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Anatomy Versus Physiology-Guided Ablation for Persistent Atrial Fibrillation

Abhishek Deshmukh [1], Li Zhong [1], Joshua Slusser[3], Peilin Xiao[1], Pei Zhang[1], David Hodge[3], Mélèze Hocini [2] , Christopher McLeod [1] , David Bradley [1] , Thomas Munger [1],Douglas Packer [1] , Yong- Mei Cha [1]

[1]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota.
[2]Bordeaux University Hospital, LIRYC institute, Pessac, France.
[3]Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota.

Abstract

Background: Pulmonary vein isolation remains the cornerstone of atrial fibrillation (AF) ablation. However, due to high recurrence rates, especially in patients with persistent AF, PV antral isolation, complemented by linear ablation, autonomic modulation, and ablation of complex fractionated electrograms, have been attempted to increase the odds of success. However, the optimum approach for a complementary strategy in addition to PVI for persistent AF is unknown.

Methods: We performed a prospective randomized trial by assigning 92 patients with persistent AF in 1:1 ratio to pulmonary-vein isolation plus ablation of electrograms showing complex fractionated activity (45 patients), or pulmonary-vein isolation plus additional linear ablation across the left atrial roof and mitral valve isthmus (47 patients). The duration of follow-up was five years. The primary endpoint was freedom from any documented recurrence of atrial fibrillation after a single ablation procedure.

Results: At a 12-month follow-up, 9 (23%) patients had AF recurrence in the linear ablation and 8 (21%) patients in the CFAE groups. At a mean follow-up duration of 59±36 months, 48.3% of patients in the linear ablation group and 44.6% of patients in the CFAE group were free from AF (p=0.403). There were no significant differences between the two groups for independent predictors of freedom from AF. The overall procedure time and radiation exposure were higher in the PVI+linear ablation group. There were five adverse events noted, two in the linear group (pericardial effusion not requiring drain) and 3 in the CFAE group (1 pseudoaneurysm, one effusion requiring pericardiocentesis and one effusion nor requiring drain).

Conclusion: Among patients with persistent atrial fibrillation, we found no difference in maintenance of sinus rhythm in either linear ablation or ablation of complex fractionated electrograms was performed in addition to pulmonary vein isolation in short- and long-term follow-up.

Introduction

Since the seminal report by Dr. Michel Haïssaguerre, catheter-based ablation for atrial fibrillation (AF) has evolved and been highly effective for the elimination of atrial fibrillation (AF) compared to antiarrhythmic medications.[1] The overall freedom from AF is dependent on the duration of AF, with success rates ranging between 75% and 90% in patients with paroxysmal AF. [1, 2] In contrast, the success rate is lower in the setting of persistent AF.[3]. PV isolation has been the cornerstone of AF ablation. However, due to a relatively high recurrence rate, especially in patients with persistent AF, other ablation techniques have been developed, involving a PV antral isolation, often complemented by ablation lines, and ablation of complex fractionated atrial electrograms. (CFAE)[2 4]

Furthermore, several randomized studies have produced conflicting results regarding the benefit of adding linear ablation lines, CFAE ablation, both or none. [5-8] Methods of targeting left, and right atrial areas of complex, fractionated or high-frequency electrograms have been developed to improve AF success rates.[9-13] Thus a broad spectrum of approaches ranging from strictly anatomical to more physiology-guided ablation has been utilized. However, the optimum approach for a complementary strategy in addition to PVI for persistent AF remains elusive.

Hence we designed a prospective study to establish freedom from AF with combined wide area circumferential ablation and linear ablation, vs. combined wide area circumferential ablation and CFAE ablation.

Key Words

Atrial Fibrillation, Post-Operative Atrial Fibrillation, Valvular Heart Surgery, Time Varying Risk.

Corresponding Author
Yong-Mei Cha MD
Department of Cardiovascular Diseases, Mayo Clinic,
200 First St SW, Rochester, MN 55905, USA.

Methods

Study design

We prospectively randomized patients undergoing pulmonary vein isolation to either additional linear ablation, versus the adjunctive ablation targeting fractionated or high-frequency electrograms ablation for the treatment of AF. Ninety-two patients with symptomatic persistent AF were randomized to PVI+ additional linear ablation group vs. PVI + physiology guided CFAE ablation. Inclusion criteria consisted of a history of symptomatic persistent AF, age ≥21 years, the recommendation for catheter-based, wide-area pulmonary vein isolation, and provision of informed consent. Patients with an unstable medical condition including, but not limited to, acute myocardial infarction, recent stroke, decompensated congestive heart failure, or recent major surgeries, pregnant or breastfeeding women, those unable to give informed consent and those for whom it was not feasible to be followed up at Mayo Clinic were excluded from the study.

Ablation procedures

Patients presented to the clinical electrophysiology laboratory in the fasting stage. All patients underwent general anesthesia. Multiple 5-8 Fr sheaths were placed in the femoral veins; Catheters were positioned in the coronary sinus, left atrium, and other chambers as necessary with electrodes coupled to the input amplifiers of a multi-channel recording system. Catheter positioning and ablation were guided with fluoroscopy. Two long 8 Fr sheaths were advanced, crossing the interatrial septum into the left atrium. An 8 Fr open irrigation-tipped catheter was advanced via one sheath, with a 15 - 25 mm lasso catheter advanced via the second. All patients were heparinized to maintain an ACT of 300 - 400 throughout the entire procedure using both bolus and infusion heparin.

An electroanatomic mapping system (CARTO, Biosense Webster Inc.) was used to create geometries of each ostium of the four pulmonary veins. After that, LA mapping was performed in AF, which was induced if not already present, incorporating 75-100 points into the LA surrogate geometry. The venoatrial junction was taken as the point of confluence between each pulmonary vein and the left atrium; the intracardiac ultrasound was used to confirm that specific location. Multiple electrical and anatomic features were registered, and off-line analyzed to assess left atrial substrate.

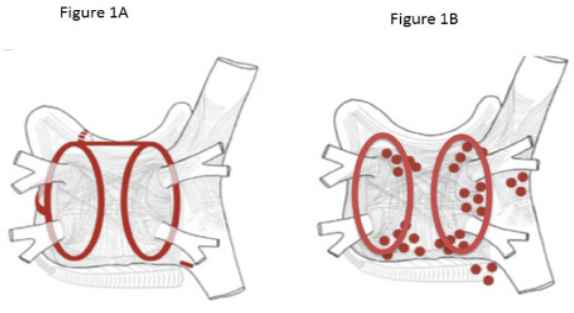

Figure 1: Schematic of common lesion sets employed in AF ablation. A: The circumferential ablation lesions that are created in a circumferential fashion around the right and the left PVs and linear ablation line in the left atrial room and mitral isthmus. B: Ablation targeting complex fractionated activity electrograms (CFAE). Modified with permission from Calkins et al. Heart Rhythm 2012; 9:632–696.e21.2

Table 1: Patient Demographics and Clinical Characteristics

Variable	Linear (N=47)		CFAE (N=45)		P-value
Age (years)	60.9	(8.3)	60.5	(10.2)	0.85
Gender, n (%)					0.15
. Male	41	(87%)	34	(76%)	
. Female	6	(13%)	11	(24%)	
Body Mass Index	34.9	(6.8)	34.4	(7.8)	0.73
LA Volume (cc/m^2)	44.4	(11.9)	45.9	(11.5)	0.56
Duration of Ablation	41.7	(23.4)	34.4	(16.2)	0.09
Diabetes, n (%)	5	(11%)	10	(23%)	0.16
Coronary Artery Disease, n (%)	7	(16%)	5	(11%)	0.53
Chronic Kidney Disease, n (%)	3	(6%)	1	(2%)	0.33
Hypertension, n (%)	27	(61%)	27	(61%)	1.00
Congestive Heart Failure, n (%)	5	(11%)	5	(11%)	1.00
Chronic Obstructive Pulmonary Disease, n (%)	3	(6%)	3	(7%)	0.96
RV Systolic Pressure	28.8	(7.9)	28.4	(7.6)	0.81
Antiarrhythmic Drug Therapy, n (%)	14	(30%)	9	(20%)	0.28
ACE Inhibitor/ARB, n (%)	14	(30%)	12	(27%)	0.74
Beta Blocker, n (%)	35	(74%)	36	(80%)	0.53
Calcium Channel Blocker, n (%)	11	(23%)	10	(22%)	0.89
Statin, n (%)	25	(53%)	31	(69%)	0.12
Rhythm, n (%)					0.43
. Sinus	4	(9%)	2	(4%)	
. AFib/Flutter	43	(91%)	43	(96%)	
LV Ejection Fraction	53.7	(12.5)	53.4	(12.7)	0.90
LV End Diastolic Diameter	52.0	(7.3)	52.1	(6.6)	0.93
LV End Systolic Diameter	36.1	(8.7)	35.6	(7.1)	0.78
LV Volume Mass	103.5	(29.8)	94.9	(22.9)	0.15
Right Atrial Enlargement, n (%)					0.89
. Normal	5 (11%)		9	(20%)	
. Mild	11(24%)		7	(16%)	
. Moderate	14(30%)		11	(25%)	
. Severe	16(35%)		17	(39%)	
Mitral Regurgitation, n (%)					0.12
. Normal	29	(62%)	21	(48%)	
. Mild	15	(32%)	16	(36%)	
. Moderate	3	(6%)	7	(16%)	
Tricuspid Regurgitation, n (%)					0.23
. Normal	31	(67%)	25	(56%)	
. Mild	12	(26%)	15	(33%)	
. Moderate	3	(7%)	4	(9%)	
. Severe	0	(0%)	1	(2%)	

Table 2: Approach to Linear Ablation

Variable	Linear group (N=47)		CFAE group (N=45)		P-value
1C Line Completed, n (%)					
. Yes	45	(96%)			
. No	2	(4%)			
IC line Bidirectional Block, n (%)					
. Yes	29	(64%)			
. No	16	(36%)			
1A Line Completed, n (%)					
. Yes	46	(98%)			
. No	1	(2%)			
IA line Bidirectional Block, n (%)					
. Yes	39	(85%)			
. No	7	(15%)			
CTI, n (%)					0.62
. Yes	38	(83%)	38	(86%)	
. No	8	(17%)	6	(14%)	
CTI Bidirectional Block, n (%)					0.56
. Yes	37	(95%)	38	(97%)	
. No	2	(5%)	1	(3%)	
AF termination					
. During PVI, n (%)	5	(11%)	2	(5%)	0.28
. During Linear Ablation, n (%)	2	(4%)	0	(0%)	0.37
. During CFAE Ablation, n (%)	0	(0%)	3	(7%)	0.79
Spontaneous ERAF, n (%)	3	(6%)	5	(11%)	0.42

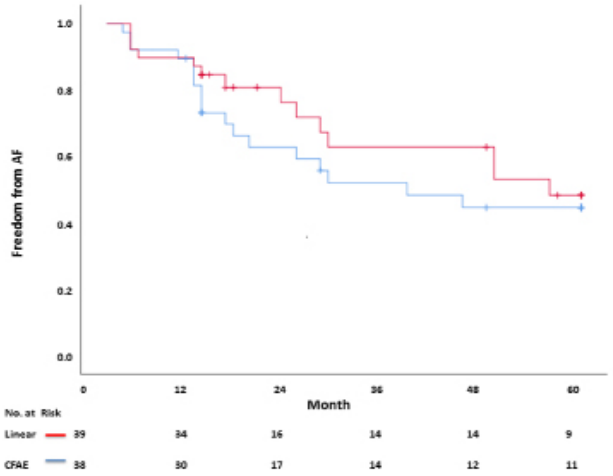

Figure 2: shows Kaplan-Meier AF free rate at short-term and long-term follow-up post PVI+linear and PVI+CFAE ablations.

Ablation: PV isolation + linear lines

Each patient in the linear group underwent wide area circumferential pulmonary vein isolation and then adjunctive left atrial lines. In all, one ablative ring was placed around the left pulmonary veins at a distance of 5-15 mm outside the venoatrial junction. The second ring was placed around the right pulmonary veins at an equivalent distance. All energy deliveries were made using 25 - 50 watts of radiofrequency energy delivered via a 3.5 mm irrigation tip catheter with 0.9 NS flow infused at 10 - 30 ml/min. Each ablative lesion was juxtaposed to the immediately preceding lesion using 3-mm marker annotation on the surface of the CARTO map (figure 1A). The endpoint of the circumferential ablation was the elimination of all PV potentials as assessed by lasso catheter mapping (entrance block and exit block if pulmonary vein ectopy was present). The termination of AF during ablation was recorded. Mitral isthmus linear lesion was created from the mitral valve annulus to the left wide area circumferential ablative ring. Coronary sinus ablation was undertaken to facilitate the mitral isthmus line block when needed. An additional left atrial roof lesion was created from the left superior to the right superior pulmonary veins with care taken to maintain this line of block well anteriorly and superiorly to the region of the

Table 3: Voltage Mapping Area

Variable	Linear (N=47)		CFAE (N=45)		P-value
Total Mapping Points	84.4	(25.5)	103.3	(30.6)	0.003
Minimum Voltage	0.1	(0.1)	0.1	(0.0)	0.17
Median Voltage	0.6	(0.4)	0.5	(0.2)	0.16
Maximum Voltage	3.5	(2.9)	3.1	(1.6)	0.51
Mean Total Voltage	0.5	(0.2)	0.5	(0.2)	0.93
Left WACA					
Mapping Points	7.3	(9.8)	10.8	(10.0)	0.10
CFAE Points	5.4	(11.0)	7.1	(7.4)	0.39
% CFAE Points	71.0	(64.2)	72.2	(33.6)	0.92
Mean Voltage	0.5	(0.3)	0.5	(0.3)	0.71
Right WACA					
Mapping Points	8.9	(12.1)	11.0	(8.6)	0.33
CFAE Points	5.3	(9.5)	6.6	(5.2)	0.40
% CFAE Points	65.1	(37.9)	68.2	(33.0)	0.71
Mean Voltage	0.4	(0.1)	0.5	(0.2)	0.16
Roof					
Mapping Points	10.7	(7.8)	16.3	(11.2)	0.007
CFAE Points	2.3	(2.8)	3.9	(4.0)	0.026
% CFAE Points	26.3	(28.9)	21.0	(20.4)	0.36
Mean Voltage	0.6	(0.4)	0.6	(0.5)	0.77
Area of Low Voltage (cm2)	8.6	(8.0)	11.1	(8.5)	0.18
Posterior Wall					
Mapping Points	9.2	(8.1)	15.9	(9.6)	<.001
CFAE Points	4.1	(4.3)	5.8	(5.2)	0.10
% CFAE Points	42.3	(30.2)	34.6	(26.8)	0.25
Mean Voltage	0.5	(0.2)	0.4	(0.2)	0.52
Area of Low Voltage (cm^2)	12.7	(7.9)	12.2	(7.1)	0.76
Septum					
Mapping Points	5.7	(5.6)	10.6	(7.8)	<.001
CFAE Points	1.2	(2.0)	3.1	(3.5)	0.001
% CFAE Points	19.7	(25.0)	26.3	(29.7)	0.35
Mean Voltage	0.6	(0.3)	0.6	(0.3)	0.89
Area of Low Voltage (cm^2)	7.7	(7.7)	10.1	(7.0)	0.15

Table 4: Procedure Time and Dosage

Variable	Linear (N=47)		CFAE (N=45)		P-value
WACA					
Procedure Time, min	99.3	(42.2)	90.2	(33.8)	0.26
Flouro Time, min	30.9	(24.2)	30.0	(19.0)	0.86
Radiation Dose, mgy	917.8	(817.6)	904.9	(729.5)	0.94
RF Time, min	55.6	(21.3)	54.7	(15.1)	0.82
Linear or CFAE Ablation					
Procedure Time, min	43.9	(31.6)	34.4	(16.2)	0.08
Flouro Time, min	10.8	(4.4)	8.6	(7.4)	0.37
Radiation Dose, mgy	537.3	(420.4)	255.0	(220.0)	<.001
RF Time, min	26.0	(14.9)	21.8	(29.5)	0.42
Total Procedure Time, min	369.5	(97.9)	352.3	(100.0)	0.41
Total Flouro Time, min	88.5	(37.5)	80.6	(34.7)	0.31
Total Radiation Dose, mgy	2689.6	(1588.7)	2501.1	(1509.0)	0.56
Total RF Time, min	98.1	(33.4)	84.0	(18.8)	0.023

esophagus. Additional linear ablation in the form of the left atrial septal line and anterior mitral annulus line was undertaken as an option per operator's discretion.

PV isolation + ablation of complex fractionated electrograms

Patients randomized to the CFAE group underwent wide area circumferential pulmonary vein isolation, and ablation targeting CFAE manifested as repetitive firing at any site of point-to-point mapping with an electrogram cycle length 50-120 msec, with or without intervening return to baseline between each electrogram component using CARTO CFAE software. The wide area circumferential ablation of each pulmonary vein was performed first. CFAE were identified using an approach as described by Nadamanee.[12] The search for complex, fractionated, or rapid electrograms specifically targeted regions superior and medial to the left superior pulmonary vein, inferior and medial to the left inferior pulmonary vein, superior and lateral to the right superior pulmonary vein, and inferior and lateral to the right inferior pulmonary vein. Left atrial septal and roof were also evaluated for CFAE. Figure 1B shows the 5 CFAE mapping regions. The region of CFAE was annotated on the surface of the electroanatomic map. The low voltage mapping point was defined as ≤0.5 mV. RF applications were delivered at those identified CFAE sites until the local potentials were eliminated.

DC cardioversion was allowed when AF persists after completion of WACA and LA linear or CFAE ablation. AF was reinitiated by using rapid atrial pacing up to 300 bpm with isoproterenol infusion. If AF was inducible, repeat DCCV was undertaken to assess the presence of early recurrence of AF.

The patients underwent a cavotricuspid flutter ablation for a documented typical atrial flutter or empiric linear ablation based on the operator preference. The lesions were performed in a linear manner connecting the tricuspid annulus and the IVC. The bidirectional block was confirmed by differential pacing and reversal of activation sequence by pacing on either side of the line of the block.

Table 5: Univariate analysis for AF free at 12 months

Variable	Odds Ratio	95% CI	P-value
Age (years)	0.965	(0.903, 1.031)	0.287
Gender	1.047	(0.256, 4.280)	0.949
Body Mass Index	0.998	(0.927, 1.075)	0.964
LA Volume (cc/m^2)	0.960	(0.916, 1.005)	0.080
CFAE (vs. Linear) Ablation	1.125	(0.383, 3.308)	0.831
Duration of CFAE Ablation	0.989	(0.940, 1.042)	0.688
Duration of Linear Ablation	1.005	(0.973, 1.037)	0.768
Diabetes	0.267	(0.076, 0.938)	0.039
Coronary Artery Disease	0.346	(0.084, 1.421)	0.141
Chronic Kidney Disease	0.842	(0.082, 8.656)	0.885
Hypertension	1.140	(0.362, 3.593)	0.823
Congestive Heart Failure	0.808	(0.147, 4.446)	0.806
Chronic Obstructive Pulmonary Disease	>999.999	(<0.001, >999.999)	0.974
LA Volume Index	0.935	(0.851, 1.026)	0.156
RV Systolic Pressure	0.978	(0.916, 1.045)	0.509
Antiarrhythmic Drug Therapy	1.250	(0.378, 4.133)	0.715
ACE Inhibitor/ARB	0.718	(0.206, 2.504)	0.603
Beta Blocker	1.420	(0.356, 5.661)	0.619
Calcium Channel Blocker	0.172	(0.021, 1.403)	0.100
Statin	1.500	(0.491, 4.584)	0.477
LV Ejection Fraction	1.030	(0.989, 1.074)	0.158
LV End Diastolic Diameter	0.945	(0.873, 1.022)	0.155
LV End Systolic Diameter	0.923	(0.859, 0.991)	0.028
LV Volume Mass	0.992	(0.972, 1.012)	0.424
Right Atrial Enlargement	0.502	(0.266, 0.948)	0.034
Mitral Regurgitation	0.659	(0.307, 1.417)	0.286
Tricuspid Regurgitation	0.506	(0.227, 1.130)	0.097
Mean Total Voltage	5.764	(0.253, 131.193)	0.272
Left WACA % CFAE Points	0.993	(0.975, 1.011)	0.441
Left WACA Mean Voltage	0.504	(0.059, 4.304)	0.531
Right WACA % CFAE Points	0.982	(0.963, 1.002)	0.072
Right WACA Mean Voltage	4.006	(0.039, 406.988)	0.556
Avg. Left/Right WACA % CFAE Points	0.987	(0.968, 1.006)	0.181
Avg. Left/Right WACA Mean Voltage	0.635	(0.038, 10.569)	0.752
Roof % CFAE Points	0.970	(0.946, 0.995)	0.018
Roof Mean Voltage	15.923	(0.883, 286.977)	0.061
Posterior Wall % CFAE Points	0.990	(0.970, 1.011)	0.357
Posterior Wall Mean Voltage	147.429	(0.857, >999.999)	0.057
Septum % CFAE Points	0.983	(0.962, 1.005)	0.123
Septum Mean Voltage	0.330	(0.037, 2.927)	0.319

Monitoring During Ablation

Esophageal position and temperature were monitored during all left atrial ablations using a nasogastric tube containing a temperature probe continually repositioned in the esophagus at the level of the ablation catheter to avoid any temperature rise above 38˚C. The

pacing was performed through the ablation catheter at all locations before ablation in the anterior right PVs at ten mA output and 10 ms pulse duration to ensure a lack of phrenic nerve capture. Patients were on heparin throughout the procedure with target ACT 300-400.

Post-procedure care and follow-up

All the patients were monitored in the hospital for at least 24 hours. An additional inpatient stay was permitted if an antiarrhythmic medication was added. All patients received heparin overnight and resume warfarin after the procedure. 12-lead ECG and Chest X-ray were obtained on the next day. Patients were dismissed within 24-48 hours after ablation. Antiarrhythmic drugs were prescribed as per the physician's discretion. All patients were followed up at 3 and 12 months with an ECG and a Holter to assess AF recurrence. The long-term follow-up results were evaluated by ECGs or Holter monitoring documented in the medical records. For patients with recurrent AF or atrial flutter, redo pulmonary vein isolation may be undertaken to reisolate the reconnected pulmonary veins. Any other atypical or typical flutters were mapped and ablated. Sustained attempts were made to achieve bidirectional block across the linear ablation lesion set.

Statistical Analysis

Continuous variables are presented as mean (SD). Discrete variables are summarized as frequency (percentage). Comparisons between groups are made using the Student t-test for continuous variables and the Pearson X^2 test for categorical variables. Further assessment of potential associations with freedom from documented recurrence of AF was assessed utilizing a logistic regression model. Statistical significance is defined as a 2-tailed P value of less than 0.05. Statistical analyses were completed with SAS 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

Patient characteristics

A total of 92 patients were enrolled between September 2009 and January 2013 and were randomly assigned to PVI + linear ablation (47 patients) and PVI + CFAE group (45 patients). Baseline demographics, medication use, comorbidities, and echo characteristics were balanced between the two groups, as shown in Table 1. The mean age was 60.7 years (male sex 81.5%). More than half of the study patients (61%) had hypertension. On average, the LV systolic function was preserved. More than ninety percent of patients were in AF at the time of ablation. The majority of patients were taking beta-blockers or calcium channel blockers. Twenty percent of patients in the CFAE group were on AAD compared to 30% in the linear group. Among the antiarrhythmic medications, 8/92 were on propafenone, 7/92 were on amiodarone, 5/92 were on sotalol, 1/92 on dofetillide, 2/92 flecainde. There was no significant difference of specific antiarrhythmic in both groups.

Acute ablation results

All patients underwent pulmonary vein isolation. There was an entrance block noted in all the veins.

In the linear group, mitral isthmus ablation was attempted in 96% of the patients, and the bidirectional block was confirmed in 64% of these patients. The left atrial roof line was attempted in 98 % of the patients, and the bidirectional block was confirmed in 85% of these patients. Eighty-three percent of this group underwent a CTI line with a bidirectional block confirmed in 95 % of these patients. (Table 2)

In the CFAE group, the average LA mapping point taken was higher than the linear ablation group (mean points 103.3 vs. 84.4, p=0.003). The total points obtained and CFAE points were higher on the anterior wall and septum in the CFAE group than in the linear group. Yet, the percent of CFAE points remained similar in these areas between the two groups. Among the five regions of left WACA ring, right WACA ring, left atrial roof, posterior wall, and septum, the CFAE points were more frequently seen within the WACA rings than other LA areas (65-72% vs. 20-42%, p<0.0001 Table 3). In AF, the mean voltage was highest at the roof and septum (0.6 mv) and lowest on the posterior wall (CFAE group) (0.4 mv). (Table 3) All CFAE points were ablated.

In the linear group, termination of AF was seen in 11% during PVI and 4% during linear ablation, and early recurrence of AF (ERAF) was observed in 6% of the patients. In the CFAE group, termination of AF was seen in 5% of patients during PVI and 7% during CFAE ablation, and ERAF was observed in 11 % of patients. If AF was not terminated during ablation, cardioversion was performed in remaining patients.

Procedure time and complications

The mean time for performing WACA was 94.9 minutes. Besides, the mean time for linear ablation was 43.9 minutes in addition to PVI. The mean time for CFAE ablation was 34.4 minutes in addition to PVI. The total radiation dose was 2689.6 ± 1588.7 mGy in the linear ablation group and 2501.1 ± 1509.0 mGy in the CFAE group. (P=0.56) There was no difference in total procedure time (linear group 369.5 ±97.9 minutes vs. CFAE 352.3±100.0 minutes, p=0.41). The total RF ablation time was longer in the linear group 98.1±33.4 minutes compared to the CFAE group 84.0±18.8 minutes (p=0.023) (Table 4).

There were five adverse events noted, 2 in the linear group (pericardial effusion not requiring drain) and 3 in the CFAE group (one pseudoaneurysm, one effusion requiring pericardiocentesis and one effusion nor requiring drain). There was no procedure-related death, atrioesophageal fistula, stroke, or pulmonary vein stenosis (>70% pulmonary vein narrowing).

Ablation outcomes

At a 12-month follow-up, 9 of 39 (23%) patients had AF recurrence in the linear ablation and 8 of 38 (21%) patients in the CFAE groups (p=0.83) after 3-month blanking time. Twelve (32%) patients in the linear group and 13 (34 %) in the CFAE group were taking AADs to achieve rhythm control. One patient in the linear group and 7 patients in the CFAE group underwent redo ablation at 12 months

(P=0.023). Thirteen (33%) patients in the linear ablation group and 16 (42%) patients in the CFAE group had AF related hospitalization within 12 months (P=0.43). Rehospitalizations for AF included 3-month blanking time.

On univariate analysis and multivariate analysis, neither PVI+linear nor PVI+CFAE group independently predicted freedom from AF at short-term follow-up. There were no specific demographic, clinical, or ablation related characteristics predictive for maintenance of sinus rhythm. (Table 5)

At a mean follow-up duration of 59±36 months, 48.3% of patients in the linear ablation group and 44.6% of patients in the CFAE group were free from AF (p=0.403, Figure 2). There was no significant difference between the two groups. The Cox regression analysis showed hazard ratio 1.34 (95% CL, 0.666-2.695, p=0.412).

Discussion

In a prospective, randomized study, we report no difference in the maintenance of sinus rhythm with PVI+linear ablation vs. PVI + CFAE ablation in short- and long-term follow-up. The overall freedom from AF was 77 % in the PVI+linear group and 79 % in the PVI + CFAE group in one year of follow-up. This outcome was achieved by concurrent use of AADs in one thirds of and repeat ablation in 8% of study patients. Approximately one-third of patients required hospitalization to manage recurrent AF, including within 3-month blanking time. The wide range of clinical presentation of AF and targeted therapy is fundamentally governed by the variable extent of interaction between AF triggers (or drivers) and the necessary "substrate" created by electrophysiologically and structurally remodeled atrial tissue capable of supporting and maintaining AF.14 The pathogenesis of AF is complex and multifactorial. Pulmonary vein (PV) triggers have been demonstrated to play a critical role in both the initiation and perpetuation of AF. Although elimination of PV arrhythmogenicity has been highly effective for paroxysmal AF, it has modest efficacy in the long-term for persistent AF, suggesting that mechanisms beyond the PVs also contribute to the perpetuation of AF in these patients. AF-free survival after catheter ablation is significantly lower for patients with persistent AF. A systematic review of outcomes following ablation found an approximately 20% AF-free survival at 12 months with pulmonary vein isolation alone.[15] The focus has been directed to deciphering AF mechanisms, including targeting non-pulmonary vein triggers, rotors, complex fractionated atrial electrograms, and cardiac autonomic ganglia activity. Several ablation strategies have been proposed including linear ablation, ablation of complex fractionated atrial electrograms, a "stepwise" approach of the incremental extent of atrial ablation until AF terminates, targeting rotors using proprietary software, and the abolishment of autonomic ganglia.[4]

The STAR-AF study of ablation strategies for persistent AF showed no improvement in ablation efficacy for linear lesions plus PVI vs. PVI alone.[5] The RASTA AF trial also concluded that that additional substrate modification beyond PVI does not improve single-procedure efficacy in patients with persistent AF.[13]

The Catheter Ablation of Persistent Atrial Fibrillation (CHASE-AF) study also revealed that the addition of linear lesions and defragmentation of PVI did not improve outcomes for the ablation of persistent AF compared with PVI alone.[16] Our study showed similar short-term, and long-term ablative results with additional left atrial lines vs. CFAE targeted ablation. It has been widely demonstrated that incomplete block across the ablation lines can be responsible for atrial tachycardia /atrial flutter recurrence. In our cohort, we were able to demonstrate that bidirectional block was confirmed in mitral isthmus in 64%, roofline in 85%, and CTI in 95% of cases. The most considerable difficulty with linear ablation is in achieving and confirming complete block across the lesions. It is particularly difficult for the mitral isthmus line, which may require extensive ablation within the coronary sinus to accomplish. Incomplete linear lesions may be proarrhythmic and may lead to refractory atrial flutters that are often highly symptomatic.

Meta-analysis has reported long-term success rates of 80%, with significant heterogeneity in the success of single-procedure outcomes.[17] The stepwise approach for ablation for long-standing persistent AF has been championed by the Bordeaux group. [18] In a recent study that used a stepwise ablation strategy, including isolation of thoracic veins, ablation of CFAEs, and linear ablation until AF was terminated, linear ablation was necessary in more than 85% of the patients for termination of persistent AF. [19] Our study had a meager acute AF termination rate despite pulmonary isolation with concomitant left atrial substrate modification. Yet, AF recurrence rate is not high with a low AF termination rate during the ablation at 12 months follow up.

In the original study by Nademanee and associates, ablation of CFAEs without routine isolation of the PVs was reported to result in freedom from AF in 91% of the 121 patients with paroxysmal or chronic AF. Despite these encouraging acute outcomes, the follow-up data were disappointing, with a 1-year single procedure efficacy of 35% and a 5-year efficacy of 17%.[19]. Unfortunately, improved results with CFAE ablation in patients with persistent AF have not been uniformly reported, and the scientific basis for CFAE ablation is not universally accepted. An approach using PVI and CFAE ablation has been reported as producing success rates of 29% to 74% after a single procedure. [4, 20] Moreover, results from the STAR AF II trial have shown that the addition of further ablation (lines or CFAEs) to PVI increased ablation time but did not reduce the recurrence of AF in 589 patients with persistent AF.[5] At 18 months, the percentage of patients who were free from AF recurrence after one procedure without antiarrhythmic medication did not significantly differ among groups. Similar findings were reported in the CHASE-AF trial, which indicated that the addition of defragmentation and linear ablation to PVI did not improve ablation outcomes for persistent AF compared with PVI alone. [16]However, the findings of the long-term results of CFAEs and linear ablation for persistent AF were uncertain. Our study found no significant difference in AF recurrent rate between CFAEs and linear ablation group at a mean follow-up duration of 5 years. Less than 50% of patients who had persistent AF and underwent ablative therapy remained in sinus rhythm in either additional linear or CFAE ablation groups. A difficulty in targeting CFAEs is that most may be due to passive activation and lack specificity to indicate drivers of AF. Thus primary CFAE-guided ablation may lead to excessive and unnecessary ablation in the LA. As

mentioned, the target sites for antral PVI overlap considerably with CFAE sites in many patients. In our study, the majority of the CFAE points were noted in the left and right WACA regions compared to the rest of the left atrium. The ring of WACA, including these CFAE points, may have the advantage of maintaining sinus rhythm and minimize unnecessary ablation. More selective targets may be needed to characterize an individual patient's specific arrhythmic substrate.

We acknowledge certain important limitations. This is a single center, small randomized study. We did not include a group assigned to pulmonary vein isolation only. The mechanism of recurrence of AF could not be ascertained whether it was dependent on PVs. Maneuvers to improve the durability of pulmonary vein isolation (e.g., adenosine provocation), use of contact force, pacing on ablation lesions may have influenced outcomes. However, we did not use such maneuvers, and data supporting the utility of this approach were not available at the time of this study. Recurrence was noted on 24-hour Holter, whether the recurrences could have been higher due to continuous monitoring remains to be seen. Quality of life data and long term data and findings on repeat ablation could not be ascertained. The accuracy of long-term AF recurrence could be dampened from retrospective data collection.

Conclusion

In conclusion, we report no difference in the maintenance of sinus rhythm rates in patients undergoing PVI+CFAE vs. PVI+linear ablation in short- and long-term follow-up periods.

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