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Atrial fibrillation cycle length as a predictor for the extent of substrate ablation

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Aims Atrial fibrillation (AF) cycle length (CL) has been demonstrated to be one of the predictors for termination during ablation for AF. We evaluated the AF CL gradient between right atrium (RA) and left atrium (LA) and their mean AF CL in predicting the extent of substrate ablation.

Methods and results One-hundred and thirty-six patients undergoing first ablation for persistent AF were studied. Stepwise ablation, sequentially in the following order: pulmonary veins (PV), LA, and RA, was performed to achieve AF termination. Stepwise ablation terminated AF in 110 patients (81%). In the AF termination group, AF was terminated by PV isolation (PVI) (Group P), PVI plus LA ablation (Group L), and PVI plus LA plus RA ablation (Group R) in 14 patients (13%), 49 patients (44%), and 47 patients (43%), respectively. Group R had much shorter mean AF CL than Group L (156 ± 18 vs. 174 ± 24 ms, $P < 0.001$) and mean AF CL in Group L was much shorter than Group P (174 ± 24 vs. 209 ± 36 ms, $P = 0.004$). The RA to LA AF CL gradient was not significantly different between left-side ablation (Group P + Group L) and additional RA ablation (Group R) ($P = 0.177$). Mean AF CL >180.50 ms predicted AF termination by PVI (Group P) with 79% sensitivity and 84% specificity while mean AF CL >165.25 ms predicted AF termination by left-side ablation (Group P + Group L) with 67% sensitivity and 75% specificity. After a mean follow-up of 15 ± 7 months, freedom from arrhythmia recurrence was significantly higher in left-side ablation (Group P + Group L) than additional RA ablation (Group R) ($P = 0.024$).

Conclusion Baseline mean AF CL may identify the subset of patients in whom persistent AF can be terminated by different extent of substrate ablation, which may in turn predict the chance of recurrence. However, baseline RA to LA AF CL gradient cannot predict the need for additional RA ablation.

Keywords Atrial fibrillation • Cycle length • Right atrium

Introduction

Persistent atrial fibrillation (AF) can be terminated by catheter ablation using a stepwise approach.[1–4] The concept of this procedure is to combine pulmonary vein isolation (PVI) with substrate modification, which usually includes ablation of complex fractionated atrial electrogram (CFAE) and linear ablation. Since the report of stepwise ablation, there were increasingly more works on the need for substrate modification in right atrium (RA) in order to achieve AF termination in patients with persistent AF.[3–5] However, electrophysiological parameters that can predict the need for RA ablation in patients with persistent AF remain unclear. Atrial fibrillation cycle length (CL) has been demonstrated to be one of the predictors for termination during AF ablation.[6–9] It is not uncommon to note that there is variable degree of RA and left atrium (LA) AF CL gradient at the beginning of AF ablation procedure in patients with persistent AF. Areas with shorter CL are thought to be the critical substrate for driving or maintaining the fibrillatory circuits in AF.[10] The question whether shorter AF CL in RA than LA translates into need for RA ablation has not been investigated. Moreover, whether mean AF CL plays a role in predicting the extent of substrate ablation remains to be elucidated.

In this study, we evaluated RA and LA AF CL gradient and their mean AF CL in predicting the extent of substrate ablation. We also

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What's new?

- Mean atrial fibrillation (AF) cycle length (CL) may identify the subset of patients in whom persistent AF can be terminated by different extent of substrate ablation.
- Need for additional right atrium (RA) ablation may indicate higher rate of AF recurrence.
- Right atrium to left atrium AF CL gradient cannot predict any need for additional RA ablation.

assessed the clinical outcomes in patients with different extent of substrate ablation.

Methods

Study population

One-hundred and thirty-six patients who underwent first-time catheter ablation for symptomatic drug-refractory persistent AF in Korea University Anam Hospital from January 2012 to December 2013 were retrospectively reviewed. Atrial fibrillation was defined as persistent according to current guidelines (sustained beyond 7 days or lasting <7 days but necessitating cardioversion). All patients were in AF spontaneously at the beginning of the procedure. The Institutional Review Board of Anam Hospital of Korea University approved this study and informed consent was obtained from all patients.

Pre-procedure management

Amiodarone was discontinued at least 1 month before the procedure and all other antiarrhythmic medications were discontinued at least five half-lives before ablation. All patients received anticoagulant therapy with warfarin for at least 1 month before the procedure (target international normalized ratio: 2 : 3). Transthoracic and transoesophageal echocardiography was performed on the day before the procedure in all patients to measure LA diameter and exclude LA thrombus. Cardiac CT or MRI was obtained before catheter ablation to evaluate the pulmonary vein (PV), LA, and RA anatomy.

Electrophysiological study

All catheters were inserted via the femoral veins. A duo-decapolar catheter (St Jude Medical Inc.) was placed at the low RA and coronary sinus (CS) to record both electrograms, while a decapolar catheter (Bard Electrophysiology Inc.) was positioned at the high RA. A 2 mm quadripolar catheter was positioned at either the right ventricle or the superior vena cava. Intracardiac electrograms were recorded using Prucka CardioLab electrophysiology system (General Electric Health Care System Inc.) or EP-Workmate electrophysiology system (St Jude Medical Inc.). Two transseptal long sheaths (SL1, St Jude Medical Inc.) were introduced into the LA using the standard Brockenbrough technique under fluoroscopic guidance. A 20-pole electrode mapping catheter (AFocus II, St Jude Medical Inc.) was placed in the ostium of either the right or left PVs and used to record PV potentials. Left atrium and RA geometries were created using three-dimensional electroanatomical mapping (NavX System, St Jude Medical Inc.) and merged with images from cardiac CT or MRI. A quadripolar catheter was placed at the non-coronary aortic cusp as a reference. The activated clotting time was maintained between 300 and 350 s.

Ablation procedure for persistent atrial fibrillation

Our ablation sequence for persistent AF was in the following order: PVI, LA CFAE ablation, RA CFAE ablation, and linear ablation (optional). In brief, PVI was performed in all patients and confirmed by mapping catheter showing the disappearance of all PV potentials or dissociation of PV and LA activities. After PVI, an LA CFAE map was created to guide the subsequent LA CFAE ablation. Right atrium CFAE sites were ablated when AF was maintained after PVI and ablation of all LA CFAE areas. If AF persisted after all LA and RA CFAE areas were abolished, a tailored approach including additional linear ablation was applied on individual basis. Complex fractionated atrial electrogram in NavX system was defined as multicomponent atrial electrograms, including (i) atrial electrograms with ≥ 2 deflections, perturbation of the baseline, and/or continuous electrical activity; or (ii) atrial electrograms with a short CL ≤ 120 ms over a 6 s period.[11] Our procedural endpoint was AF termination. Patients with AF that were converted to sinus rhythm (SR) directly or through an intermediate step of atrial tachycardia (AT) by ablation were defined as AF termination group. Any AT that occurred during procedure was mapped by activation and entrainment mapping and ablated accordingly. Patients with AF or subsequent AT that could not be terminated by ablation underwent cardioversion and were defined as non-termination group. For ablation, radiofrequency energy was delivered with an upper temperature limit of 48°C, a power of 30 W, and an irrigation flow rate of 13 mL/min using a conventional, open, irrigated-tip catheter (CoolFlex, St Jude Medical Inc.). Near the oesophagus, power delivery was reduced to 25 W.

Atrial fibrillation cycle length measurement

All the patients were in AF at the beginning of procedure. Atrial fibrillation CL was measured after catheter positioning and before transseptal puncture. Intracardiac recording of LA was achieved by the distal 10 electrodes of duo-decapolar catheter (St Jude Medical Inc.) inside CS while electrograms of RA were obtained by the proximal 10 electrodes of the same duo-decapolar catheter at low RA and 10 electrodes of decapolar catheter (Bard Electrophysiology Inc.) at high RA. Bipolar electrograms were analysed for measuring AF CL with high-pass filter set at 30 Hz and low-pass filter set at 300 Hz. The LA AF CL was measured manually with online calipers from the electrograms at lateral LA (recorded from the most distal two electrodes of duo-decapolar catheter inside CS) while lateral RA electrograms (recorded from the most proximal two electrodes of duo-decapolar catheter at low RA or most distal two electrodes of decapolar catheter at high RA) were used to measure the RA AF CL. Measurements of LA and RA AF CL were always made simultaneously. Atrial fibrillation CL was calculated by averaging 30 consecutive cycles to ensure accurate and reproducible measurements. All analysis was made by the same electrophysiologist who was blinded to the clinical and procedural information. The time interval between each signal was measured at a sweep speed of 100 mm/s using electronic calipers. When depolarization of more than one overlapping muscle fascicles were simultaneously recorded, care was taken to identify activities in each fascicle by comparing the activation patterns recorded at adjacent sites and AF CL was then measured from the fascicle with more consistent and prominent electrogram signals (*Figure 1A*). For multicomponent fractionated electrograms, AF CL measurement could be difficult and effort was paid to find out the deflections with higher amplitude, frequency, and consistency for AF CL measurement (*Figure 1B*). The RA to LA AF CL gradient was quantified by dividing RA AF CL by LA AF CL. The mean AF CL was the average of LA and RA AF CL.

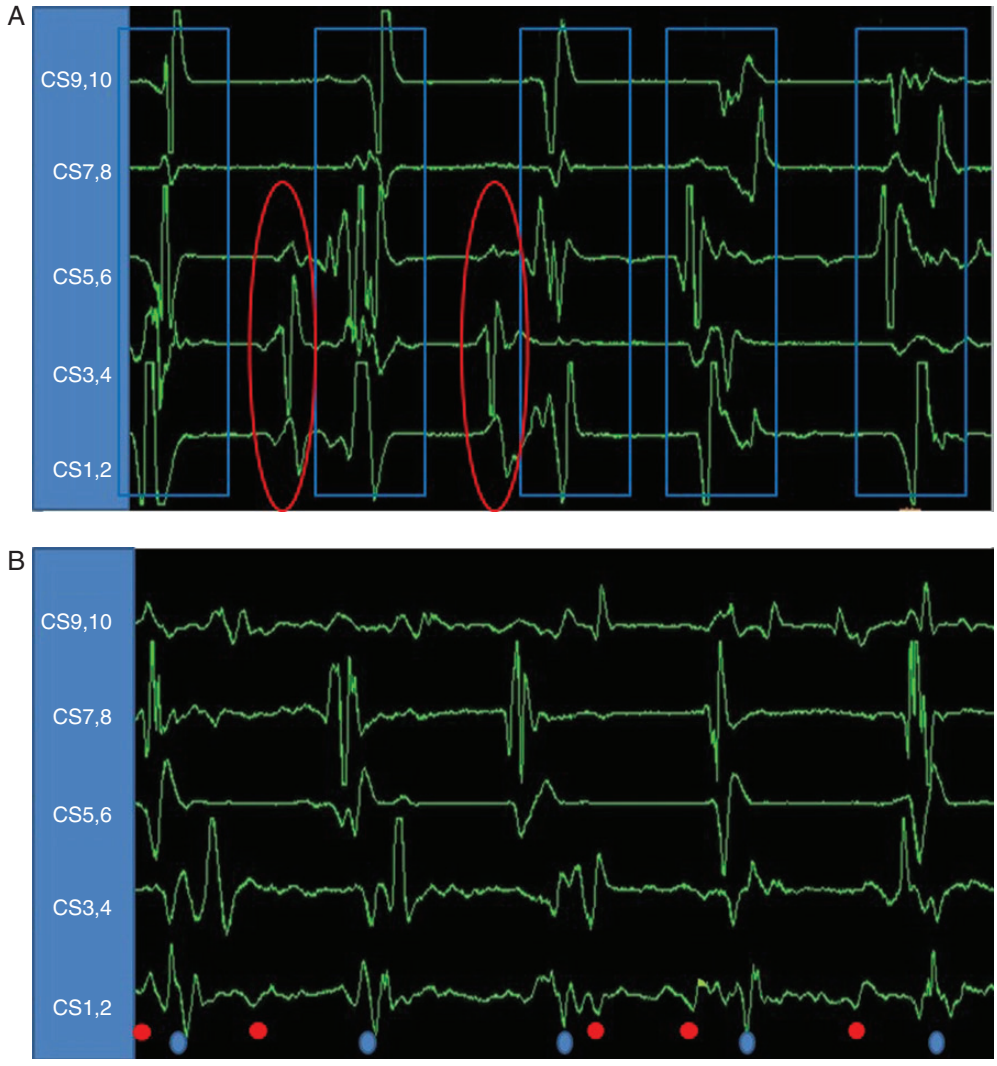

Figure 1 Measurement of LA AF CL in complex activation patterns. (*A*) In this complex electrograms, electrogram signals within red circle and blue rectangle were from two different atrial muscle fascicles. Muscle fascicle with more consistent and prominent signals (signals within blue rectangle in this case) was counted for AF CL measurement. (*B*) In this multicomponent fractionated electrograms, deflections of higher amplitude, frequency, and consistency (blue dots) were counted for AF CL measurement while other smaller and inconsistent deflections (red dots) were ignored. LA, left atrium; AF, atrial fibrillation; CL, cycle length.

Follow-up

Patients were followed up at outpatient clinics 1 or 2 weeks after discharge, then every 2–4 weeks during the first 3 months (blanking period) to monitor early recurrence of arrhythmia. Patients who had early recurrence were cardioverted to SR with DC shock. They were then seen every 3 months after the blanking period. Antiarrhythmic drugs were given in all patients in the blanking period and stopped after blanking period if no early recurrence of arrhythmia was observed. For patients with early recurrence, whether antiarrhythmic drugs were continued after blanking period was at the discretion of the physicians. Electrocardiography (ECG) was routinely performed during every follow-up. In asymptomatic patients, 24 h Holter monitoring was performed at 3, 6, 9, and 12 months after discharge. Symptomatic patients were asked to report to our clinic early and loop recorder would be considered if ECG and 24 h Holter monitoring could not demonstrate any arrhythmia recurrence. Atrial fibrillation or AT after blanking period was defined as recurrence and the time of recurrence was recorded. In patients with AF or AT occurring during follow-up, antiarrhythmic drugs were given at the discretion of the physicians.

Statistical analysis

Continuous variables are presented as arithmetic means ± standard deviation. Categorical variables are expressed as absolute numbers and percentages. Differences in continuous variables were analysed by independent Student's *t*-test or one-way analysis of variance test as appropriate and categorical variables by χ^2 test or Fisher's exact test as appropriate. To analyse independent predictive factors of AF termination, the need for RA ablation and clinical success, univariate factors presenting with a *P*-value of <0.1 were analysed using logistic regression or cox regression (multivariate analysis) as appropriate. Diagnostic

performance of predictors was evaluated by receiver-operator characteristic (ROC) analysis. The optimal cut point was chosen as the combination of the highest sensitivity and specificity. Cumulative event rates (recurrence of arrhythmia) were calculated according to the Kaplan–Meier method and the log-rank test was used to detect significant difference between groups. All tests were two-tailed, and statistical significance was assumed for *P*-values < 0.05. Statistical analysis was performed using the software SPSS 19.0 (SPSS, Inc.).

Results

A total of 136 patients were studied. The mean age was 57.4 $\pm$ 11.3 years old and 83% were males. The mean duration of AF since diagnosis was 5.6 $\pm$ 4.8 years and the mean duration in persistent AF was 10 $\pm$ 5 months; 35% of patients had long-standing persistent AF. The mean AF CL (average of LA and RA AF CL) was 167.6 $\pm$ 27.3 ms. Stepwise ablation converted AF to SR, either directly or through an intermediate step of AT, in 110 patients (81%) while in the remaining 26 patients (19%), AF or subsequent AT could not be terminated by ablation and required cardioversion. Concerning procedural complications, one patient developed cardiac tamponade during procedure requiring pericardiocentesis. Ablation procedure could be continued and completed after pericardiocentesis in this case. One patient developed right femoral haematoma after procedure and it resolved with conservative treatment.

Mean atrial fibrillation cycle length and procedural termination of atrial fibrillation

Baseline characteristics of AF termination group and non-termination group were shown in *Table 1*. The group of patients with AF termination had significantly fewer history of hypertension (28.2 vs. 53.8%, $P = 0.012$) and shorter LA diameter (43.1 $\pm$ 5.4 vs. 47.5 $\pm$ 6.7 mm, $P = 0.001$) compared with non-termination group. Baseline mean AF CL was significantly shorter (153 $\pm$ 12 vs. 171 $\pm$ 29 ms, $P < 0.001$) in AF non-termination group than in AF termination group (*Figure 2A*). However, there was a notable overlap of values between two groups. Nevertheless, long mean AF CL was rarely observed in patients in whom AF could not be terminated. The ROC curve analysis of the mean AF CL for AF termination yielded an area under curve (AUC) of 0.715 ($P = 0.001$) (*Figure 3A*). Mean AF CL >157.75 ms predicted AF termination with 68% sensitivity and 69% specificity.

Predictors of procedural atrial fibrillation termination

Using univariate logistic regression technique, hypertension ($P = 0.015$), LA diameter ($P = 0.001$), and mean AF CL ($P = 0.004$) were found to be predictors for AF termination. There was also a trend that coronary artery disease ($P = 0.070$) was also a predictor for AF termination. By multivariate stepwise logistic regression technique incorporating the variables with *P*-value <0.1 in univariate analysis, hypertension [OR = 0.30 (95% CI: 0.11–0.85), $P = 0.023$], LA diameter [OR = 0.85 (95% CI: 0.77–0.95), $P = 0.003$], and mean AF CL [OR = 1.06 (95% CI: 1.02–1.09), $P = 0.001$] were shown to be independent predictors for AF termination (*Table 2*).

Extent of substrate ablation to achieve atrial fibrillation termination

Atrial fibrillation was terminated by catheter ablation in 110 patients. Patients in whom AF was converted to SR or AT after PVI were regarded as Group P. If AF was converted to SR or AT after PVI plus LA CFAE ablation, then these patients were regarded as Group L. If AF was converted to SR or AT only when RA CFAE ablation was added to PVI and LA CFAE ablation, these patients were labelled as Group R. Among these 110 patients, there were 14 patients (13%) in Group P, 49 patients (44%) in Group L, and 47 patients (43%) in Group R. Their baseline characteristics were not significantly different between groups (*Table 3*). However, significant difference was found in their mean AF CL with shorter mean AF CL in Group L than Group P (174 $\pm$ 24 vs. 209 $\pm$ 36 ms, $P = 0.004$) and even shorter mean AF CL in Group R than Group L (156 $\pm$ 18 vs. 174 $\pm$ 24 ms, $P< 0.001$) (*Figure 2B*). The ROC curve analysis of the mean AF CL for AF termination by PVI (Group P) yielded an AUC of

Table 1 Baseline characteristics of AF termination group and non-termination group

	All ($n = 136$)	AF termination ($n = 110$)	Non-AF termination ($n = 26$)	*P*-value
Age at procedure (years)	57.4 $\pm$ 11.3	56.8 $\pm$ 11.1	59.9 $\pm$ 12.1	0.200
Sex (M/F)	113/23	92/18	21/5	0.772
AF duration (years)	5.6 $\pm$ 4.8	5.3 $\pm$ 4.7	7.0 $\pm$ 5.2	0.100
Comorbid conditions				
Diabetes	11 (8.1%)	9 (8.2%)	2 (7.7%)	1.000
Hypertension	45 (33.1%)	31 (28.2%)	14 (53.8%)	***0.012***
Heart failure	6 (4.4%)	5 (4.5%)	1 (3.8%)	1.000
Coronary artery disease	6 (4.4%)	3 (2.7%)	3 (11.5%)	0.084
MVD	9 (6.6%)	7 (6.4%)	2 (7.7%)	0.682
Echocardiographic parameters				
LA diameter (mm)	44.0 $\pm$ 5.9	43.1 $\pm$ 5.4	47.5 $\pm$ 6.7	***0.001***
LVEF (%)	54.5 $\pm$ 5.4	54.5 $\pm$ 5.6	54.4 $\pm$ 4.6	0.932

AF, atrial fibrillation; MVD, mitral valve disease; LA, left atrium; LVEF, left ventricular ejection fraction.
The bold values represents $P < 0.05$.

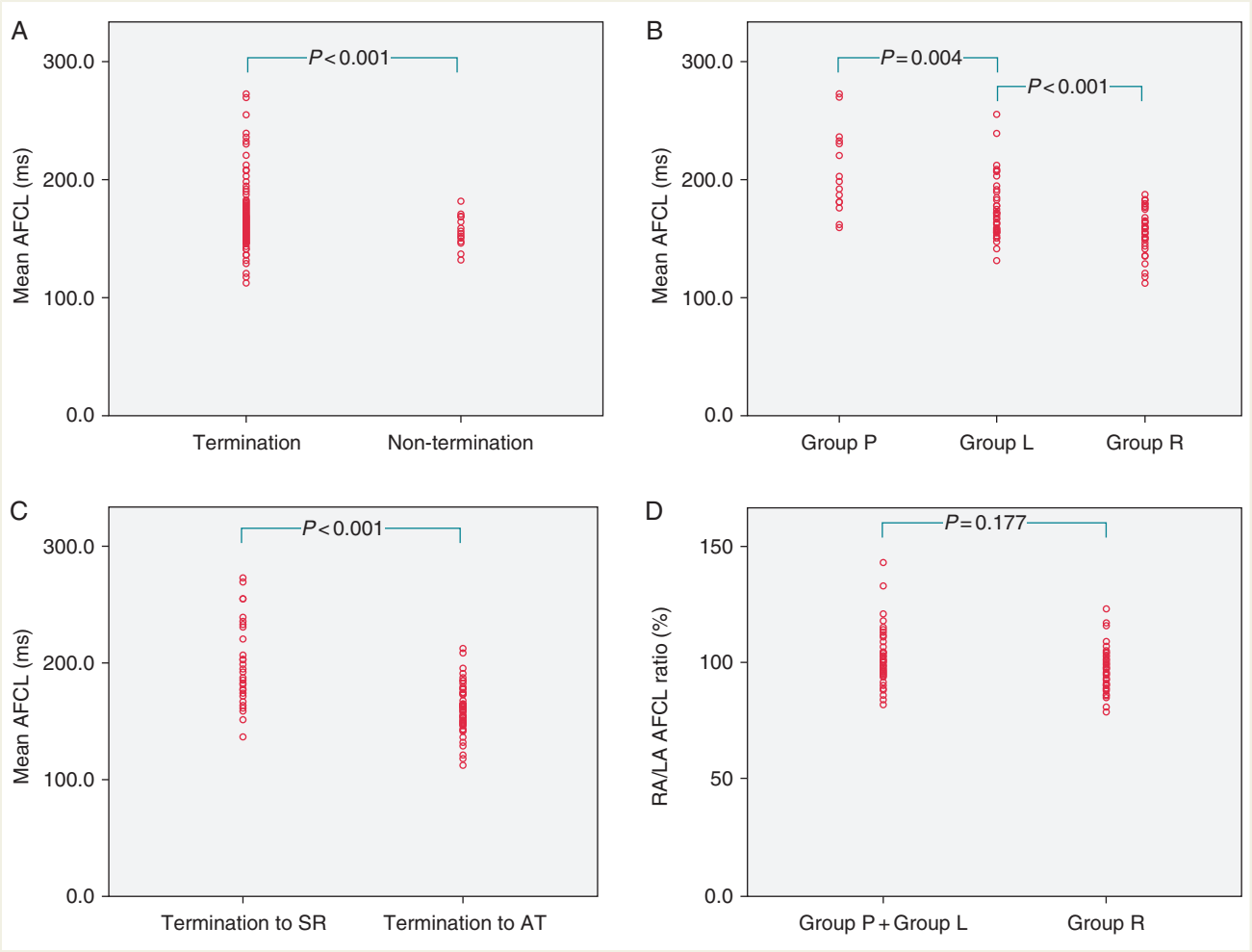

Figure 2 Scatterplot showing individual values of mean AF CL in patients (*A*) with and without procedural AF termination, (*B*) with AF termination by PVI (Group P), by PVI + LA CFAE ablation (Group L) and by PVI + LA CFAE + RA CFAE ablation (Group R), (*C*) with AF termination directly to SR and to AT before back to SR, (*D*) scatterplot showing individual values of RA to LA AF CL gradient in patients with termination by left-side ablation (Group P + Group L) and by additional RA ablation (Group R). PVI, pulmonary vein isolation; CFAE, complex fractionated atrial electrogram; RA, right atrium; AT, atrial tachycardia; SR, sinus rhythm; other abbreviations as in *Figure 1*.

0.876 ($P < 0.001$) (*Figure 3B*). Mean AF CL >180.50 ms predicted AF termination by PVI with 79% sensitivity and 84% specificity. The AUC for ROC curve of the mean AF CL for AF termination by left-side ablation (Group P + Group L) was 0.779 ($P < 0.001$) (*Figure 3C*). Mean AF CL >165.25 ms predicted AF termination by left-side ablation with 67% sensitivity and 75% specificity. The ablation time for Group P, Group L, Group R, and non-termination group was 67 ± 13, 112 ± 37, 159 ± 48, and 170 ± 51 min, respectively ($P < 0.001$).

Left atrium and right atrium atrial fibrillation cycle length and extent of substrate ablation

Among these 110 patients who could achieve AF termination by catheter ablation, the LA AF CL was 171.8 ± 27.2 ms while the RA AF CL was 170.1 ± 33.0 ms at the beginning of the procedure. Baseline LA AF CL was longer than RA AF CL in 61 patients (55%) while RA AF CL was longer than LA AF CL in 45 patients (41%). The LA AF CL was equal to RA AF CL in four patients (4%). The mean difference between LA and RA AF CL was 1.7 ms, with the largest difference being 90 ms.

We hypothesize that critical substrate for driving or maintaining AF is usually located at areas with shorter AF CL. Therefore, LA AF CL should be shorter than RA AF CL if AF was terminated by left-side ablation. However, among the 63 patients in whom AF termination was achieved by left-side ablation (Group P + Group L), up to 32 of them (51%) had shorter AF CL in RA than in LA. *Figure 4* showed an example of a patient in whom AF was terminated by left-side ablation despite a shorter baseline AF CL in RA. For the 47 patients in whom AF termination was achieved by additional RA ablation (Group R), 16 of them (34%) had shorter AF CL in LA than in RA. The RA to LA AF CL gradient (ratio of the RA AF CL divided by the LA AF CL) was not significantly different between left-side ablation and additional RA ablation group (100 ± 11 vs. 97 ± 9%, $P = 0.177$) (*Figure 2D*).

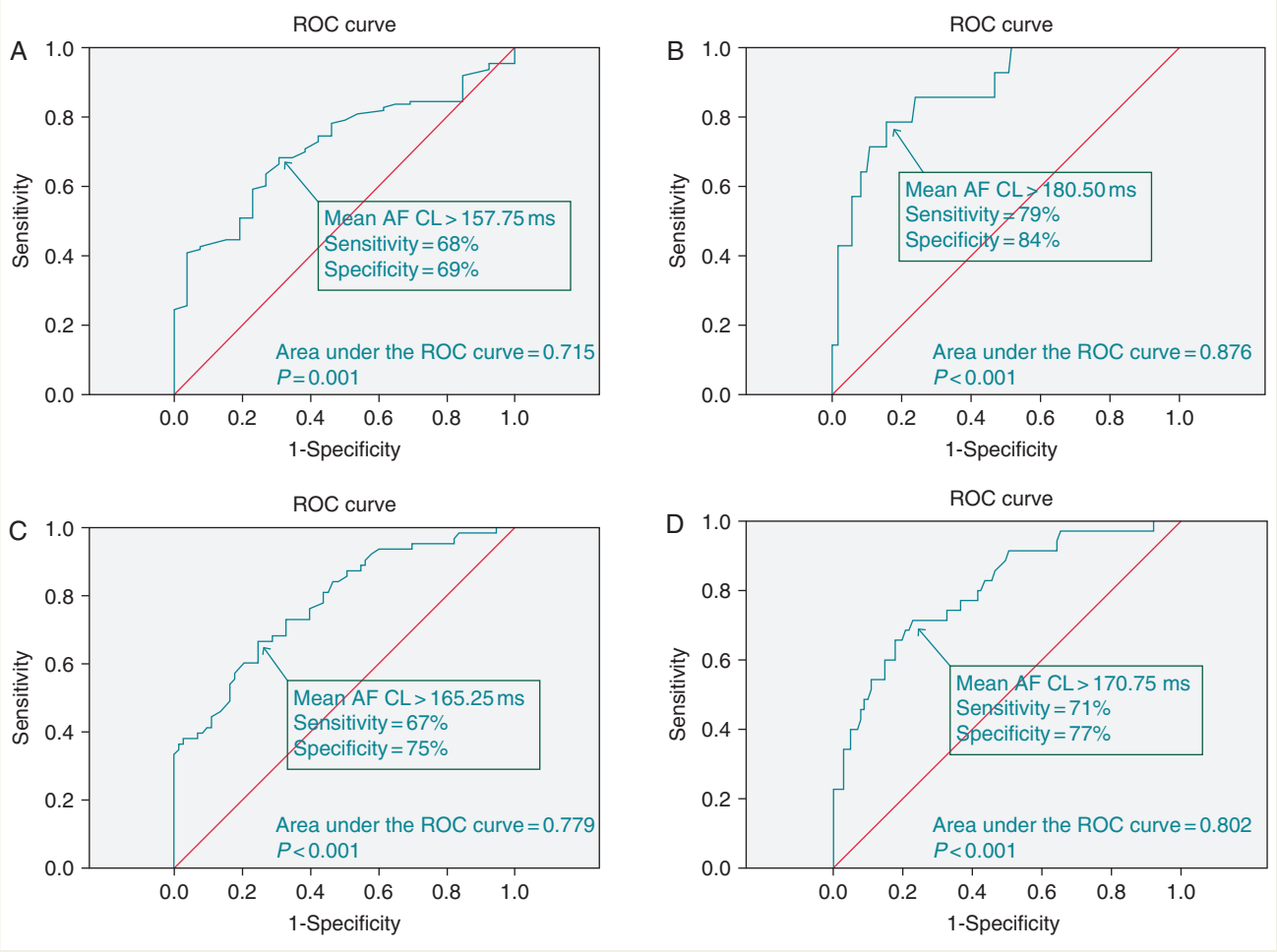

Figure 3 Procedural outcome according to mean AF CL. Receiver operating curve analysis of mean AF CL to predict (*A*) AF termination during stepwise ablation, (*B*) AF termination by PVI (Group P), (*C*) AF termination by left-side ablation (Group P + Group L), (*D*) AF termination directly to SR. Arrows show optimal cutoff point for sensitivity and specificity. Abbreviations as in *Figures 1* and *2*.

Table 2 Logistic regression for AF termination

	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Age at procedure	0.98 (0.94–1.01)	0.200		
Sex (M)	1.22 (0.41–3.65)	0.726		
AF duration	0.94 (0.86–1.01)	0.105		
Comorbid conditions				
Diabetes	1.07 (0.22–5.27)	0.934		
Hypertension	0.34 (0.14–0.81)	**0.015**	0.30 (0.11–0.85)	**0.023**
Heart failure	1.19 (0.13–10.65)	0.876		
Coronary artery disease	0.22 (0.04–1.13)	**0.070**	0.63 (0.08–5.25)	0.670
MVD	0.82 (0.16–4.18)	0.807		
Echocardiographic parameters				
LA diameter	0.87 (0.80–0.94)	**0.001**	0.85 (0.77–0.95)	**0.003**
LVEF	1.00 (0.93–1.09)	0.931		
Mean AF CL	1.04 (1.01–1.06)	**0.004**	1.06 (1.02–1.09)	**0.001**

AF, atrial fibrillation; MVD, mitral valve disease; LA, left atrium; LVEF, left ventricular ejection fraction; CL, cycle length.
The bold values represents $P < 0.1$.

Table 3 Baseline characteristics of Group P, Group L, and Group R

	All ($n = 110$)	Group P ($n = 14$)	Group L ($n = 49$)	Group R ($n = 47$)	*P*-value
Age at procedure (years)	56.8 ± 11.1	57.6 ± 9.0	57.7 ± 9.7	55.5 ± 13.0	0.612
Sex (M/F)	92/18	12/2	41/8	39/8	0.971
AF duration (years)	5.3 ± 4.7	5.4 ± 6.1	5.6 ± 4.7	4.9 ± 4.4	0.782
Comorbid conditions					
Diabetes	9 (8.2%)	1 (7.1%)	7 (14.3%)	1 (2.1%)	0.093
Hypertension	31 (28.2%)	3 (21.4%)	12 (24.5%)	16 (34.0%)	0.486
Heart failure	5 (4.5%)	0 (0%)	3 (6.1%)	2 (4.3%)	0.620
Coronary artery disease	3 (2.7%)	1 (7.1%)	0 (0%)	2 (4.3%)	0.245
MVD	7 (6.4%)	2 (14.3%)	3 (6.1%)	2 (4.3%)	0.401
Echocardiographic parameters					
LA diameter (mm)	43.1 ± 5.4	42.4 ± 4.9	43.2 ± 5.9	43.3 ± 5.1	0.855
LVEF (%)	54.5 ± 5.6	55.9 ± 5.5	54.4 ± 6.0	54.2 ± 5.3	0.586

AF, atrial fibrillation; MVD, mitral valve disease; LA, left atrium; LVEF, left ventricular ejection fraction.

Mean atrial fibrillation cycle length and mode of atrial fibrillation termination

Mean AF CL was also evaluated with respect to the mode of AF termination. Atrial fibrillation was terminated via an intermediate step of AT in 75 patients (68%) and directly into SR in the remaining 35 patients (32%). Termination into SR directly was associated with significantly longer mean AF CL when compared with termination into AT before back to SR (191 ± 34 vs. 161 ± 20 ms, $P < 0.001$) (*Figure 2C*). The ROC curve analysis of the mean AF CL for termination to SR directly yielded an AUC of 0.802 ($P < 0.001$) (*Figure 3D*). Mean AF CL >170.75 ms predicted AF termination to SR directly with 71% sensitivity and 77% specificity.

Predictors of atrial fibrillation termination with need for additional right atrium ablation

Using univariate logistic regression technique, diabetes ($P = 0.078$) and mean AF CL ($P < 0.001$) were found to have a *P*-value < 0.1 for prediction of AF termination with need for additional RA ablation. By multivariate stepwise logistic regression technique incorporating the above two variables, only mean AF CL [OR = 0.95 (95% CI: 0.93–0.98), $P < 0.001$] was shown to be independent predictor for AF termination with need for additional RA ablation (*Table 4*).

Follow-up and clinical outcome

After a mean follow-up of 15 ± 7 months, 46 out of 136 patients (34%) developed recurrence after blanking period. The type of recurrence was AF in 36 patients and AT in 10 patients. Six patients with recurrence underwent second ablation procedure. The Kaplan–Meier curves and recurrence figures were the results after a single procedure. Among 90 patients without AF recurrence, 26 of them (29%) were still on antiarrhythmic drugs after blanking period. Use of antiarrhythmic drugs after blanking period was not a predictor for AF recurrence ($P = 0.607$). When compared with patients without AF recurrence, patients with AF recurrence were found to have more hypertension (50.0 vs. 24.4%, $P = 0.03$), more coronary artery disease (10.9 vs. 1.1%, $P = 0.017$), longer AF duration (7.1 ± 5.2 vs. 4.8 ± 4.5 years, $P = 0.007$), longer LA diameter (45.9 ± 5.7 vs. 43.0 ± 5.8 mm, $P = 0.007$), and longer ablation time (157 ± 55 vs. 123 ± 49 min, $P < 0.001$). Arrhythmia recurrence was significantly lower in AF termination group when compared with non-termination group (27 vs. 62%, $P = 0.001$). The group with AF termination by left-side ablation (Group P + Group L) had a much lower arrhythmia recurrence rate than those with AF termination by additional RA ablation (Group R) (19 vs. 38%, $P = 0.025$). The arrhythmia recurrence rate was not significantly different between Groups P and L (14 vs. 20%, $P = 0.607$). However, the mean AF CL was not significantly different between those with and without AF recurrence (166 ± 30 vs. 168 ± 26 ms, $P = 0.726$). *Figure 5* displayed Kaplan–Meier arrhythmia-free survival curves stratified according to AF termination with different extent of substrate ablation. However, by multivariate stepwise cox regression, only AF duration [OR = 1.06 (95% CI: 1.01–1.13), $P = 0.049$] was independent predictors for AF recurrence.

Discussion

Main findings

The present study evaluated whether the analysis of baseline mean AF CL and AF CL gradient between RA and LA could help stratify the procedural and long-term outcome of patients undergoing persistent AF ablation. The major findings of this study are: (i) Mean AF CL, but not RA to LA AF CL gradient, helps characterize the extent of substrate ablation needed to achieve AF termination in patients with persistent AF. (ii) Mean AF CL >180.50 ms identifies patients in whom AF is likely to be terminated by PVI while mean AF CL >162.25 ms identifies patients in whom AF is likely to be terminated by left-side ablation. (iii) The need for additional RA ablation to achieve AF termination during procedure translates into higher AF recurrence rate.

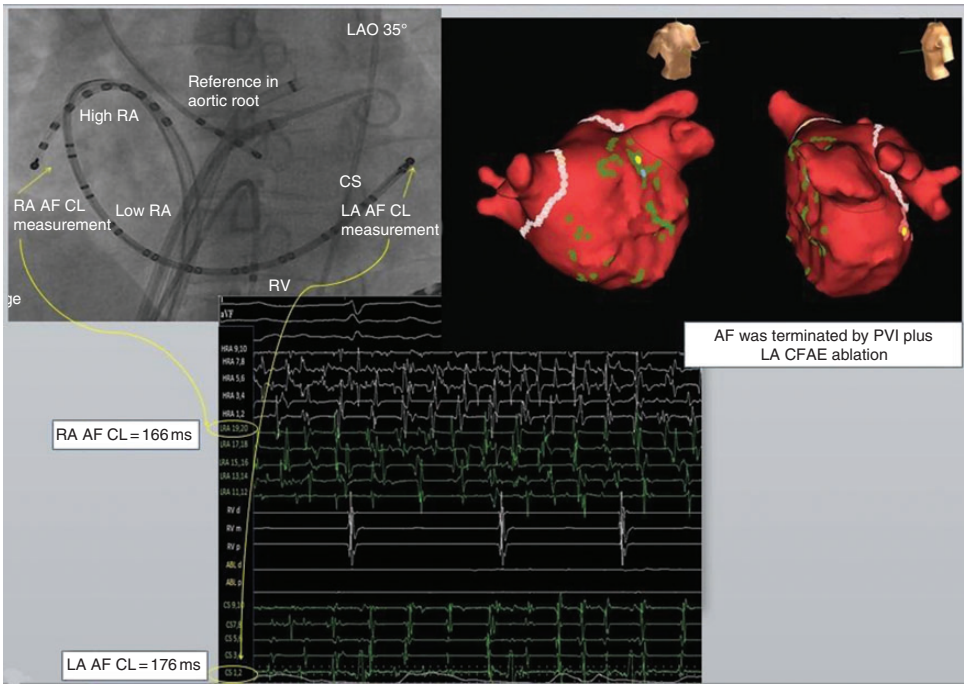

Figure 4 Tracings from a 55-year-old man with persistent AF in the beginning of AF ablation procedure. LA AF CL was recorded from CS 1,2 electrodes (which corresponded to lateral LA) and RA AF CL was recorded from LRA 19,20 electrodes (which corresponded to lateral RA). RA AF CL (166 ms) was shorter than LA AF CL (176 ms) with mean AF CL between two atria being 171 ms. PVI followed by LA CFAE ablation terminated AF directly to SR. No additional RA ablation was needed in this patient. This example illustrated that even there is shorter AF CL in RA than LA, AF can be terminated without additional RA ablation. CS, coronary sinus; LRA, low right atrium. Other abbreviations as in *Figures 1* and *2*.

Table 4 Logistic regression for need for additional RA ablation

	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Age at procedure	0.98 (0.95–1.02)	0.318		
Sex (M)	0.92 (0.33–2.54)	0.872		
AF duration	0.97 (0.89–1.06)	0.489		
Comorbid conditions				
Diabetes	0.15 (0.02–1.24)	**0.078**	0.25 (0.03–2.47)	0.236
Hypertension	1.65 (0.72–3.81)	0.240		
Heart failure	0.89 (0.14–5.54)	0.900		
Coronary artery disease	2.76 (0.24–31.33)	0.414		
MVD	0.52 (0.10–2.78)	0.441		
Echocardiographic parameters				
LA diameter	1.01 (0.94–1.08)	0.800		
LVEF	0.98 (0.92–1.05)	0.610		
Mean AF CL	0.95 (0.93–0.97)	**<0.001**	0.95 (0.93–0.98)	**<0.001**
RA/LA AF CL ratio	0.97 (0.94–1.01)	0.180		

AF, atrial fibrillation; MVD, mitral valve disease; LA, left atrium; LVEF, left ventricular ejection fraction; CL, cycle length; RA, right atrium.
The bold values represents $P < 0.1$

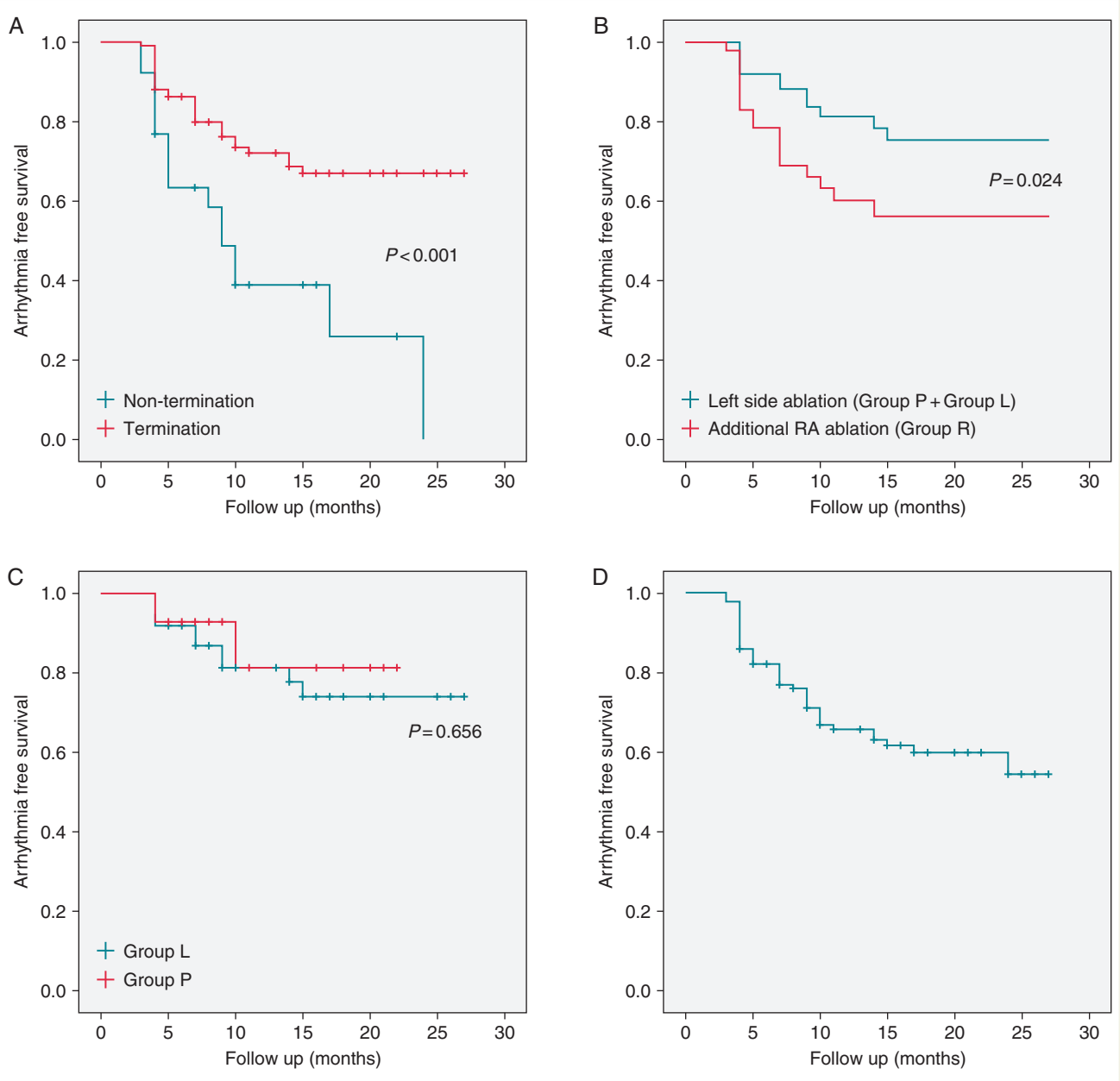

Figure 5 Kaplan–Meier arrhythmia-free survival curves (after a single procedure) stratified according to (*A*) AF termination or AF non-termination, (*B*) AF termination by left-side ablation (Group P + Group L) or by additional RA ablation (Group R), (*C*) AF termination by PVI (Group P) or PVI + LA CFAE ablation (Group L), (*D*) whole study population. Abbreviations as in *Figures 1 and 2*.

Implication of baseline mean atrial fibrillation cycle length and right atrium to left atrium atrial fibrillation cycle length gradient

It is clear that the pathogenesis of AF is often multifaceted. Increased atrial mass, decreased conduction velocity, and decreased atrial refractoriness with increased dispersion are all pro-fibrillatory factors.[12,13] It was shown that stepwise ablation of PV and atrial structures is accompanied by prolongation of AF CL and eventually termination of AF.[4] The reason why AF CL can be used as a surrogate parameter for the effect of ablation on the arrhythmic process is postulated to be related to its relationship with arrhythmogenic sources.[14] In a study using computer simulation of AF, an inverse relation was shown between the number of arrhythmogenic sources operating in persistent AF and the AF CL.[15] In our study, we demonstrated that baseline mean AF CL could not only predict AF termination, but also the extent of substrate ablation needed. In brief, the shorter the baseline mean AF CL is, the more substrate ablation is needed. Although there was a notable overlap of mean AF CL values between the three groups (Group P, Group L, and Group R), the ROC curve analysis of mean AF CL yielded a reasonably high

AUC of 0.876 and 0.779 for AF termination by PVI (Group P) and left-side ablation (Group P + Group L), respectively. These cutoff values of mean AF CL may be helpful to predict AF termination by PVI or by left-side ablation with reasonable sensitivity and specificity. Surprisingly, AF recurrence could not be predicted by mean AF CL although mean AF CL predicted the extent of substrate ablation and the need for additional RA ablation predicted higher AF recurrence. The reason may be that mean AF CL is only a weak predictor for the extent of substrate ablation (odds ratio for need for additional RA ablation: 0.95) and therefore its subsequent influence on AF recurrence can be counterbalanced by other factors of greater impact.

Our study also demonstrated that baseline mean AF CL helps to differentiate which patients can be terminated to SR directly. Therefore, shorter AF CL may not only be a marker for the extensiveness of AF substrate in different atrial regions, but also reflect the presence of arrhythmogenic substrate for AT.

Right atrium to LA AF CL gradient is usually regarded as impulse propagation from one atrium to another atrium across interatrial pathways. Therefore, the atrium with shorter AF CL is supposed to harbour the critical substrate driving or maintaining fibrillatory circuits.[10] In our study, we specifically looked at the baseline difference between RA and LA AF CL and correlated it with the extent of substrate ablation. Surprisingly, RA to LA AF CL gradient was not significantly different between termination by left-side ablation group (Group P + Group L) and termination by additional RA ablation group (Group R). There may be two explanations to account for that. Firstly, previous studies demonstrated that CFAE may often represent tissue heterogeneity, anisotropic conduction, and wave break with fibrillatory conduction instead of sites that are critical for maintaining AF.[16–18] Secondly, ganglionic plexus (GP) was shown to be located in areas with fractionated atrial potentials and ablation over those areas can eliminate other CFAE sites by the interruption of the axons extending from the GP to CFAE areas.[19] In our study, extensive LA CFAE ablation may have an impact to RA substrate by ablating the GP axons.

Implication of additional right atrium ablation in persistent atrial fibrillation

At the beginning of the era of AF ablation, most of the effort was focused on PVI and LA ablation. It is well recognized that LA harbours most of the initiators or perpetuators of AF.[20] However, the clinical outcome of AF ablation by PVI and LA ablation only in patients with persistent AF remained suboptimal.[21] Many electrophysiologists started to explore additional ablation strategy including RA ablation to improve outcome. Data from bi-atrial multielectrode mapping confirmed the presence of AF sources in both atria.[22] Haissaguerre's group employed RA ablation as the last step of stepwise approach which achieved AF termination in up to 85% of patients.[4] In our study, among 110 patients in whom AF termination was achieved, 43% required additional RA ablation on top of PVI and LA ablation. However, if additional RA ablation was needed to terminate AF during the procedure, it inferred higher AF recurrence rate compared with those in whom AF could be terminated by left-side ablation. The reason behind could be that the need for additional RA ablation indicates more extensive substrate and higher disease severity which in turn leads to poorer long-term outcome. Another possibility is that RA ablation itself may be proarrhythmic. In order to define clearly the role of RA ablation on clinical outcomes in persistent AF ablation, it will be beneficial in a future study to randomize patients who do not convert to SR after PVI and LA ablation to receive either cardioversion or RA ablation.

Limitations

There were several limitations in our study. First, it was a retrospective cohort study. Selection bias could not be fully controlled. Secondly, ablation was targeted to the RA only after ablation in the LA was completed. The contribution of the RA in patients with persistent AF might be underestimated. Last but not least, our study only utilized baseline LA and RA AF CL for analysis. Hocini *et al.*[23] showed that RA and LA AF CL following LA ablation might also be a good predictor of need for additional RA ablation.

Conclusion

Baseline mean AF CL may identify the subset of patients in whom persistent AF can be terminated by different extent of substrate ablation, which may in turn predict the chance of recurrence. However, baseline RA to LA AF CL gradient cannot predict the need for additional RA ablation.

Conflict of interest: none declared.

References

1. Haissaguerre M, Sanders P, Hocini M, Takahashi Y, Rotter M, Sacher F *et al.* Catheter ablation of long-lasting persistent atrial fibrillation: critical structures for termination. *J Cardiovasc Electrophysiol* 2005;**16**:1125–37.
2. Haissaguerre M, Hocini M, Sanders P, Sacher F, Rotter M, Takahashi Y *et al.* Catheter ablation of long-lasting persistent atrial fibrillation: clinical outcome and mechanisms of subsequent arrhythmias. *J Cardiovasc Electrophysiol* 2005;**16**:1138–47.
3. Rostock T, Steven D, Hoffmann B, Servatius H, Drewitz I, Sydow K *et al.* Chronic atrial fibrillation is a biatrial arrhythmia: data from catheter ablation of chronic atrial fibrillation aiming arrhythmia termination using a sequential ablation approach. *Circ Arrhythmia Electrophysiol* 2008;**1**:344–53.
4. O'Neill MD, Jaïs P, Takahashi Y, Jönsson A, Sacher F, Hocini M *et al.* The stepwise ablation approach for chronic atrial fibrillation: evidence for a cumulative effect. *J Interv Card Electrophysiol* 2006;**16**:153–67.
5. Chen YL, Ban JE, Park YM, Choi JI, Park SW, Kim YH. The spatial distribution of atrial fibrillation termination sites in the right atrium during complex fractionated atrial electrograms-guided ablation in patients with persistent atrial fibrillation. *J Cardiovasc Electrophysiol* 2013;**24**:949–57.
6. Drewitz I, Willems S, Salukhe TV, Steven D, Hoffmann BA, Servatius H *et al.* Atrial fibrillation cycle length is a sole independent predictor of a substrate for consecutive arrhythmias in patients with persistent atrial fibrillation. *Circ Arrhythm Electrophysiol* 2010;**3**:351–60.
7. Platonov PG, Corino VD, Seifert M, Holmqvist F, Sörnmo L. Atrial fibrillatory rate in the clinical context: natural course and prediction of intervention outcome. *Europace* 2014;**16** Suppl 4:iv110–9.
8. Miwa Y, Minamiguchi H, Bhandari AK, Cannom DS, Ho IC. Amiodarone reduces the amount of ablation during catheter ablation for persistent atrial fibrillation. *Europace* 2014;**16**:1007–14.
9. Limantoro I, de Vos CB, Delhaas T, Weijs B, Blaauw Y, Schotten U *et al.* Clinical correlates of echocardiographic tissue velocity imaging abnormalities of the left atrial wall during atrial fibrillation. *Europace* 2014;**16**:1546–53.
10. Verma A, Novak P, Macle L, Whaley B, Beardsall M, Wulffhart Z *et al.* A prospective, multicenter evaluation of ablating complex fractionated electrograms (CFEs) during atrial fibrillation (AF) identified by an automated mapping algorithm: acute effects on AF and efficacy as an adjuvant strategy. *Heart Rhythm* 2008;**5**:198–205.
11. Li WJ, Bai YY, Zhang HY, Tang RB, Miao CL, Sang CH *et al.* Additional ablation of complex fractionated atrial electrograms after pulmonary vein isolation in patients with atrial fibrillation: a meta-analysis. *Circ Arrhythm Electrophysiol* 2011;**4**:143–8.

12. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation: a study in awake chronically instrumented goats. *Circulation* 1995;**92**:1954–68.
13. Fareh S, Villemaire C, Nattel S. Importance of refractoriness heterogeneity in the enhanced vulnerability to atrial fibrillation induction caused by tachycardia-induced atrial electrical remodeling. *Circulation* 1998;**98**:2202–9.
14. Haissaguerre M, Sanders P, Hocini M, Hsu LF, Shah D, Scavée C *et al.* Changes in atrial fibrillation cycle length and inducibility during catheter ablation and their relation to outcome. *Circulation* 2004;**109**:3007–13.
15. Haissaguerre M, Lim KT, Jacquemet V, Rotter M, Dang L, Hocini M *et al.* Atrial fibrillatory cycle length: computer simulation and potential clinical importance. *Europace* 2007;**9**(Suppl 6):64–70.
16. Lazar S, Dixit S, Callans DJ, Lin D, Marchlinski FE, Gerstenfeld EP. Effect of pulmonary vein isolation on the left-to-right atrial dominant frequency gradient in human atrial fibrillation. *Heart Rhythm* 2006;**3**:889–95.
17. Hunter RJ, Diab I, Tayebjee M, Richmond L, Sporton S, Earley MJ *et al.* Characterization of fractionated atrial electrograms critical for maintenance of atrial fibrillation: a randomized, controlled trial of ablation strategies (the CFAE AF trial). *Circ Arrhythm Electrophysiol* 2011;**4**:622–9.
18. Sanders P, Berenfeld O, Hocini M, Jais P, Vaidyanathan R, Hsu LF *et al.* Spectral analysis identifies sites of high frequency activity maintaining atrial fibrillation in humans. *Circulation* 2005;**112**:789–97.
19. Nakagawa H, Scherlag BJ, Patterson E, Ikeda A, Lockwood D, Jackman WM. Pathophysiologic basis of autonomic ganglionated plexi ablation in patients with atrial fibrillation. *Heart Rhythm* 2009;**6**:S26–34.
20. Calo L, Lamberti F, Loricchio ML, De Ruvo E, Colivicchi F, Bianconi L *et al.* Left atrial ablation versus biatrial ablation for persistent and permanent atrial fibrillation: a prospective and randomized study. *J Am Coll Cardiol* 2006;**47**:2504–12.
21. Matsuo S, Lim KT, Haissaguerre M. Ablation of chronic atrial fibrillation. *Heart Rhythm* 2007;**4**:1461–3.
22. Saksena S, Skadsberg ND, Rao HB, Filipecki A. Biatrial and three dimensional mapping of spontaneous atrial arrhythmias in patients with refractory atrial fibrillation. *J Cardiovasc Electrophysiol* 2005;**16**:494–504.
23. Hocini M, Nault I, Wright M, Veenhuyzen G, Narayan SM, Jaïs P *et al.* Disparate evolution of right and left atrial rate during ablation of long-lasting persistent atrial fibrillation. *J Am Coll Cardiol* 2010;**55**:1007–16.

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An unusual case of oleandrin poisoning suggesting its possible antiarrhythmic activity

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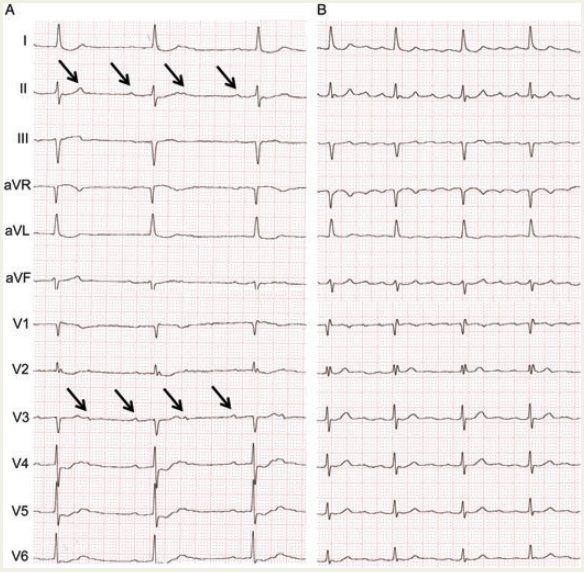
About 6 h after a meal which included an undefined amount of snails collected under a plant of Nerium oleander, a 77-year-old woman with permanent atrial fibrillation (AF) documented for over 5 years, presented with bradycardia associated with gastrointestinal and neurological symptoms due to oleandrin poisoning. Laboratory findings showed a serum digoxin level of 7.8 ng/mL (therapeutic range: 0.5–2.0 ng/mL), although the patient had never taken digoxin. The ECG surprisingly showed sinus rhythm at 96 bpm with 2:1 atrioventricular block, and repolarization abnormalities suggestive of digitalis effect (*Panel A*). In the following days, with the progressive reduction of oleandrin serum concentration, the patient showed an improvement of symptoms and the ECG showed the transition from sinus rhythm to an atypical atrial flutter (*Panel B*), and finally to AF.



Oleandrin is a toxic cardiac-glycoside-like that can induce tachy (atrial and ventricular ectopic arrhythmias) and bradyarrhythmias (sinus bradycardia, sinoatrial and atrioventricular blocks). This is the first report of oleandrin poisoning associated with cardioversion of a very long-lasting AF. The possible antiarrhythmic activity of oleandrin appeared to be dose-dependent as suggested by the finding that with the progressive reduction of its serum concentration there was a gradual desynchronization of the atrial electrical activity.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/unusual_case_of_oleandrin_poisoning.