the lack of positive findings in these trials. Selection criteria for substrate modification lesion sets were often empiric and subjective. Patient selection for substrate modification is also usually based on the patient's clinical presentation, though the correlation between AF type and the extent of atrial structural disease thought to perpetuate AF remains unclear. Additionally, extensive atrial ablation can lead to iatrogenic post-ablation atrial tachycardia.[10,11] As in our study, more atrial tachyarrhythmias were inducible with PVIEA compared to PVIA. However, non-inducibility was not associated with sinus rhythm maintenance. It is possible that the number of patients was too small to demonstrate a difference. Incompletely ablated tissue (e.g. when the linear block is not achieved) allows for new areas of arrhythmogenesis. Thus, extensive ablation may lead to overtreatment with unnecessarily increased procedure duration, arrhythmia, altered atrial mechanics, and x-ray exposure. At the same time, patients with non-paroxysmal AF may be undertreated with PVI alone. Taken altogether, it has been postulated that neither CFAEs nor lines are the correct supplemental targets for ablation.[10,12] It may be prudent to identify more selective targets to address a patient's specific arrhythmic substrate. Indeed, alternative strategies beyond the ablation of CFAEs and lines have been investigated. This includes ablation of low-voltage areas (LVAs),[13–16] isolation of the left atrial appendage (LAA),[17,18] vein of Marshall ethanol infusion,[19] and alternative energy sources such as pulsed field ablation (PFA).[20]

4.3 | LVA ablation

Atrial fibrosis plays an important role in the genesis and persistence of AF. It increases intercellular distance, which causes reduced electrical coupling, slows electrical conduction, and disperses atrial refractory periods. Left atrial scarring can be detected by late enhancement magnetic resonance imaging (MRI) and correlates with reduced electrogram amplitudes in endocardial voltage maps.[21,22] Low-voltage areas (LVA), which reflect endocardial scar and structural defects and remodeling in atrial tissue, may be a predictor of arrhythmia recurrence after AF ablation.[23,24] In light of the association between abnormal atrial tissue, AF perpetuation, and failure of AF ablation, a voltage-guided substrate modification targeting LVA has been proposed to be a more individualized approach to AF ablation that addresses issues surrounding conventional substrate modification. However, the results of RCTs have been inconclusive. In STABLE-SR, 229 patients with non-paroxysmal AF were randomized to an ablation protocol that included LVA ablation versus without.[13] Kaplan–Meier survival analysis did not demonstrate a difference in freedom from atrial tachyarrhythmias between groups at 18 months ($p = .33$). In VOLCANO, 62 patients with paroxysmal AF and LVA were randomized to PVI with LVA ablation versus PVI alone.[14] There was no difference in AF recurrence-free survival rate between groups after 12 months of follow-up (57% vs. 53%; $p = .67$). The DECAAF II trial (NCT02529319) tested the hypothesis that targeting atrial fibrosis identified by MRI would improve ablation outcomes in those with persistent AF.[15] Preliminary results have shown no difference in outcomes comparing PVI alone versus PVI with fibrosis-guided ablation. The SUPPRESS-AF trial will be a multicenter RCT comparing PVI alone versus PVI with LVA ablation in 340 patients.[16]

4.4 | LAA ablation

The role of the LAA in initiating and maintaining AF has not been widely reported. The LAA has the same embryological origin as the left atrium, and its tissue characteristics may lead to AF initiation akin to that of the PVs. Thus, the potential utility in isolating it to increase ablation efficacy has been considered.[25] In the BELIEF trial, 173 patients with persistent AF were randomly assigned to PVI with extensive ablation according to their standard protocol versus PVI with extensive ablation plus empirical LAA isolation.[17] After 12 months, Kaplan–Meier analysis demonstrated greater freedom from atrial arrhythmia recurrence in the group with empirical LAA isolation (56% vs. 28%; $p < .01$). These results are in contrast to the aMAZE trial (NCT02513797), where those with persistent AF were randomized to PVI alone versus PVI with LAA ligation with the Lariat system (AtriCure).[18] Preliminary results demonstrate no improvement in arrhythmic outcomes between groups.

4.5 | Vein of Marshall ethanol infusion

The vein of Marshall is an embryological remnant of the left superior vena cava. It has been implicated in the pathogenesis of AF as a source of AF triggers and AF maintenance, as well as a tract of autonomic innervation that modulates the electrophysiologic properties of atrial tissue.[26–29] The VENUS trial was a RCT of 350 patients that compared RF ablation versus RF ablation with the vein of Marshall ethanol infusion.[19] RF ablation included PVI and additional lesions at the discretion of the operator, including isolation of the posterior wall, mitral isthmus, and CFAE. At 6 and 12 months, the proportion of patients with freedom from AF or atrial tachycardia was greater in the group with the vein of Marshall ethanol infusion (49% vs. 38%; $p = .04$). The improved rhythm control from the vein of Marshall ethanol infusion may be related to enhanced atrial denervation, more reliable conduction block at the mitral isthmus, or elimination of AF triggers.[30–32]

4.6 | Pulsed field ablation

Pulsed field ablation (PFA) is a novel approach to AF ablation that limits collateral tissue damage without compromising its ability to ablate myocardial tissue.[33,34] In contrast to contemporary ablative energy sources, including RF, cryothermy, and laser ablation, PFA uses a non-thermal ablative mechanism that preferentially ablates myocardial tissue. PersAFOne was a single-arm study of 25 patients evaluating the safety and efficacy of biphasic, bipolar PFA using a multispline catheter for PVI and left atrial posterior wall ablation.[20] Additionally, a focal PFA catheter was used for cavotricuspid isthmus ablation. Invasive mapping was done 75 days after the index procedure, which demonstrated durable posterior wall ablation in 100% of patients and durable PVI in 96% of patients. A durable cavotricuspid isthmus block was observed in all eight patients. By forming irreversible nanoscale pores, PFA destabilizes cell membranes and induces cell death. Myocardial tissue displays a lower threshold for injury. Thus, because of its novel non-thermal mechanism of ablation, PFA is able to uniquely ablate the atrial myocardium without damaging adjacent structures, including the phrenic nerve or esophagus. Additionally, PFA also spares the extracellular matrix, preventing disruption of tissue planes that characterize adjacent thermal damage. It is conceivable that lesions produced by contemporary ablative energy sources are mechanistically ineffective or are not durable enough to address persistent AF. PFA may be able to address these issues. Larger clinical studies assessing the utility of PFA in persistent AF will be revealing.

4.7 | Limitations

Our study had several limitations. First, patients were ablated based on operator discretion. Despite similar baseline characteristics,

differences in burden and severity may not be completely accounted for. Second, even with close follow-up, outpatient electrocardiographic monitoring, telemetry recordings, and remote electrocardiographic capabilities, rhythm monitoring was not continuous. It is possible that patients had undetected AF recurrences, which would lead to a falsely elevated rate of sinus rhythm maintenance. Third, as our study was of consecutive patients, it is possible that laboratory experience might have influenced outcomes over time. Fourth, our study had a small sample size, which meant that it was difficult to detect a significant difference in clinical outcomes between groups. However, the findings of our study agree with existing RCTs.

5 | CONCLUSION

AF ablation with PVIA or PVIEA produces similar sinus rhythm maintenance overall and when stratified by catheter power and duration setting and AF type. Importantly, PVIEA induced more atrial tachyarrhythmias after ablation, while PVIA produced shorter procedure times. Although PVI alone likely undertreats persistent AF, conventional substrate modification has not been shown to improve rhythm outcomes. Alternative strategies of substrate modification or alternative energy sources may be the key to improving outcomes in those with persistent AF.

AUTHORS' CONTRIBUTIONS

DF design, manuscript, supervision. JJ data collection, analysis, manuscript. NU data collection, analysis, manuscript. AM data collection, analysis, manuscript. SB data collection, analysis, manuscript. SD data collection, analysis, manuscript. EW data collection, analysis. DJ data collection, analysis. ZP data collection, analysis.

ACKNOWLEDGMENTS

Not applicable.

CONFLICT OF INTEREST

The authors declare that they have no competing interests. The results presented in this paper have not been published previously in whole or part, except in abstract form.

FUNDING INFORMATION

The authors have no sources of funding for this research to declare.

DATA AVAILABILITY STATEMENT

Data are safely kept in a password-protected security system at Thomas Jefferson University Hospital. The datasets used and/or analyzed during the current study are de-identified and available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by our institutional review board. This article does not contain any studies with animals performed by any of the authors.

CODE AVAILABILITY

Not applicable.

CONSENT FOR PUBLICATION

Not applicable.

ORCID

Joey Junarta https://orcid.org/0000-0002-9411-1478
Daniel R. Frisch https://orcid.org/0000-0002-7645-6405

TWITTER

Joey Junarta @JunartaMD
Sean J. Dikdan @SDikdan
Naman Upadhyay @NamanUpadhyayMD
Sairamya Bodempudi @ramz9012
Daniel R. Frisch @FrischMd

REFERENCES

1. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659–66.
2. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: executive summary. Heart Rhythm. 2017;14(10):e445–94.
3. Tilz RR, Rillig A, Thum AM, Arya A, Wohlmuth P, Metzner A, et al. Catheter ablation of long-standing persistent atrial fibrillation: 5-year outcomes of the Hamburg sequential ablation strategy. J Am Coll Cardiol. 2012;60(19):1921–9.
4. Brooks AG, Stiles MK, Laborderie J, Lau DH, Kuklik P, Shipp NJ, et al. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. Heart Rhythm. 2010;7(6):835–46.
5. Nademanee K, McKenzie J, Kosar E, Schwab M, Sunsaneewitayakul B, Vasavakul T, et al. A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol. 2004;43(11):2044–53.
6. Sanders P, Jais P, Hocini M, Hsu LF, Scavee C, Sacher F, et al. Electrophysiologic and clinical consequences of linear catheter ablation to transect the anterior left atrium in patients with atrial fibrillation. Heart Rhythm. 2004;1(2):176–84.
7. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015;372(19):1812–22.
8. Vogler J, Willems S, Sultan A, Schreiber D, Luker J, Servatius H, et al. Pulmonary vein isolation versus defragmentation: the CHASE-AF clinical trial. J Am Coll Cardiol. 2015;66(24):2743–52.
9. Wynn GJ, Panikker S, Morgan M, Hall M, Waktare J, Markides V, et al. Biatrial linear ablation in sustained nonpermanent AF: results of the substrate modification with ablation and antiarrhythmic drugs in nonpermanent atrial fibrillation (SMAN-PAF) trial. Heart Rhythm. 2016;13(2):399–406.
10. Dixit S, Marchlinski FE, Lin D, Callans DJ, Bala R, Riley MP, et al. Randomized ablation strategies for the treatment of persistent

atrial fibrillation: RASTA study. Circ Arrhythm Electrophysiol. 2012;5(2):287–94.
11. Rostock T, Drewitz I, Steven D, Hoffmann BA, Salukhe TV, Bock K, et al. Characterization, mapping, and catheter ablation of recurrent atrial tachycardias after stepwise ablation of long-lasting persistent atrial fibrillation. Circ Arrhythm Electrophysiol. 2010;3(2):160–9.
12. Shah AJ, Pascale P, Miyazaki S, Liu X, Roten L, Derval N, et al. Prevalence and types of pitfall in the assessment of mitral isthmus linear conduction block. Circ Arrhythm Electrophysiol. 2012;5(5):957–67.
13. Yang B, Jiang C, Lin Y, Yang G, Chu H, Cai H, et al. STABLE-SR (electrophysiological substrate ablation in the left atrium during sinus rhythm) for the treatment of nonparoxysmal atrial fibrillation: a prospective, multicenter randomized clinical trial. Circ Arrhythm Electrophysiol. 2017;10(11):e005405.
14. Masuda M, Asai M, Iida O, Okamoto S, Ishihara T, Nanto K, et al. Additional low-voltage-area ablation in patients with paroxysmal atrial fibrillation: results of the randomized controlled VOLCANO trial. J Am Heart Assoc. 2020;9(13):e015927.
15. Marrouche NF, Greene T, Dean JM, Kholmovski EG, Boer LM, Mansour M, et al. Efficacy of LGE-MRI-guided fibrosis ablation versus conventional catheter ablation of atrial fibrillation: the DECAAF II trial: study design. J Cardiovasc Electrophysiol. 2021;32(4):916–24.
16. Sunaga A, Masuda M, Inoue K, Tanaka N, Watanabe T, Furukawa Y, et al. The efficacy and safety of left atrial low-voltage area guided ablation for recurrence prevention compared to pulmonary vein isolation alone in patients with persistent atrial fibrillation trial: design and rationale. Clin Cardiol. 2021;44(9):1249–55.
17. Di Biase L, Burkhardt JD, Mohanty P, Mohanty S, Sanchez JE, Trivedi C, et al. Left atrial appendage isolation in patients with long-standing persistent AF undergoing catheter ablation: BELIEF trial. J Am Coll Cardiol. 2016;68(18):1929–40.
18. Lee RJ, Lakkireddy D, Mittal S, Ellis C, Connor JT, Saville BR, et al. Percutaneous alternative to the maze procedure for the treatment of persistent or long-standing persistent atrial fibrillation (aMAZE trial): rationale and design. Am Heart J. 2015;170(6):1184–94.
19. Valderrábano M, Peterson LE, Swarup V, Schurmann PA, Makkar A, Doshi RN, et al. Effect of catheter ablation with vein of Marshall ethanol infusion vs catheter ablation alone on persistent atrial fibrillation: the VENUS randomized clinical trial. JAMA. 2020;324(16):1620–8.
20. Reddy VY, Anic A, Koruth J, Petru J, Funasako M, Minami K, et al. Pulsed field ablation in patients with persistent atrial fibrillation. J Am Coll Cardiol. 2020;76(9):1068–80.
21. Jadidi AS, Cochet H, Shah AJ, Kim SJ, Duncan E, Miyazaki S, et al. Inverse relationship between fractionated electrograms and atrial fibrosis in persistent atrial fibrillation: combined magnetic resonance imaging and high-density mapping. J Am Coll Cardiol. 2013;62(9):802–12.
22. Oakes RS, Badger TJ, Kholmovski EG, Akoum N, Burgon NS, Fish EN, 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.
23. Verma A, Wazni OM, Marrouche NF, Martin DO, Kilicaslan F, Minor S, et al. Pre-existent left atrial scarring in patients undergoing pulmonary vein antrum isolation: an independent predictor of procedural failure. J Am Coll Cardiol. 2005;45(2):285–92.
24. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA. 2014;311(5):498–506.
25. Salzberg SP, Hürlimann D, Corti R, Grünenfelder J. Heart team approach for left atrial appendage therapies: in addition to stroke prevention-is electrical isolation important? Ann Cardiothorac Surg. 2014;3(1):75–7.
26. Lee SH, Tai CT, Hsieh MH, Tsao HM, Lin YJ, Chang SL, et al. Predictors of non-pulmonary vein ectopic beats initiating paroxysmal atrial fibrillation: implication for catheter ablation. J Am Coll Cardiol. 2005;46(6):1054–9.
27. Kamanu S, Tan AY, Peter CT, Hwang C, Chen PS. Vein of Marshall activity during sustained atrial fibrillation. J Cardiovasc Electrophysiol. 2006;17(8):839–46.
28. Ulphani JS, Arora R, Cain JH, Villuendas R, Shen S, Gordon D, et al. The ligament of Marshall as a parasympathetic conduit. Am J Physiol Heart Circ Physiol. 2007;293(3):H1629–35.
29. Kim DT, Lai AC, Hwang C, Fan LT, Karagueuzian HS, Chen PS, et al. The ligament of Marshall: a structural analysis in human hearts with implications for atrial arrhythmias. J Am Coll Cardiol. 2000;36(4):1324–7.
30. Báez-Escudero JL, Morales PF, Dave AS, Sasaridis CM, Kim YH, Okishige K, et al. Ethanol infusion in the vein of Marshall facilitates mitral isthmus ablation. Heart Rhythm. 2012;9(8):1207–15.
31. Dave AS, Báez-Escudero JL, Sasaridis C, Hong TE, Rami T, Valderrábano M. Role of the vein of Marshall in atrial fibrillation recurrences after catheter ablation: therapeutic effect of ethanol infusion. J Cardiovasc Electrophysiol. 2012;23(6):583–91.
32. Báez-Escudero JL, Keida T, Dave AS, Okishige K, Valderrábano M. Ethanol infusion in the vein of Marshall leads to parasympathetic denervation of the human left atrium: implications for atrial fibrillation. J Am Coll Cardiol. 2014;63(18):1892–901.
33. Koruth JS, Kuroki K, Iwasawa J, Viswanathan R, Brose R, Buck ED, et al. Endocardial ventricular pulsed field ablation: a proof-of-concept preclinical evaluation. Europace. 2020;22(3):434–9.
34. Koruth JS, Kuroki K, Kawamura I, Brose R, Viswanathan R, Buck ED, et al. Pulsed field ablation versus radiofrequency ablation: esophageal injury in a novel porcine model. Circ Arrhythm Electrophysiol. 2020;13(3):e008303.

How to cite this article: Junarta J, Dikdan SJ, Upadhyay N, Molin A, Bodempudi S, Warner E, Pulmonary vein isolation alone versus pulmonary vein isolation with additional extensive ablation for paroxysmal and persistent atrial fibrillation. J Arrhythmia. 2022;38:589–597. https://doi.org/10.1002/joa3.12727