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Disparate Evolution of Right and Left Atrial Rate During Ablation of Long-Lasting Persistent Atrial Fibrillation

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Objectives The purpose of this study was to assess whether additional ablation in the right atrium (RA) improves termination rate in long-lasting persistent atrial fibrillation (PsAF).

Background Prolongation of atrial fibrillation (AF) cycle length (CL) measured from the left atrial appendage predicts favorable outcome during catheter ablation of PsAF. However, in some patients, despite prolongation of AF CL in the left atrium (LA) with ablation, AF persists. We hypothesized that this persistence is due to RA drivers, and that these patients may benefit from RA ablation.

Methods In all, 148 consecutive patients undergoing catheter ablation of PsAF (duration 25 ± 32 months) were studied. AF CL was monitored in both atria during stepwise ablation commencing in the LA. Ablation was performed in the RA when all LA sources in AF had been ablated and an RA-LA gradient existed. The procedural end point was AF termination.

Results Two distinct patterns of AF CL change emerged during LA ablation. In 104 patients (70%), there was parallel increase of AF CL in LA and RA culminating in AF termination (baseline: LA 153 ms [range 140 to 170 ms], RA 155 ms [range 143 to 171 ms]; after ablation: LA 181 ms [range 170 to 200 ms], RA 186 ms [range 175 to 202 ms]). In 24 patients (19%), RA AF CL did not prolong, creating a right-to-left frequency gradient (baseline: LA 142 ms [range 143 to 153 ms], RA 145 ms [range 139 to 162 ms]; after ablation: LA 177 ms [range 165 to 185 ms], RA 152 ms [range 147 to 175 ms]). These patients had a longer AF history (23 months vs. 12 months, $p = 0.001$), and larger RA diameter (42 mm vs. 39 mm, $p = 0.005$), and RA ablation terminated AF in 55%. In the remaining 20 patients, biatrial ablation failed to terminate AF.

Conclusions A divergent pattern of AF CL prolongation after LA ablation resulted in a right-to-left gradient, demonstrating that the right atrium is driving AF in ≈20% of PsAF. (J Am Coll Cardiol 2010;55:1007–16) © 2010 by the American College of Cardiology Foundation

Left atrium (LA) tissue is often necessary to ablate in addition to pulmonary vein isolation (PVI) to achieve optimal results in patients with long-lasting persistent atrial fibrillation (PsAF) (1–12). During ablation, prolongation of atrial fibrillation (AF) cycle length (CL) occurs in the left atrium with its magnitude predicting procedural termination of AF. However, the need for right atrium (RA) ablation has not yet been clearly established in studies using surgery or catheter ablation (13), with some studies showing no utility of RA ablation and other studies showing benefit (14). As a result, it is unclear whether it is possible to identify a subset of patients who may benefit from additional RA ablation for long-lasting PsAF.

We hypothesized that failure to terminate AF after LA ablation is due to RA drivers, and these patients may benefit from additional RA ablation. Furthermore, we evaluated the

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Abbreviations and Acronyms

AF = atrial fibrillation
AT = atrial tachycardia
CL = cycle length
CS = coronary sinus
LA = left atrium
LAA = left atrial appendage
PsAF = persistent atrial fibrillation
PV = pulmonary vein
PVI = pulmonary vein isolation
RA = right atrium
RF = radiofrequency
RAA = right atrial appendage
SR = sinus rhythm
SVC = superior vena cava

clinical and procedural factors predictive of the need for RA ablation, the extent of ablation required, its impact on AF termination, and long-term clinical outcome.

Methods

Study population. This study population consisted of 148 consecutive patients (119 males, age 58 ± 10 years) with symptomatic long-lasting PsAF referred for catheter ablation. Baseline characteristics are presented in Table 1.

Electrophysiologic study. All patients provided written informed consent. Antiarrhythmics agents were discontinued ≥5 half-lives before ablation, with the exception of amiodarone. Before the procedure, patients were receiving oral anticoagulant agents targeting an international normalized ratio of 2 to 3 for at least 1 month, and transesophageal echocardiography was performed within 5 days to exclude atrial thrombus. A transthoracic echocardiogram was performed within 1 week preceding the procedure. The RA and LA longitudinal and transverse diameters were measured in the apical view at end-systole from the tip of the mitral or tricuspid valve to the posterior wall of the LA or RA, and the LA parasternal diameter in the parasternal long-axis view at end-systole from the trailing edge of the posterior aortic wall to the leading edge of the posterior LA.

Surface electrocardiogram and bipolar endocardial electrograms were monitored continuously and stored on a computer-based digital amplifier/recorder system (Labsystem Pro, Bard Electrophysiology, C. R. Bard Inc., Lowell, Massachusetts). Intracardiac electrograms were filtered from 30 to 500 Hz.

The following catheters were introduced through the right femoral vein for the electrophysiological study: 1) a steerable quadripolar or decapolar catheter (Xtrem, formerly ELA Medical LLC, Plymouth, Minnesota), 5-mm electrode spacing, was positioned within either the coronary sinus (CS) with the proximal electrode positioned at 4 to 5 o'clock along the mitral annulus or the left atrial appendage (LAA) or the lateral RA; 2) a 10-pole circumferential catheter was used for mapping the pulmonary veins (Lasso, Biosense-Webster, Diamond Bar, California), and was introduced after transseptal access through a long sheath (SLO, St. Jude Medical, Sylmar, California) perfused continuously with heparinized D5W; after PVI, this catheter was placed in either the LAA or RAA; and 3) an irrigated-tip radiofrequency (RF) ablation catheter with a distal 3.5-mm tip (Thermocool, Biosense-Webster). For RA ablation, the ablation catheter was introduced through the long sheath. After transseptal puncture, a single bolus of heparin, 50 IU/kg, was administered.

Study protocol. The procedural end point was termination of AF to either an intermediate atrial tachycardia (AT) or directly to sinus rhythm (SR) by RF application during the index procedure. After restoration of SR, PVI was rechecked and conduction across any of the linear lesions performed (15,16). Additional RF applications were performed to achieve PVI and linear block. No attempt at reinduction was made. Duration of RF in the RA was limited to 25 min, as LA ablation of fractionated activity is

Table 1 Baseline Characteristics

	LA Termination (n = 104)	RA Termination (n = 24)	Nontermination (n = 20)	p Value
Age, yrs	58 ± 10	60 ± 11	58 ± 11	0.72
Males	79%	83%	80%	0.89
AF duration	12 (6–20)*†	23 (12–48)*	35 (12–72)†	<0.001*†
Hypertension	27%	23%	28%	0.92
SHD	41%	46%	50%	0.74
Emboli	5%	5%	12%	0.56
Heart failure	19%	8%	26%	0.76
No AAD	2.5 (2–3)	3 (1–3)	3 (2–3)	0.75
LVEDD	53 (48–57)	52 (48–61)	54 (50–60)	0.33
LVESD	36 (30–41)	35 (28–44)	39 (34–44)	0.45
LVEF	56 ± 13	59 ± 12	55 ± 14	0.49
LA parasternal	48 ± 8*	48 ± 7*†	57 ± 9*†	<0.001*†
LA longitudinal	61 ± 7*	61 ± 7*†	67 ± 9†	0.01*†
LA transversal	45 (42–50)*	43 (40–47)*†	51 (45–57)†	0.009*†
RA longitudinal	54 (49–58)*	56 (52–61)	58 (53–66)*	0.02*
RA transversal	39 ± 7*	42 ± 7	45 ± 8*	0.005*

Values are mean ± SD, %, or n (range). Data compared using analysis of variance (ANOVA) for means, ANOVA on ranks for medians, and chi-square test for categorical data. *Statistically significant p values ≤0.05. †Statistically significant difference between marked variables.

AAD = antiarrhythmic drug; AF = atrial fibrillation; LA = left atrium; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; RA = right atrium; SHD = structural heart disease.

normally completed within this time. If AF persisted, SR was restored by electrical cardioversion.

Left atrial ablation. OSTIAL PVI. Ostial PVI was performed with the end point of the abolition or dissociation of electrical activity in all PVs. After PVI, the Lasso catheter was withdrawn from the long sheath and advanced via an introducer to the right atrial appendage (RAA) for monitoring RA AF CL while the ablation catheter or the decapolar catheter was advanced in the LAA for monitoring AF CL.

ELECTROGRAM-GUIDED ABLATION. Electrogram-guided ablation was performed at LA sites displaying complex electrogram features: continuous electrical activity, complex rapid and fractionated electrograms, a gradient of activation (a temporal gradient of at least 70 ms between the distal and proximal bipoles on the roving distal ablation electrode) that may represent local circuits (8). Areas commonly targeted in ablation of fractionated electrograms included the inferior LA/CS, base of the LAA, the LA roof, and the LA septum, although any areas harboring fractionated electrograms were targeted. When ablation of the inferior LA did not result in organization of the CS, additional ablation within the CS was performed. The end point of electrogram-guided ablation was the transformation of complex fractionated electrograms into discrete electrograms and slowing of local CL compared with LAA AF CL or the elimination of electrograms.

LINEAR ABLATION. Linear ablation was performed if AF persisted after the previous steps, and targeted the LA roof, then the mitral isthmus, with the end point of significant reduction (>80%) or abolition of local electrograms.

Right atrial ablation. Ablation was carried out in the RA if a frequency gradient from RA to LA (RAA AF CL less than LAA AF CL) was observed after elimination of all LA sources in AF. Complex fractionated atrial electrograms were targeted using the same criteria as in the LA.

RIGHT ATRIAL SUBSTRATE ABLATION. Right atrial substrate ablation was performed at the anterior, lateral, and posterior RA.

ABLATION IN THE RAA. Ablation in the RAA was guided by the Lasso catheter, which was inserted into the body of the RAA, with ablation proximal to the catheter. The end point of ablation was organization and slowing of RAA electrograms and not RAA isolation.

CAVOTRICUSPID ISTHMUS ABLATION. Cavotricuspid isthmus ablation was performed in all patients to achieve bidirectional conduction block (17).

SUPERIOR VENA CAVA (SVC) ISOLATION. SVC isolation was performed (using the same technique and end point as used for the PVs) only if it was identified as an AF source on the basis of descending RA activation using either the decapolar or RF catheter, with distal to proximal activation within the SVC (18).

AF CL. The effect of ablation was monitored, as previously described (19), by evaluation of the AF CL. The AF CL in the RAA was measured with the RF or decapolar catheter before ablation and continuously monitored using the Lasso catheter after PVI. In the LAA, AF CL was measured before ablation, after PVI, after ablation of LA tissue, and after linear lesion using the RF catheter. The AF CL was averaged over 30 s of consecutive cycles using automated CL monitoring software (Labsystem Pro, Bard Electrophysiology) (Fig. 1). The electrograms within the body of the appendages are usually unfractionated and of high amplitude (0.5 to 2.0 mV), thereby facilitating unambiguous automatic annotation. Each automated annotation was

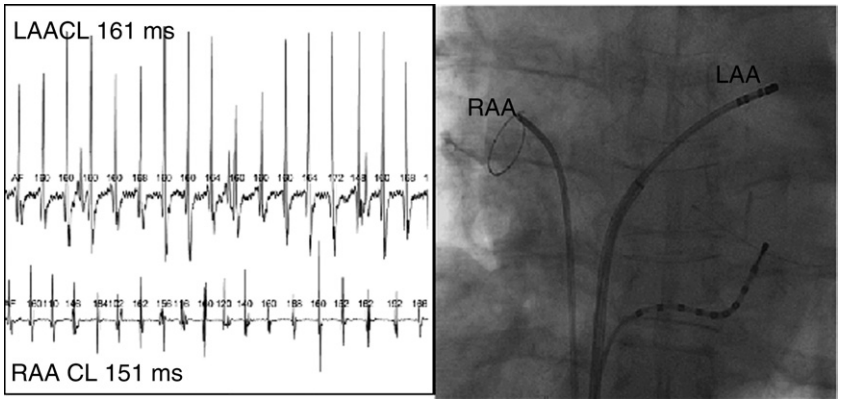

Figure 1 Measurement of AF CL

A circular mapping catheter and the ablation catheter are placed in the right atrial appendage (RAA) and left atrial appendage (LAA), respectively. Using automated software with manual correction where necessary, the atrial fibrillation (AF) cycle length (CL) is measured synchronously using unambiguous recordings. The mean AF CL is determined from 30 s continuous recording, and in this example, the CL of the right atrium is 151 ms and the left atrium is 161 ms.

verified manually and corrected using online calipers at a paper speed of 100 mm/s. In addition, the sites of AF termination were noted. A significant impact of ablation was defined by termination of AF or prolongation of the AF CL by 5 ms or more.

Termination of AF was defined as a transition from AF to SR directly or through 1 or more intermediate AT without antiarrhythmic drugs. The AF was defined by beat-to-beat variability in cycle length and *f*-wave morphology, whereas AT was defined as an organized atrial rhythm with a stable cycle length, a consistent endocardial activation sequence in both atria, and a monomorphic P-wave. Organized AF (type 1 AF) was defined as irregular atrial cycle length with beat-to-beat variation of ≥20 ms, and a consistent activation pattern for 75% of the time (20,21). A frequency gradient between the AF CL in the LA and RA was considered present if a difference of ≥5 ms was observed.

Ablation parameters. The RF energy was delivered to atrial tissue with a power of 25 to 35 W using irrigation rates of 5 to 60 ml/min (0.9% saline through a Cool Flow pump, Biosense-Webster) to achieve the desired power delivery. Within the CS, power was reduced to 15 to 20 W distally and 30 W at the CS ostium. Power was limited to 25 W in either appendage. Temperature was limited to 50°C. The duration of RF delivery was measured at each point.

Follow-up. All patients were monitored in the hospital for at least 5 days after their procedure for extensive ambulatory monitoring. After ablation, all antiarrhythmic drugs were not initiated unless otherwise indicated. Patients were reevaluated at 1, 3, 6, and 12 months, and in the absence of AF or symptoms, followed up with their referring physician. At each visit, exercise testing and ambulatory 48-h monitoring were performed to detect asymptomatic arrhythmias. In the event of symptomatic or asymptomatic arrhythmia recurrence, patients were offered additional ablation at least 3 months after the index procedure and after a trial of drug therapy (class IC drug with the addition of beta-blockers, or in case of concomitant structural heart disease, amiodarone was administered). Cessation of anticoagulant therapy was considered 6 to 9 months after the last procedure in the absence of recurrence or concomitant indications.

Statistical analysis. Data are expressed as mean ± SD for normally distributed continuous variables, and as the median (25th, 75th percentiles) for non-normally distributed variables. Data are expressed as absolute numbers and percentages for categorical variables. Continuous variables were compared between groups using Student *t* test, or the Mann-Whitney rank test, and within each group using a paired *t* test or Wilcoxon signed-rank test. Categorical variables were compared with the chi-square test or Fisher exact test. Statistical significance was established at $p < 0.05$.

Multivariate analyses were performed using a multiple linear regression test and included all parameters with a significance <0.1 from the univariate analysis. Kaplan-Meier analyses for AF-free survival were performed for all 3 groups and were compared using a log-rank analysis.

Results

Sinus rhythm was restored by ablation without pharmacological or direct current cardioversion in 128 patients (86%) (Fig. 2). The total procedure and fluoroscopic times were 252 ± 60 min and 79 ± 19 min (3.75 frames/s), respectively. The total RF ablation duration delivered in both atria was 85 ± 25 min. PVI was achieved in all patients. During LA ablation, 2 distinctive patterns of AF CL evolution were observed in patients in whom procedural termination of AF was achieved. The AF CL in each group and at every step is depicted in Table 2.

Group 1: parallel increase in AF CL during LA ablation. In 104 patients (70%), there was a parallel increase of AF CL in the LA and RA culminating in AF termination. At baseline, AF CL was 153 ms (range 140 to 170 ms) in LA and 155 ms (range 143 to 171 ms) in RA; prolonging after PV isolation to 164 ms (range 152 to 180 ms) and 170 ms (range 152 to 184 ms) ($p < 0.001$ LA vs. RA) and during LA ablation before termination to 181 ms (range 170 to 200 ms) and 186 ms (range 175 to 202 ms) ($p = 0.009$ LA vs. RA), respectively (Fig. 3A). In addition to the parallel pattern of evolution, AF CL remained significantly shorter in LA than RA before AF termination. The AF terminated directly to SR in 19 (18%) or via an intermediate AT in 85 (82%).

A total of 171 different ATs were mapped in 85 patients (1.9 ± 1.1 per patient), and were macro–re-entrant in 90 (53%) and focal in 81 (47%). The mechanisms of 6 ATs could not be defined because of inadvertent termination or other factors. Macro–re-entrant tachycardias were terminated by linear ablation at the mitral isthmus (n = 45), LA roof (n = 22), or CTI (n = 23). Eighty-one centrifugal AT

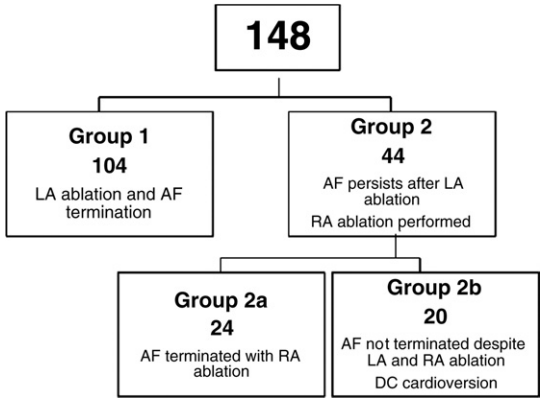

Figure 2 Patient Flow Chart

AF = atrial fibrillation; DC = direct current; LA = left atrium; RA = right atrium.

Table 2 Procedural Characteristics and Clinical Outcome

	LA Termination (n = 104)	RA Termination (n = 24)	RA Nontermination (n = 20)	p Value
Baseline RAA CL, ms	155 (143–171)*	145 (139–162)	144 (130–155)*	0.04*
Baseline LAA CL, ms	153 (140–170)*	142 (143–153)	140 (133–158)*	0.03*
RAA CL after PVI, ms	170 (152–184)*	151 (142–161)*	153 (129–173)	0.02*
LAA CL after PVI, ms	164 (152–180)	160 (153–170)	155 (137–165)	0.49
RAA CL after LA ablation, ms	186 (175–202)*†	152 (147–173)*	160 (143–175)†	<0.001*†
LAA CL after LA ablation, ms	181 (170–200)	177 (165–185)	165 (156–195)	0.09
Total RF duration, min	81 ± 24*	89 ± 23	104 ± 19*	<0.001*
Procedure duration, min	240 (200–286)	270 (231–330)	270 (215–290)	0.08
Fluoroscopic duration, min	82 (62–97)	85 (76–101)	94 (79–102)	0.12
Long-term clinical success, n	97 (93%)*	21 (88%)†	11 (55%)*†	<0.001*†

Values are n (range), mean ± SD, n (%). Data compared using analysis of variance (ANOVA) for means, ANOVA on ranks for medians, and chi-square test for categorical data. *Statistically significant p values ≤0.05. †Statistically significant difference between marked variables.
CL = cycle length; LAA = left atrial appendage; PVI = pulmonary vein isolation; RAA = right atrial appendage; RF = radiofrequency.

were ablated, 47% consistent with focal mechanisms and 53% with localized re-entry.

The RF delivery in the LA lasted 34 ± 14 min for PVI, 19 ± 9 min for electrogram-based ablation, and 20 ± 15 min for the roof and mitral isthmus lines.

Group 2: divergent progression of AF CL during LA ablation. In 44 patients (30%), AF CL remained shorter in the RA than the LA, and AF did not terminate after LA ablation. In these patients, AF CL at baseline was 140 ms (range 133 to 156 ms) in LA and 145 ms (range 135 to 160 ms) in RA; it changed after PVI to 160 ms (range 152 to 170 ms) in LA and 151 ms (range 142 to 162 ms) in RA ($p < 0.05$ LA vs. RA), and during LA ablation before termination to 177 ms (range 164 to 194 ms) in LA, and 156 ms (range 146 to 175 ms) in RA ($p < 0.001$ LA vs. RA) (Figs. 3B and 3C).

The RA ablation terminated AF in 24 of these patients (55%, group 2a) directly to SR in 3 and through intermediate AT in 21 (87%). The remaining 20 patients underwent electrical cardioversion (45%, group 2b).

Group 2a: AF termination after RA ablation. Termination of AF by ablation in the RA was preceded by an increase in RA AF CL from 145 ms (range 139 to 162 ms) to 181 ms (171 to 209 ms) ($p = 0.002$). Applications of RF for 13 ± 7 min at these sites increased right and left AF CL by 14 ± 9 ms and 6.2 ± 5 ms, respectively. Sites where ablation prolonged RA AF CL were widely distributed but preferentially clustered on the anterior RA, RAA, and lateral RA. Ablation at the anterior RA and the RAA significantly prolonged AF CL (≥5 ms) in 14 patients (58%) whereas RF energy delivered to other sites such as posterior RA (3.4 ± 2.6 min), SVC (2.7 ± 1.6 min), right septum (1.5 ± 2.2 min), and CTI (7.1 ± 3.7 min) produced a smaller AF CL prolongation (mean of 4.6 ± 5 ms, 3 ± 5 ms, 4 ± 7.4 ms, 4 ± 7.4 ms, and 4.3 ± 7.3 ms, respectively).

Sites where ablation terminated AF were the RAA and anterior RA in 13, posterior RA in 3, CTI in 3, right septum in 3, lateral RA in 1, and terminal crest in 1 (Fig. 4). Electrograms at these sites demonstrated very rapid activity, with an average local CL of 136 ± 66 ms.

A total of 36 AT were mapped and ablated in 21 patients after RA ablation (1.6 ± 0.9 per patient). Underlying mechanisms were macro–re-entry in 17 (9 perimitral flutter, 5 rotating around the right PVs and 3 CTI dependent flutters), and centrifugal AT in 13 (10 focal and 3 localized reentry): 3 from the PVs, 3 from anterior LA, 2 around fossa ovalis, 2 from RA sites, and 3 from other sites, and ablation restored SR.

In these patients, RF delivery was 33 ± 13 min for PVI, 23 ± 9 min for LA electrogram-based ablation, and 16 ± 7 min for roof and mitral isthmus lines. In the RA, total RF delivery was 9 ± 5.8 min, with an additional 3.2 ± 2.6 min for the CTI line.

Group 2b: failure to terminate AF. In 20 patients, AF did not terminate despite biatrial ablation, and direct current cardioversion was needed to restore SR. In this subgroup, baseline AF CL was 140 ms (range 133 to 158 ms) and 144 ms (range 130 to 155 ms) in LA and RA, respectively (p = NS compared with group 2a). The LA ablation of fractionated electrograms and linear lesion at the LA roof and at the mitral isthmus prolonged AF CL in both atria but to a lesser extent (LA 165 ms [range 156 to 195 ms], and RA 160 ms [143, 175 ms]; $p < 0.001$).

Impact of ablation. The gradient after LA ablation between right and left AF CL was significantly smaller in group 1 (3 ms [range 2 to 5 ms]) versus group 2 (group 2a, 17 ms [range 10 to 30 ms]; group 2b, 18 ms [range 7 to 21 ms], $p < 0.001$).

Compared with group 2a, ablation of electrograms at the anterior RA and RAA in group 2b resulted in a smaller increase in global AF CL (14 ± 9 ms vs. 6 ± 5 ms, $p = 0.1$). Ablation at the lateral RA increased AF CL by 7 ± 4 ms versus 6 ± 5 ms (p = NS), whereas targeting other sites such as posterior RA, right septum, and CTI resulted in smaller increases in global AF CL (3.1 ± 1.6 ms, 4.5 ± 0.7 ms, and 3 ± 2.6 ms, respectively; p = NS). At all RA sites, RF delivery was significantly longer for group 2b than for

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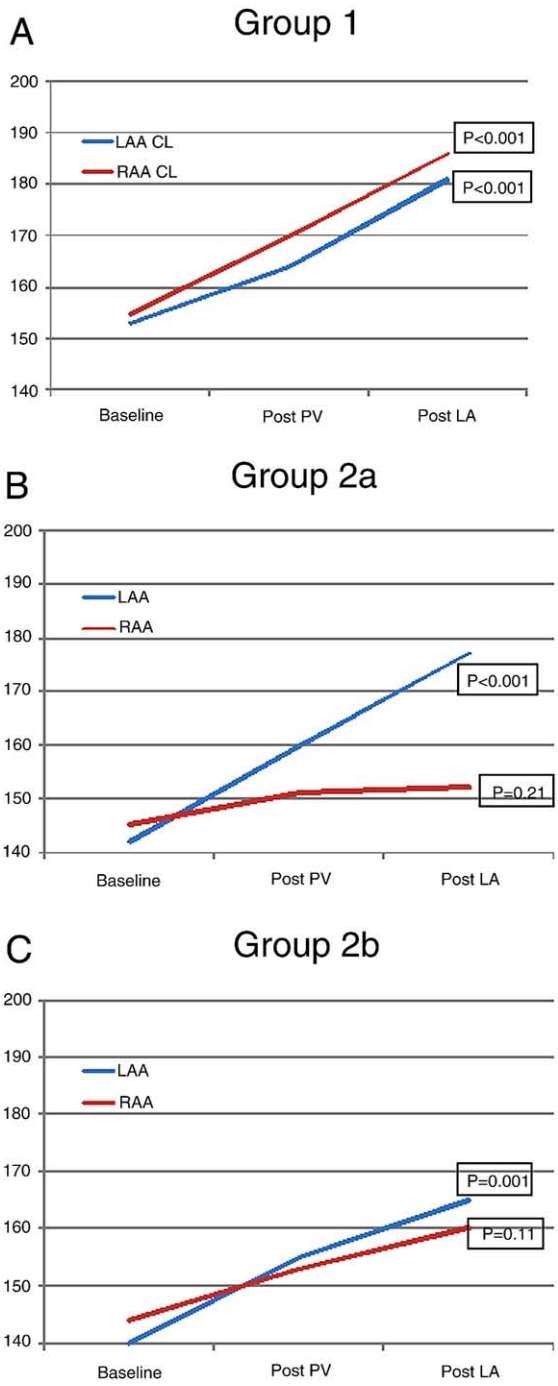


Figure 3 **Evolution of AF CL During Ablation**

(A) In group 1, AF CL measured from both the RAA **(red line)** and LAA **(blue line)** prolongs in parallel, with termination of AF occurring in the left atrium. **(B)** In group 2a, where termination occurs during right atrial ablation, the AF CL prolongs in the left atrium **(blue line)** but not in the right atrium **(red line)** with LA ablation. **(C)** In group 2b, the AF CL measured in the right atrium **(red line)** fails to prolong after pulmonary vein (PV) isolation. The **blue line** indicates the left atrium. Data were compared using analysis of variance on ranks to compare AF CL at baseline and after each step of the ablation inside each atrium, with the p value representing the difference in AF CL occurring during ablation inside each atrium. Abbreviations as in Figures 1 and 2.

group 2a in whom AF terminated (total RA ablation, 22 ± 8 min vs. 9 ± 6 min, $p < 0.001$). The LA electrogram-based ablation was also longer for group 2b than for group 2a (31 ± 15 min vs. 23 ± 10 min, $p < 0.05$).

Factors predictive of RA ablation. The pre-procedural factors that were predictive of the need for RA ablation in univariate analysis were a longer duration of continuous AF ($p < 0.001$) and a larger LA parasternal dimension ($p = 0.03$), RA size ($p < 0.01$) (Table 3). In a multivariate model including duration of AF, LA, and RA size and baseline AF CL both duration of continuous AF ($p < 0.01$) and RA size ($p < 0.05$) were predictive of the need for RA ablation. The sensitivity and specificity of a duration of continuous AF >20 months were 79% and 62%, respectively, with an area under the curve of 0.75 ($p = 0.0001$). The sensitivity and specificity of an RA diameter of >38 mm were 49% and 76%, respectively, with an area under the curve of 0.64 ($p = 0.01$).

The procedural factors that were predictive of the need for RA ablation in univariate analysis were baseline LA AF CL ($p = 0.01$), baseline RA AF CL ($p = 0.02$), RA AF CL after PVI ($p < 0.01$), RA AF CL after LA ablation ($p < 0.001$), and LA AF CL after LA ablation ($p < 0.05$) (Table 4). In a multivariate model including baseline LA AF CL, baseline RA AF CL, RA AF CL after PVI, RA AF CL after LA ablation, and LA AF CL after LA ablation, only RA AF CL after LA ablation ($p < 0.001$) and LA AF CL after LA ablation ($p < 0.001$) were predictive of the need for RA ablation. The sensitivity and specificity of an LA AF CL of ≤165 ms after LA ablation were 42% and 88%, respectively, with an area under the curve of 0.64 ($p = 0.01$). The sensitivity and specificity of an RA AF CL of ≤160 ms after LA ablation were 62% and 97%, respectively, with an area under the curve of 0.84 ($p = 0.0001$).

Factors predictive of AF termination after RA ablation. In a multivariate model including factors identified by univariate analysis as potential predictors (duration of continuous AF, LA, and RA size), only LA size ≤51 mm (odds ratio: 0.87, 95% confidence interval: 0.79 to 0.96, $p = 0.003$) was independently predictive of AF termination after RA ablation.

Follow-up and subsequent clinical outcome. With a follow-up of 22 ± 9 months and a mean of 1.5 procedures per patient, 129 patients (87%) were in SR. There was a disparate clinical outcome among the 3 groups (Fig. 5). The success rate after a single procedure was 46% for patients in whom AF terminated, and 10% for patients in whom AF did not terminate ($p = 0.005$). After the last procedure, stable SR was maintained in 93% of patients in group 1 (including 16% receiving an antiarrhythmic drug), 88% in group 2a (including 38% with an antiarrhythmic drug), and only 55% of patients in group 2b (including 36% with an antiarrhythmic drug). The detailed follow-up is depicted as a flow chart in Figure 6.

Adverse affects. Two patients had pericardial tamponade (during LA ablation) that required pericardiocentesis. In another patient, a transient ischemic attack occurred on the day after the procedure.

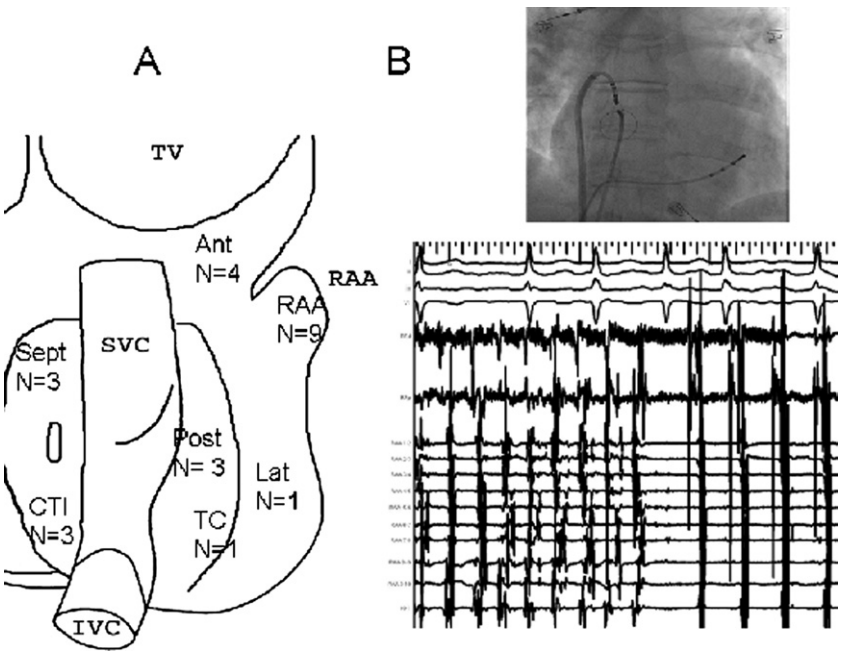


Figure 4 Sites of AF Termination Within Right Atrium

(A) AF = atrial fibrillation; Ant = anterior right atrium; CTI = cavotricuspid isthmus; IVC = inferior vena cava; Lat = lateral right atrium; Post = posterior right atrium; RAA = right atrial appendage; Sept = right atrial septum; SVC = superior vena cava; TC = terminal crest; TV = tricuspid valve. **(B) Upper panel:** Site of AF termination at the base of the RAA. **Lower panel:** Lasso recordings within the right appendage showing conversion of the AF to atrial tachycardia.

Discussion

This study presents new information on the relative role of the left and right atria in the maintenance of long-lasting PsAF. We found that 1) biatrial monitoring of AF CL revealed 2 patterns of AF CL evolution: parallel RA and LA CL prolongation in the majority of patients and divergent evolution of AF CL in 20% of patients, with a right to left frequency gradient; 2) for patients in whom LA and RA AF CL prolonged in parallel, LA ablation alone resulted in AF termination; 3) for patients with an RA to LA frequency gradient, ablation targeted to the RA terminated AF in 50% of patients; 4) in these patients, the anterior RA and RAA appeared to be critical structures to maintain AF, and ablation at these sites resulted in termination of AF in 55% of all patients where termination occurred in the RA; and 5) pre-procedural and procedural independent predictors of the need for RA ablation were duration of continuous AF, RA size, and right and left AF CL after LA ablation.

Previous studies. Prior studies have indicated that the RA may drive AF in some cases, and dominant frequency mapping in persistent AF uncovered in RA dominant frequency max sites in 16% of patients (22). There are clear reports of AF termination during exclusive or dominant

Table 3 Pre-Procedural Characteristics Used in Logistic Regression Model

	LA Termination (n = 104)	RA ablation (n = 44)	p Value
AF duration	12 (6–20)	24 (12–66)	<0.001
LVEDD	53 (48–57)	54 (48–60)	0.29
LVESD	36 (30–41)	38 (31–44)	0.32
LVEF	56 ± 13	58 ± 13	0.53
LA parasternal	48 ± 8	52 ± 9	0.03
LA longitudinal	61 ± 7	63 ± 8	0.13
LA transversal	45 (42–50)	46 (43–53)	0.11
RA longitudinal	54 (49–58)	56 (52–65)	0.01
RA transversal	40 (34–44)	42 (39–50)	0.01

Values are n (range) or mean ± SD. Data compared using Student *t* test for means and Mann-Whitney rank test for medians. Univariate data p ≤ 0.25 used in multiple logistic regression model.

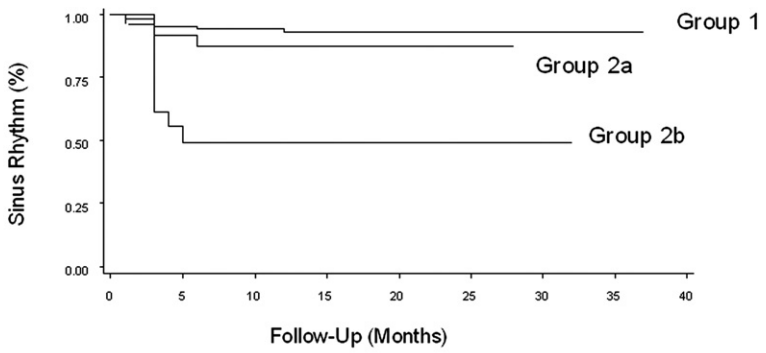
Abbreviations as in Table 1.

Table 4 Procedural Characteristics Used in Logistic Regression Model

	LA Termination (n = 104)	RA Ablation (n = 44)	p Value
Baseline RAA CL, ms	155 (143–171)	145 (135–160)	0.02
Baseline LAA CL, ms	153 (140–170)	140 (133–156)	0.01
RAA CL after PVI, ms	170 (152–184)	151 (142–162)	0.005
LAA CL after PVI, ms	164 (152–180)	160 (152–170)	0.49
RAA CL after LA ablation, ms	186 (175–202)	156 (146–175)	<0.001
LAA CL after LA ablation, ms	181 (170–200)	177 (164–194)	0.04

Values are n (range). Data compared using Mann-Whitney rank test. Univariate data p ≤ 0.25 used in multiple logistic regression model.

Abbreviations as in Table 2.



		Follow-Up (months)				
		3	6	9	12	24
Patients at risk	Group 1	97	89	80	72	37
	Group 2a	22	21	12	10	4
	Group 2b	17	8	7	5	2

Figure 5 **Arrhythmia-Free Survival by Site of Arrhythmia Termination**

Kaplan-Meier analysis of the recurrence of any atrial arrhythmia (atrial fibrillation or atrial tachycardia): group 1, left atrial termination; group 2a, right atrial termination; and group 2b, nontermination. Log rank $p < 0.0001$.

ablation in the RA, although these cases are uncommon (23,24).

In the present study, in the majority of patients with long-lasting PsAF, LA ablation prolonged AF CL in both atria, culminating in AF termination, clearly indicating that the LA was driving the RA and thus the fibrillatory process. It follows that RA ablation is not appropriate for all patients, which may explain why some studies do not show a benefit of indiscriminate RA ablation (13,25).

However, our results are similar to those of other studies in which both the LA and RA have been targeted. In a recent study using biatrial ablation, AF termination occurred in the RA in 26% of patients (14). Interestingly, as in our study, there was a frequency gradient from the RA to the LA in these patients. In an earlier study based on electrogram-targeted ablation, 60% of PsAF could be terminated, of which 15% occurred in the RA (1). A subsequent study compared LA ablation to biatrial ablation in 80 patients with PsAF; procedural termination of AF was more frequent with biatrial than with LA ablation (85% vs. 24%) (24). However, AF-free survival without antiarrhythmic medications in that study was limited to 35% to 47%. A series of small biatrial mapping studies of chronic AF have occasionally identified rapid repetitive activations in the lateral RA (26).

Role of the RA. In 30% of our total population, AF CL in the RA did not prolong in parallel with AF CL in the LA, resulting in a right to left frequency gradient, suggesting that the substrate resides in the RA. This hypothesis was confirmed by AF termination with RA ablation in more than one-half of these patients. Interestingly, the RA AF CL was shorter in these patients after PVI, and it may be that biatrial monitoring of AF CL with ablation targeted to the chamber with the shortest AF CL after PVI will avoid unnecessary ablation.

Although sites associated with AF termination in the RA were widely distributed, the 2 predominant areas were the anterior RA and RA appendage. Although RA focal or reentrant tachycardias have been mainly described in superior vena cava, crista terminalis, or atrial septum, the overlapping heterogeneity of trabeculated fibers between RAA and RA body (27) may constitute a critical milieu for perpetuation of AF in some patients, as with the LAA.

Among patients requiring RA ablation to terminate AF, 88% converted to SR through an intermediate AT. It is notable that these ATs were mainly left atrial (73%). These data support the multiple concurrent driver hypothesis of AF (28). Somewhat speculatively, it is possible that the elimination of LA sources for AF by ablation enabled the emergence of slower RA sources. Successful ablation of these sources, in turn, terminated AF. Further studies are needed to determine if the LA AT to which AF subsequently terminated were due to preceding LA ablation, or reflected organization from still slower residual LA sources for AF.

Multivariate analysis demonstrated that duration of long-lasting PsAF, RA size, and right and left AF CL after LA ablation were independent predictors of the need of RA ablation. These variables can help identify patients who will require RA ablation. This suggests that as the AF process evolves, initial remodeling occurs in the LA, but then later the RA becomes recruited into the pathological process.

The present study does not provide information on whether some patients may have benefited from RA ablation alone. An earlier study showed that AF may originate solely from the RA could effectively be ablated by targeting

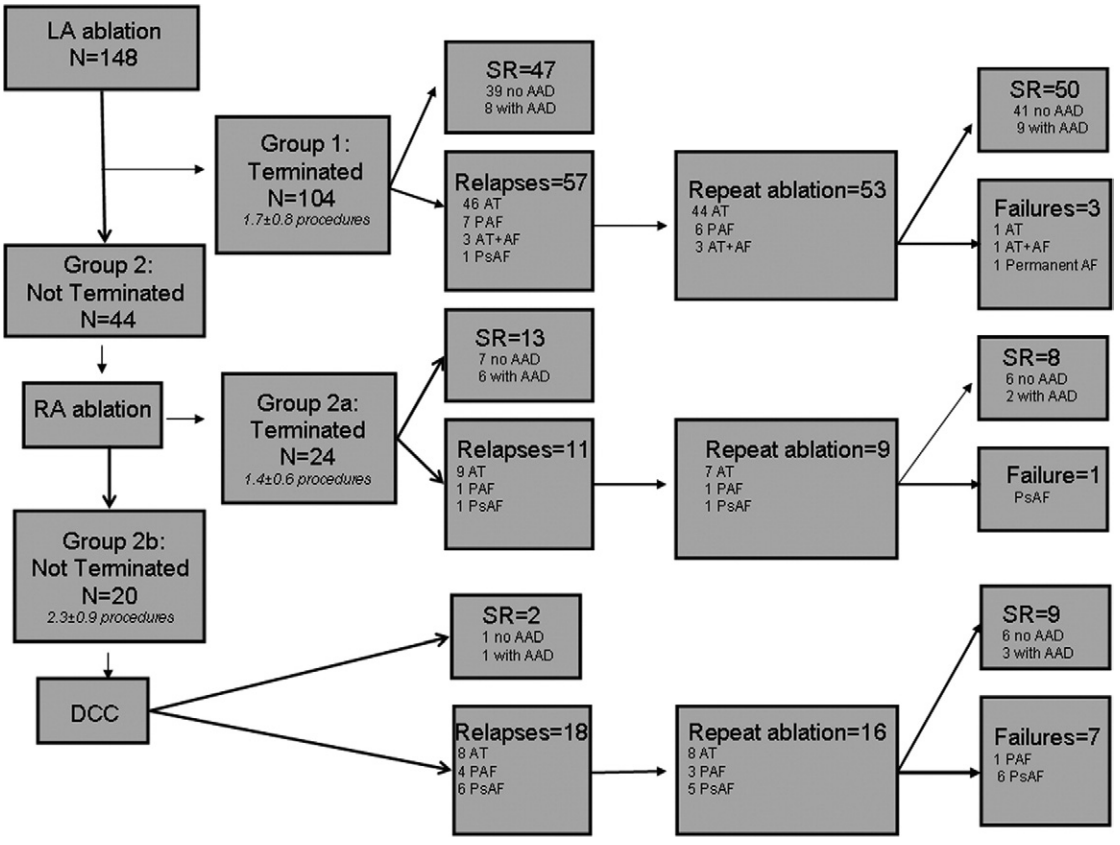


Figure 6 **Outcomes Flow Chart**

Outcome of patients in group 1 (left atrial termination), group 2a (right atrial termination), and group 2b (nontermination). AAD = antiarrhythmic drug; AF = atrial fibrillation; AT = atrial tachycardia; DCC = direct current conversion; FU = follow-up; LA = left atrium; PAF = paroxysmal atrial fibrillation; PsAF = persistent atrial fibrillation; RA = right atrium; SR = sinus rhythm.

the crista terminalis (29), although such patients only constituted 3% of the screened population.

Study limitations. The main limitation of this study is that ablation was targeted to the RA only after ablation in the LA was completed. However, a right to left frequency gradient was often apparent after PVI, suggesting that the RA could have been targeted earlier. This study may, therefore, underestimate the contribution of the RA in patients with long-lasting PsAF. Secondly, electrogram analysis based on visual inspection is somewhat subjective (30); however, this is true for prior studies, and attempts to quantify successful ablation sites using frequency analysis in long-lasting PsAF have had conflicting results (31,32). Although considerable atrial damage may result from ablation to terminate long-lasting PsAF (8), echocardiography showed that atrial systolic function was retained in all patients in SR (33). Thirdly, we measured the impact of ablation through changes in AF CL, yet it is possible that the fibrillatory process was also modulated by ablation that did not alter AF CL. Finally, it is also possible that critical drivers may be present in the RA and conduct to the LA without a frequency gradient.

Conclusions

Ablation of RA substrate is required to terminate long-lasting PsAF and achieve durable long-term results in 20% of patients. These patients tend to have a longer duration of AF, larger RA size, and shorter right and left AF CL after LA ablation, resulting in a right to left frequency gradient. Although these patients have a lower overall success rate than do patients in whom LA ablation alone is successful, additional ablation within the RA terminated AF in more than one-half, with a long-term outcome similar to that of patients who had procedural termination in the LA. Termination of AF, whether occurring in the RA or LA, is associated with an excellent long-term outcome. Further studies are needed to elucidate the complex interplay between left and right atrial sources for AF.

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