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Randomized Ablation Strategies for the Treatment of Persistent Atrial Fibrillation

RASTA Study

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Background—The single-procedure efficacy of pulmonary vein isolation (PVI) is less than optimal in patients with persistent atrial fibrillation (AF). Adjunctive techniques have been developed to enhance single-procedure efficacy in these patients. We conducted a study to compare 3 ablation strategies in patients with persistent AF.

Methods and Results—Subjects were randomized as follows: arm 1, PVI + ablation of non-PV triggers identified using a stimulation protocol (standard approach); arm 2, standard approach + empirical ablation at common non-PV AF trigger sites (mitral annulus, fossa ovalis, eustachian ridge, crista terminalis, and superior vena cava); or arm 3, standard approach + ablation of left atrial complex fractionated electrogram sites. Patients were seen at 6 weeks, 6 months, and 1 year; transtelephonic monitoring was performed at each visit. Antiarrhythmic drugs were discontinued at 3 to 6 months. The primary study end point was freedom from atrial arrhythmias off antiarrhythmic drugs at 1 year after a single-ablation procedure. A total of 156 patients (aged 59±9 years; 136 males; AF duration, 47±50 months) participated (arm 1, 55 patients; arm 2, 50 patients; arm 3, 51 patients). Procedural outcomes (procedure, fluoroscopy, and PVI times) were comparable between the 3 arms. More lesions were required to target non-PV trigger sites than a complex fractionated electrogram (33±9 versus 22±9; $P<0.001$). The primary end point was achieved in 71 patients and was worse in arm 3 (29%) compared with arm 1 (49%; $P=0.04$) and arm 2 (58%; $P=0.004$).

Conclusions—These data suggest that additional substrate modification beyond PVI does not improve single-procedure efficacy in patients with persistent AF.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00379301.

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Key Words: ablation ■ atrial fibrillation ■ catheter ablation ■ clinical trials

Pulmonary vein (PV) antral ablation is the most frequently used strategy in patients undergoing atrial fibrillation (AF) ablation.[1] However, the single procedure success rate of this approach has consistently been better in patients with paroxysmal compared with persistent AF.[2–5] This discrepancy has been attributed to the difference in the mechanism(s) underlying the 2 types of AF.[4] It has been posited that early in the course of AF, triggers predominate. As the arrhythmia becomes more established, there are changes in the underlying substrate that promote AF persistence (ie, AF begets AF).[5] This has resulted in the development of adjunctive substrate modification strategies for enhancing procedural efficacy in patients with more persistent forms of AF.[6] Among the various substrate modification strategies used, complex fractionated electrogram (CFE) ablation is the most popular.[7] However, it remains unclear whether CFE ablation uniformly enhances procedural efficacy beyond PV ablation in this patient population.[8,9]

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We, therefore, conducted a prospective randomized study to assess the efficacy of CFE ablation for enhancing single-procedure efficacy beyond PV isolation (PVI) in patients with persistent and long persistent AF. We also sought to compare this approach with a new ablation strategy of targeting

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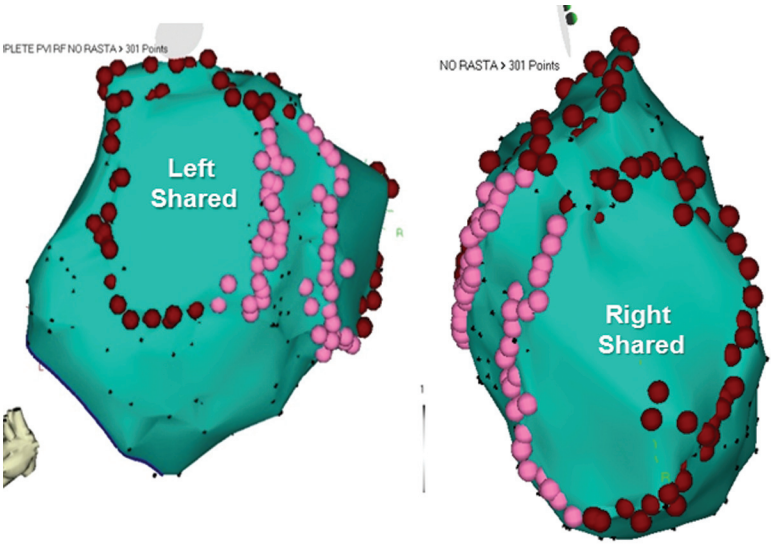

Figure 1. Electroanatomical shell of left atrium and lesion distribution for pulmonary vein isolation. Pink and red dots represent low power (≤20 W) and regular lesions, respectively.

empirically common non-PV trigger sites of AF. The latter strategy was based on our center's experience of documenting certain common anatomic regions that typically harbor non-PV AF triggers.[2] We hypothesized that additional lesions beyond PVI, whether at CFE locations or non-PV AF trigger sites, should enhance the single-procedure efficacy of AF ablation in patients with persistent AF.

Methods

Study Design

This was a single-center study in which participating subjects were randomized to undergo AF ablation by 1 of the following 3 strategies: arm 1, PVI, followed by a stimulation protocol to identify non-PV triggers of AF that were also targeted (this is the *standard approach* for AF ablation at our center)[3]; arm 2, standard approach + empirical ablation at sites that we have previously identified and reported as common areas from which non-PV triggers of AF originate[2]; and arm 3, standard approach + ablation of left atrial (LA) CFE sites identified using an automated computer algorithm.[9,10] All subjects with drug-refractory AF undergoing their first ablation procedure that fulfilled American College of Cardiology, European Society of Cardiology, American Heart Association, and Heart Rhythm Society defined criteria for persistent or long-lasting persistent AF[4] were eligible to participate in the study. The exclusion criteria included aged <30 years, inability to provide informed consent, and any contraindication to undergoing AF ablation. The study protocol and consent forms were approved by the institutional review board of the University of Pennsylvania. The *primary study end point* was freedom from AF and/or organized atrial tachyarrhythmias (OATs) off antiarrhythmic drugs (AADs) at 1 year after a single-ablation procedure. AF and/or OAT occurring in the first 6 weeks after the ablation (blanking period) were censored. Beyond this, any symptomatic or asymptomatic AF or OAT episode that lasted for >30 seconds was categorized as a recurrence. The *secondary study end points* were as follows: (1) *arrhythmia control*, which was defined as freedom from or infrequent (≤6, self-terminating) AFs and/or OATs, either off or on previously ineffective AADs at 1 year after a single ablation procedure; (2) total procedure time; (3) total fluoroscopy time; and (4) occurrence of serious adverse events that included death, pericardial effusion causing tamponade or requiring pericardiocentesis, cerebrovascular events, significant PV stenosis (symptomatic or asymptomatic >70% reduction in PV diameter in ≥1 veins), left atrial-esophageal fistula, diaphragmatic paralysis, and any vascular complication requiring transfusion or intervention.

Ablation Protocol

All AADs, except amiodarone, were discontinued 5 half-lives before the procedure (amiodarone was discontinued 2 weeks before the procedure). Our standard approach for AF ablation has been previously described.[2] Briefly, catheters were placed in coronary sinus (CS) and posterior right atrium (RA), and a diagnostic ultrasonographic catheter (5.5–10 MHz, 8F, AcuNav; Diamond Bar, CA) was advanced in RA. Two transseptal punctures were made, through which the ablation and decapolar circular mapping catheters (Lasso, Biosense Webster, Inc; Diamond Bar; adjustable circumference, 15–25 mm; interelectrode spacing, 1–2 mm) were advanced into the LA. A bolus of unfractionated heparin was administered before the first transseptal puncture, and infusion was titrated to maintain an activated clotting time >325 seconds for the duration of the procedure. Wide-area circumferential PVI was performed by isolating the left and right pairs of veins en bloc (Figure 1). At the initiation of the study, our center was performing AF ablation using the 8-mm-tip catheter (NaviStar, Biosense Webster, Diamond Bar). The energy delivery settings were as follows: power, ≤70 W (<50 W over the posterior LA); and temperature, ≤50°C. During the study, we switched to the 3.5-mm open irrigation tip catheter (Navistar Thermocool, Biosense Webster). The energy delivery settings were as follows: power, ≤40 W (≤20 W over the posterior LA); and temperature, ≤42°C. Lesions were delivered for a maximum of 40 seconds to achieve an impedance decrease of 5 to 10 Ω at the ablation site; over the posterior LA, lesion duration was restricted to 20 seconds. *Successful PVI* was defined by loss of PV potentials (entry block) and failure to capture the LA during pacing from all bipoles of the Lasso catheter (output, 10 mA; pulse width, 2 milliseconds; exit block). These were repeated after 20 to 60 minutes to exclude acute PV reconnection, for which additional RF lesions were delivered. After PVI, a stimulation protocol was performed to identify non-PV triggers. This protocol consisted of the following: (1) isoproterenol infusion (starting at 3 μg and incrementing every 3 minutes to 6, 12, and 20 μg) and (2) cardioversion of AF induced by LA or RA pacing (15-beat runs at an amplitude of 10 mA and a pulse width of 2 milliseconds; decrementing by 10 milliseconds from 250 to 180 milliseconds and/or failure to capture).[2]

Arm 2: Empirical Ablation at Common Non-PV Trigger Sites

After the standard ablation approach, additional lesions were given using 3D electroanatomical guidance at the following locations: (1) 10 to 12 lesions from the 3- to the 8-o'clock position along the mitral annulus (MA), (2) 4 to 6 lesions at the limbus of the fossa ovalis from both LA and RA, (3) 4 to 6 lesions at the eustachian ridge and posterior-inferior to the CS ostium, (4) 8 to 10 lesions along the mid

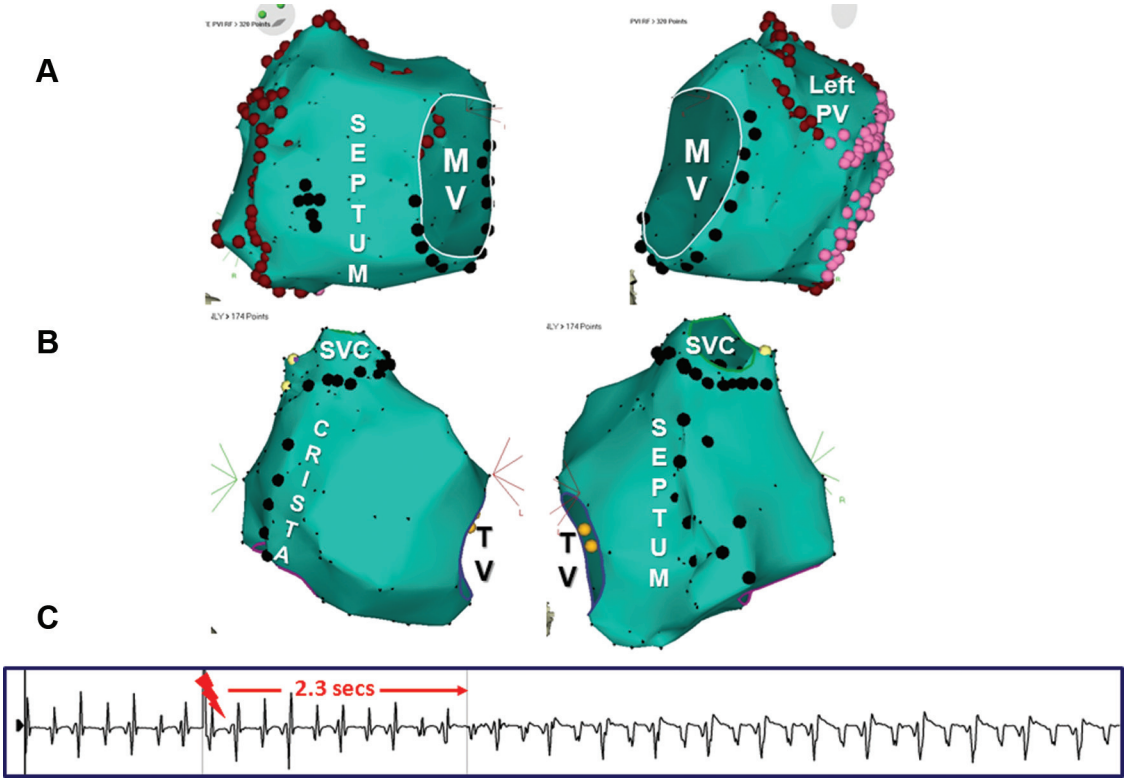

Figure 2. Lesion distribution in arm 2. **A** and **B**, Left and right atria, respectively. Red/pink dots represent lesions around pulmonary veins (PVs), and black dots represent lesions delivered at common non-PV trigger sites. **C**, Local electrogram attenuation within 2.3 seconds of energy delivery. MV indicates mitral valve; TV, tricuspid valve; SVC, superior vena cava.

and lower third of the crista terminalis, and (5) lesions encircling the superior vena cava, sparing the lateral border when phrenic nerve capture was present. The end point of each lesion delivery was local electrogram attenuation (≥50% reduction in electrogram amplitude or reversal of polarity) using a power of ≥20 W for at least 20 seconds, with a concomitant 5- to 10-Ω decrease in impedance (Figure 2).

Arm 3: Left Atrial CFE Ablation

After PVI, if patients remained in AF, then a 3D electroanatomical LA CFE map was constructed using the circular mapping (only for NavX) and/or ablation catheter (both NavX and CARTO). In patients who were in sinus rhythm (SR), AF was induced with burst atrial pacing. The following settings were used to identify CFE: (1) for NavX, 5-second segments were acquired with a refractory period of 50 milliseconds (width, 10; sensitivity, 0.5–1.0 mV); (2) for CARTO, 2.5-second segments were acquired with a threshold of 0.05 to 0.5 mV. CFEs were considered present when the mean fractionation interval was <120 milliseconds.[11] Typically, 3 to 5 lesions were delivered at each CFE region and the end point was CFE abolishment using a power of ≥20 W for at least 20 seconds, with a concomitant 5- to 10-Ω decrease in impedance (Figure 3). After CFE ablation, if patients remained in AF, then SR was restored by cardioversion, PVI was confirmed (entry/exit block), and a stimulation protocol was performed.

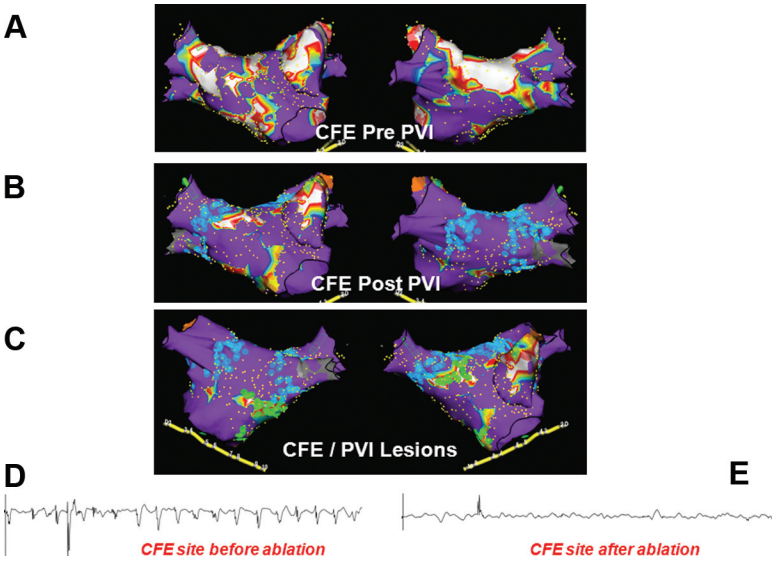

Figure 3. Lesion distribution in arm 3. **A** and **B**, Complex fractionated electrogram (CFE) distribution (white confluent areas) before and after pulmonary vein isolation (PVI; purple dots). **C**, Lesions (green dots) targeting CFE sites. **D** and **E**, CFE site electrogram recording before and after ablation, respectively.

Additional Ablation

Regardless of the initial randomization strategy, in patients who manifested typical right atrial flutter clinically or in whom this was induced by the stimulation protocol, lesions were delivered to achieve bidirectional cavotricuspid isthmus block. We also mapped and targeted any OAT manifesting a cycle length ≥240 milliseconds that developed during ablation and/or was induced by the stimulation protocol.

Repeat Ablation

For patients experiencing arrhythmia recurrence >6 weeks after the procedure, AADs were modified and a repeat ablation procedure was performed, per patient and physician preference. In patients undergoing repeat ablation, PVI was assessed and veins showing entry/exit were reisolated. Also, any linear lesions created at the time of the initial procedure to target typical atrial flutter and/or OAT, with a cycle length ≥240 milliseconds, were assessed for conduction block. Next, the stimulation protocol previously described was performed and any non-PV triggers of AF and/or OAT were mapped and ablated. No empirical LA or RA lesions (linear or otherwise) or CFE assessment/ablation was performed.

Follow-Up

After the procedure, patients were administered AADs (usually class I C agents or sotalol) and warfarin. Patients were kept in the hospital and received an unfractionated heparin infusion until an INR of ≥1.8 was achieved. Long-term follow-up consisted of at least 3 outpatient visits (at 6 weeks, 6 months, and 1 year from the date of ablation). Before or immediately after each visit, patients underwent 30-day periods of transtelephonic monitoring (auto and patient trigger capabilities). Additional transtelephonic monitoring was performed if patients reported arrhythmia symptoms in between visits. Beyond 1 year, patients were encouraged to return for outpatient evaluation semiannually, but this was not mandated and our research personnel continued to observe subjects by telephonic contact every 3 months. At each outpatient visit, patients were queried for symptoms and a 12-lead ECG was obtained. In the absence of any documented arrhythmia recurrence, AADs were discontinued between 3 and 6 months after the initial ablation. In patients with a CHADS2 score of <2 who did not manifest arrhythmia recurrences off AADs, warfarin was discontinued. In patients undergoing repeat ablation, the same follow-up approach was used.

Estimate of Sample Size

From previous studies, it appears that, in patients with persistent AF, PVI alone confers a single-procedure efficacy of ≈40%, whereas CFE ablation has enhanced this outcome to ≈70%.[2,7] Our study sample size was, thus, calculated to test for a pairwise difference of 30% in the efficacy rates between the new strategies and the standard AF ablation approach for the primary end point of freedom from atrial arrhythmias after a single ablation procedure. Assuming a type I error rate of 0.05, 80% power, and an R^2 of 20% because of other potential predictors in the logistic regression model, we estimated requiring a total of 147 patients (49 in each arm).

Statistical Analysis

The 3 groups were summarized and compared on demographic and clinical characteristics using Kruskal-Wallis tests (continuous variables) and χ^2 or Fisher exact tests (categorical variables). Kaplan-Meier survival functions were generated for each group based on the first follow-up visit (6 weeks, 6 months, 1 year) at which an atrial arrhythmia event was known to have occurred. The odds of being arrhythmia free and of having arrhythmia control at 1 year were compared between groups using logistic regression. Models were adjusted for age, sex, basal metabolic index, duration of AF, catheter platform (8 mm versus irrigated), hypertension, and sleep apnea. $P \leq 0.05$ was considered statistically significant. Analyses were conducted using PASW 18.0.

Table 1. Patient Demographics

Demographics	Arm 1 (n=55)	Arm 2 (n=50)	Arm 3 (n=51)
Age, y*	59±8	57±10	60±9
Male sex	48 (87)	42 (84)	46 (90)
AF duration, mo*	56±65	44±44	43±40
Basal metabolic index*	32±8	31±7	31±5
LVEF*	0.56±0.9	0.57±0.10	0.56±0.14
Left atrial size, cm^{2}*	4.8±0.7	4.7±0.6	4.9±0.8
Hypertension	44 (80)	30 (60)	38 (75)
Diabetes	8 (15)	4 (8)	3 (6)
Sleep apnea	21 (38)	15 (31)	11 (22)
COPD	5 (9)	3 (6)	7 (14)
History of CHF	10 (18)	9 (18)	8 (16)

Data are given as number (percentage) unless otherwise indicated.

AF indicates atrial fibrillation; LVEF, left ventricular ejection fraction; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure.

*Data are given as mean±SD.

Results

Over a 32-month period (October 2006 to June 2009), 879 patients underwent their first AF ablation procedure. Of these patients, 264 (30%) had persistent/long persistent AF, and we were able to enroll 166 (63%) of the eligible subjects. After enrollment, the ablation protocol could not be completed in 5 subjects and an additional 5 subjects did not complete the 1-year follow-up. Thus, the final group comprised 156 patients. Fifty-five subjects were randomized to arm 1 (standard approach), 50 to arm 2 (standard approach + empirical ablation at common non-PV trigger sites), and 51 to arm 3 (standard approach + LA CFE ablation). The average age of the population was 58±9 years (males, 136 [87%]) and the mean AF duration was 47±50 months. There was no significant difference in the demographic profile of the patients randomized to the 3 ablation strategies (Table 1).

Acute Procedural Outcomes

Acute procedural outcomes between the 3 study arms are shown in Table 2. Ablation was performed with the 8-mm-tip catheter in 82 patients (53%) and the open irrigated platform

Table 2. Comparison of Acute Procedural Outcomes Between the 3 Arms

Variable	Arm 1 (n=55)	Arm 2 (n=50)	Arm 3 (n=51)
Catheter tip, 8 mm/irrigated, No.	28/27	28/22	26/25
Procedure time, min	356±85	361±98	384±99
Fluoroscopy time, min	103±35	96±31	110±37
PV isolation time, min	162±69	151±63	140±57
No. of lesions/PV	31±15	31±16	30±15
Empirical non-PV or CFE ablation time, min	NA	59±24	38±21*
No. of empirical non-PV or CFE lesions	NA	33±9	22±9*
Acute PV reconnection, No. (%)	21 (38)	20 (40)	13 (26)

Data are given as mean±SD unless otherwise indicated.

PV indicates pulmonary vein; CFE, complex fractionated electrogram; NA, not applicable.

*$P<0.001$.

Table 3. Comparison of Long-Term Outcomes Between the 3 Arms

Outcomes	Arm 1 (n=55)	Arm 2 (n=50)	Arm 3 (n=51)	*P* Value
Freedom from AF/OAT after a single-ablation procedure	27 (49)	29 (58)	15 (29)	0.013
AF/OAT control after a single-ablation procedure	35 (64)	35 (70)	22 (43)	0.016
Serious adverse events	1 (2)	2 (4)	3 (8)	0.304
Early occurrence of AF	32 (58)	23 (46)	26 (51)	0.453
Early occurrence of OAT	7 (13)	10 (20)	9 (18)	0.592

Data are given as number (percentage).
AF indicates atrial fibrillation; OAT, organized atrial tachyarrhythmia.

in 74 patients (47%); this distribution was not different in the 3 study arms ($P=0.84$). For the entire cohort, the mean procedure time was 367±94 minutes and the mean fluoroscopy time was 103±35 minutes; these were not different among the 3 study arms ($P=0.301$ and $P=0.173$, respectively). A mean of 152±64 minutes was required to achieve PVI, and this was comparable in the 3 groups ($P=0.367$). Acute PV reconnection was observed in 54 patients, and this was equally distributed in the 3 study arms ($P=0.243$). In arm 2, non-PV locations were targeted by a mean of 33±10 lesions over 59±24 minutes. In arm 3, a median of 3 LA CFE locations (appendage region, anterior wall, roof, septum, and/or mitral annular region) were targeted, with a mean of 22±9 lesions over 38±21 minutes. The number of non-PV lesions and the time taken to deliver them were higher in arm 2 than in arm 3 ($P<0.001$ for both comparisons). AF termination to SR and/or OAT was infrequently observed in our study (n=5 [3%]) and was not significantly different in the 3 arms (4% in arm 1, 0% in arm 2, and 6% in arm 3; $P=0.238$). Ablation across the cavotricuspid region for clinical or induced typical atrial flutter was performed in 24 patients; this was also comparable in the 3 arms (15% in arm 1, 10% in arm 2, and 22% in arm 3; $P=0.267$). In 5 patients (2 in arm 1, 2 in arm 2, and 1 in arm 3), linear lesions were delivered to achieve block across the MA–left inferior PV region for induced MA flutter. The stimulation protocol identified triggers in the superior vena cava in 4 patients (3 in arm1 and 1 in arm 3), in the high crista region in 2 patients (1 in arm 1 and 1 in arm 2), in the LA roof in 1 patient (in arm 1), within the CS in 3 patients (1 in arm 1 and 2 in arm 2), and in the LA appendage in 1 patient (in arm 2). In addition, slow pathway modification was performed in one patient and a posterior accessory pathway was ablated in another patient (both in arm 1).

Long-Term Outcomes

The comparison among various long-term outcomes between the 3 study arms is shown in Table 3. Freedom from atrial arrhythmias after a single-ablation procedure (primary study end point) was achieved in 71 patients (46%), and this was significantly worse in arm 3 (29%) compared with arm 1 (49%, $P=0.040$) and arm 2 (58%, $P=0.004$; Figure 4). Arrhythmia control after a single-ablation procedure (secondary study end point) was achieved in 92 patients (59%), and this, too, was significantly worse in arm 3 (43%) compared with arm 1 (64%, $P=0.036$) and arm 2 (70%, $P=0.003$; Figure 4). Comparing these 2 outcomes between arm 1 and arm 2, the latter showed some improvement over arm 1 for both the primary and secondary end points (odds ratio [OR], 1.22 and 1.33, respectively), but these were not statistically significant ($P=0.657$ and $P=0.490$, respectively). The early occurrence of atrial arrhythmias (AF and/or OAT ≤6 weeks of ablation procedure) was observed in 94 patients (60%), and this was comparable among the 3 arms (arm 1, 64%; arm 2, 52%; and arm 3, 65%; $P=0.349$; Table 3). These arrhythmias manifested as AF in 81 subjects (52%) and/or OAT in 26 subjects (17%). The early occurrence of OAT was equally distributed between the 3 study arms (13% in arm 1, 20% in arm 2, and 18% in arm 3; $P=0.592$), as was AF (58% in arm 1, 46% in arm 2, and 51% in arm 3; $P=0.453$). The early occurrence of atrial arrhythmias (OR, 4.5; 95% CI, 2.0–10.0; $P<0.001$) and randomization to arm 3 (OR, 4.2; 95% CI, 1.5–12.0; $P=0.007$) were the only independent predictors of lack of freedom from AF at 1 year after a single-ablation procedure. These 2 variables also predicted lack of AF

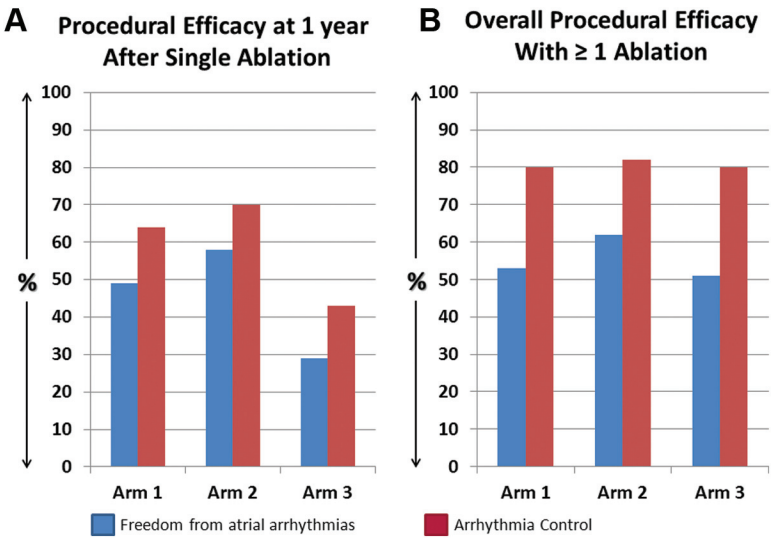

Figure 4. Long-term procedural efficacy after single ablation (**A**) and ≥1 ablation (**B**) procedure in the 3 study arms.

Table 4. Observations Made During a Repeat Procedure in the 3 Arms

Observation	Arm 1 (n=14)	Arm 2 (n=16)	Arm 3 (n=24)
Vein reconnected			
1	0	0	5 (21)
2	5 (36)	1 (6)	1 (4)
3	4 (28)	6 (39)	7 (29)
All veins reconnected	5 (36)	9 (56)	11 (46)
OAT targeted	3 (21)	3 (19)	4 (17)
PV isolation time, min*	155±91	136±71	150±81
Procedure time, min*	393±137	318±118	306±103

Data are given as number (percentage) unless otherwise indicated.
OAT indicates organized atrial tachyarrhythmia; PV, pulmonary vein.
*Data are given as mean±SD.

control after a single-ablation procedure at 1 year (for early occurrence of atrial arrhythmia: OR, 2.5; 95% CI, 1.1–5.3; $P=0.021$; for randomization to arm 3: OR, 3.3; 95% CI, 1.41–10.0; $P=0.009$).

Repeat Ablation and Overall Outcome

Fifty-seven patients (37%) underwent ≥1 repeat ablation for arrhythmia recurrence beyond the initial 6 weeks after the first procedure. Fifteen patients (27%) were originally randomized to arm 1, 17 (34%) were randomized to arm 2, and 25 (49%) were randomized to arm 3 ($P=0.061$). Fifty-four of these patients underwent the repeat ablation procedure at our center (13 patients underwent ≥2 repeat ablations). The mean age of this group was 61±9 years. The presenting rhythm at repeat ablation was sinus in 21 (39%), AF in 25 (46%), and OAT in 6 (11%). At least 1 PV demonstrated reconnection in all patients and ≥3 PVs were reconnected in most patients (75.9%, Table 4). Additional ablations to target either spontaneous or induced LA OATs were required in a few patients (n=10 [19%]). The mean procedure time for repeat ablation was 332±120 minutes. Over a follow-up of 22±9 months (19±9 months from the last ablation), with ≥1 ablation procedure, freedom from atrial arrhythmias off AADs was achieved in 86 patients (arm 1, 53%; arm 2, 62%; arm 3, 51%; $P=0.487$; Figure 4), and arrhythmia control was achieved in 126 patients (81%; arm 1, 80%; arm 2, 82%; arm 3, 80%; $P=0.963$; Figure 4).

Serious Adverse Events

Serious adverse events were observed in 7 patients (5%) and were equally distributed in the 3 study arms (Table 3; 2% in arm 1, 4% in arm 2, and 8% in arm 3; $P=0.304$). These included groin access complications in 3 patients (pseudoaneurysm in 1, arteriovenous fistula in 1, and large hematoma in 1), cerebrovascular events in 2 patients (transient ischemic attack in 1 and left cortical microembolic stroke in 1), pericardial tamponade in 1 patient, and significant pulmonary vein stenosis requiring stenting (right superior and inferior veins) in 1 patient. This patient was randomized to arm 3 and required 2 repeat ablation procedures, after which right inferior pulmonary vein was occluded and there was significant perfusion mismatch in the territory drained by right superior pulmonary vein.

Discussion

In this randomized study comparing 3 different ablation strategies in patients with persistent or long-lasting persistent AF, we found that PVI, combined with ablation of only documented non-PV triggers identified using a stimulation protocol (standard approach), was as efficacious as the standard approach, combined with empirical ablation at common sites of non-PV AF triggers, and significantly better than adding LA CFE ablation to the standard approach.

Complex Fractionated Electrogram Ablation

Although PV ablation is the cornerstone of AF ablation, the single-procedure efficacy of this approach has been less than optimal in patients with persistent AF.[2,3] This has been attributed to the substrate underlying persistent AF, which has resulted in the development of adjunctive substrate-modifying strategies.[6–11] These strategies include linear lesions across potential re-entrant channels, targeting CFEs, and ablating ganglionated plexi.[6–13] Among these strategies, CFE ablation has become popular. This technique was originally described in the seminal study by Nademanee et al[7]; by targeting CFEs exclusively, the investigators were able to achieve long-term arrhythmia control after a single procedure in up to 70% of patients with persistent AF. However, subsequent attempts by other investigators using this approach did not yield comparable results.[8,9] A potential explanation for this discrepancy was the inconsistency in CFE interpretation, which can be operator dependent. To overcome this, automated computerized algorithms have been developed. The accuracy and reproducibility of these algorithms have been previously validated.[9,10] Studies have also assessed the efficacy of this approach on arrhythmia control. However, the limitations of these studies include small sample size, short follow-up duration, combination with other substrate-modifying strategies, and heterogeneous AF type.[6–9] In the present study, we tried to overcome some of these limitations. We excluded patients with paroxysmal AF. Our ablation strategy comprised PVI followed by LA CFE ablation. We chose this sequence because in a prior study we found that CFE distribution can be significantly attenuated after PVI.[14] However, despite adjunctive CFE ablation, single-procedure efficacy in this arm was not enhanced beyond our standard ablation approach and these patients actually fared worse. This finding may be attributed to several factors, including (1) CFE ablation limited to LA only, (2) proarrhythmic effect of CFE ablation, (3) inadequate CFE ablation, and/or (4) inadequate PVI. In a previous study, Oral et al[15] demonstrated no additional benefit of right atrial CFE ablation beyond LA CFE ablation in enhancing procedural efficacy, which would support our approach. By creating zones of slow conduction, CFE ablation may promote the development of OATs; however, we do not think this played a role in our series because AF was the predominant arrhythmia in patients experiencing recurrences in this arm. This would imply either inadequate CFE ablation or inadequate PVI. In support of the former, despite attenuating and/or abolishing CFE at each ablation site, AF organization to OATs and/or SR was rare in our study, and this is different from the observations reported by some investigators.[6–9,15]

However, given the limited LA CFE ablation and no use of ibutilide in our study, the low rate of conversion to OAT or SR is not surprising. In our study, PVI time showed a trend toward being shorter in patients undergoing concomitant CFE ablation (Table 2). One explanation for this trend may be that operators were not as rigorous about validating acute PV reconnection at the end of the procedure in this arm. Consistent with this hypothesis, acute PV reconnection showed a trend toward being less common in arm 3 and more patients in this arm required repeat ablation, during which ≥1 veins had reconnected in all subjects (Tables 2 and 4).

Empirical Ablation at Common Non-PV Trigger Sites

Our center has consistently used a standard stimulation protocol to identify PV and non-PV triggers of AF. By using this method, we have found certain locations, in addition to the PVs, from which AF triggers commonly originate.[2] These locations include the inferior MA, the fossa ovalis/limbus region, the eustachian ridge, the CS ostium, the crista terminalis region, and the superior vena cava. After achieving PVI, we empirically ablated at these locations based on the hypothesis that, even in patients with persistent AF, its initiation has to occur from a focal trigger. We also posited that at or in the vicinity of the focal source, short periods of energy delivery may be sufficient to eliminate the trigger. Although this empirical ablation strategy did not significantly improve the primary or secondary study end points, it did show 22% higher odds of achieving freedom from atrial arrhythmias and 33% higher odds of achieving arrhythmia control at 1 year compared with the standard ablation approach. Although we imply that the relatively better outcomes in this arm were from ablation of non-PV AF trigger sources, we cannot prove that ablation at all the previously mentioned sites was necessary. We also cannot exclude the possibility that the benefit in this study arm may be from inadvertent ablation of ganglionated plexi and/or AF nests.[13] However, we want to emphasize that because the empirical ablation was anatomically guided and performed in SR, with the end point of local electrogram attenuation, this approach was consistently reproducible.

Role of Pulmonary Veins in Persistent AF

Although we hypothesized that additional lesions beyond PVI should enhance single-procedure efficacy in patients with persistent AF, this was not the case in our study. However, because PVI was used in all 3 arms, it may be deduced that PVs play an important role in this form of AF. In support of this, in the study patients who underwent repeat ablation for arrhythmia recurrences, ≥1 vein had reconnected in all subjects (≥3 PVs had reconnected in most subjects). Reisolating these veins without additional empirical lesions and/or CFE ablations resulted in good (≈80%) long-term AF control rates. This suggests that durable PVI may be of primary importance in improving the single-procedure efficacy of ablation procedures, even in the population with persistent AF.

Early Recurrence of Atrial Arrhythmias and Long-Term Arrhythmia Control

Early arrhythmia occurrence is not typically considered failure of the AF ablation procedure. These early arrhythmias have been attributed to atrial irritability, autonomic remodeling, and/or a transient generalized inflammatory state.[4] However, an alternative explanation may be that, in these patients, the original arrhythmic substrate has re-established. We have previously shown that early occurrence of atrial arrhythmias is an independent predictor of long-term AF recurrence in patients with paroxysmal AF.[2] In the current study, this variable was also independently associated with worse long-term arrhythmia control in patients with persistent AF. Thus, regardless of the type of AF, early occurrence of atrial arrhythmias after ablation is a bad prognosticator of long-term success.

Limitations

The study sample size was powered to test for a difference of ≥30%; thus, smaller, yet clinically meaningful, differences between the study arms may not have been detected. Procedure success was assessed by ≥3 clinic visits and multiple transtelephonic monitoring performed over the 1-year follow-up period, which may have precluded recognition of patients experiencing silent AF/OATs in the intervening time span. We switched from an 8-mm to an open irrigated catheter platform during the trial, and this was not randomized. However, the catheter tip distribution was comparable in all 3 arms. We acknowledge that poor long-term outcome in this study arm may also have been the result of a limited CFE ablation strategy: few lesions confined to the LA only. Also, more non-PV triggers were identified and targeted in arm 1, which could have influenced outcomes.

Conclusions

In patients with persistent AF, PVI, combined with ablation of AF triggers identified using a stimulation protocol, was as efficacious as this approach, combined with empirical ablation at common sites of non-PV AF triggers and was significantly better than combining it with LA CFE ablation. These data suggest that additional extensive substrate modification beyond PVI, especially LA CFE ablation, does not improve single-procedure efficacy in this patient population.

Disclosures

Drs Dixit, Marchlinski, Callans, Lin, Garcia, Cooper, Verdino, and Patel received speaking honoraria from St Jude Medical; Drs Dixit, Marchlinski, and Callans received speaking honoraria from Biosense-Webster; Drs Marchlinski, Hutchinson, and Gerstenfeld received research grants from Biosense-Webster; Dr Verdino is a consultant for Biosense-Webster; and Dr Gerstenfeld received a research grant from St Jude Medical.

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CLINICAL PERSPECTIVE

The single-procedure efficacy of pulmonary vein isolation (PVI) for ablation of persistent atrial fibrillation (AF) is less than ideal, and the approach to additional ablation is controversial. The inability to achieve durable PV isolation and consistently target AF triggers and substrate outside the PVs contribute to failures. This trial assessed the benefit of additional ablation at complex fractionated electrogram (CFE) regions or common sites of non-PF triggers in patients with persistent AF undergoing PVI plus ablation of provokable AF triggers. We randomized patients to receive no additional ablation, additional ablation of left atrial CFE sites, or ablation at predefined common sites of non-PV triggers. Single-procedure efficacy was $<50\%$ in all groups, and CFE ablation beyond PVI did not significantly enhance the single-procedure efficacy. Moreover, in those patients with arrhythmia recurrence who underwent repeat ablation, all had reconnection of at least 1 PV; targeting these alone improved long-term AF control. These findings imply that PVs remain critical in the genesis of persistent AF for many patients.