Predictive Value of Early Recurrence and Delayed Cure After Catheter Ablation for Patients With Chronic Atrial Fibrillation

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Background   Radiofrequency catheter ablation (RFCA) for curing atrial fibrillation (AF) is often followed by early recurrence and delayed cure, so the present study investigate the predictive factors this in patients with chronic AF.

Methods and Results   Ninety-two consecutive patients (70 males; mean age, 58.7±6.4 years) with chronic AF who underwent RFCA for treatment of symptomatic AF were enrolled. Early recurrence of AF (ERAF) occurred in 45 patients after ablation. Not achieving AF termination could predict ERAF (odds ratio (OR) 0.95; 95% confidence interval (CI) 0.84–1.13; p=0.02) in multivariate analysis. During a follow-up of 12±11 (range, 5–25) months, delayed cure occurred in 35.6% (16/45) of the patients with ERAF. Left atrial size and AF termination during ablation were related to delayed cure. AF termination was the only independent predictive factor for delayed cure (OR 1.47; 95% CI 1.05–1.87; p=0.02).

Conclusion   Not achieving AF termination is the only independent predictor of ERAF. Among patients with ERAF, those with a smaller left atrium and AF termination have a higher probability of delayed cure. AF termination can independently predict delayed cure. These results emphasize the importance of AF termination during ablation for patients with chronic AF.   (*Circ J* 2008; **72:** 1125–1129)

Key Words: Ablation; Atrial fibrillation; Recurrence

In patients with paroxysmal atrial fibrillation (AF), limited radiofrequency catheter ablation (RFCA) is often sufficient to achieve high success rates with low complication rates, compared with persistent and permanent AF, which requires extensive ablation.[1–3] However, these encouraging success rates for paroxysmal AF have not been achieved for chronic AF, which has been shown to be associated with a significantly higher rate of recurrence.[4] It is known that AF frequently recurs within the first month after ablation;[5,6] however, despite early recurrence of AF (ERAF), some patients have a delayed cure during the subsequent follow-up.

So far, only a few studies concerned with ERAF or delayed cure have been published[5–8] and only the pulmonary vein (PV) isolation approach was used. With the wide application of 3-dimensional (D) mapping systems to facilitate extensive ablation in chronic AF, those studies no longer reflect current developments. In the present study, we used univariate and multivariate analyses using logistic regression to assess the predictive value of clinical and procedural variables for ERAF and delayed cure after extensive abla-

tion in patients with chronic AF.

Methods

Patients

The subjects of the present study were 92 consecutive patients with chronic AF who underwent RFCA in the left atrium (LA) and coronary sinus (CS) (70 men, 22 women; mean age, 58.7±6.4 years). Chronic AF was defined as AF that had been present for ≥6 months without intervening spontaneous episodes of sinus rhythm (SR) and required cardioversion for restoration of SR. The study protocol was approved by the local ethics committee and all patients gave written informed consent before enrolment.

The baseline characteristics of the study group are presented in Table 1. Thirty-four patients (36.9%) had concomi-

Table 1   Patients' Characteristics

Age (years)	*58.7±6.4*
M/F, n (%)	*70 (76.1%)/22 (23.9%)*
Case history (years)	*5.6±3.6*
Structural heart diseases (n)*	*34 (36.9%)*
Left atrial diameter (mm)	*42±5.2*
LVEDD (mm)	*51±4.9*
LVEF (%)	*60±5.2*
AF termination (n)	*32 (34.8)*

*Includes ischemic heart disease, valvular heart disease, left ventricular hypertrophy, and hypertrophic cardiomyopathy.
LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; AF, atrial fibrillation.
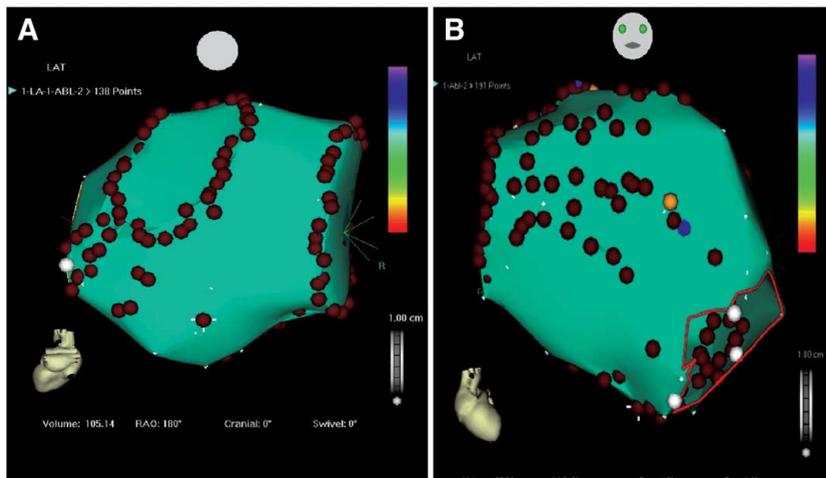
Fig 1. Termination of atrial fibrillation (AF) during radiofrequency ablation. Anteroposterior (A) and posteroanterior (B) projections of a 3-dimensional electroanatomic depiction of the left atrium. Red tags indicate ablation sites; Yellow tag indicates termination of AF during radiofrequency ablation.

tant structural heart disease (SHD): 2 patients (2.1%) with hypertrophic cardiomyopathy, 8 (8.7%) with ischemic heart disease, 6 (6.5%) with valvular heart disease, and 18 (19.6%) with moderate left ventricular hypertrophy because of primary hypertension. The patients had endured AF for 5.6±3.6 years, having failed 2.1±0.8 antiarrhythmic drugs (AADs).

Electrophysiologic Study and Irrigated RFCA

All patients underwent transesophageal echocardiography on the day of ablation to rule out LA thrombus. All AADs, with the exception of amiodarone, had been discontinued for at least 5 half lives.

A quadripolar catheter was introduced via the left subclavian vein and positioned within the CS for atrial pacing and signal reference. Two 8-F Swartz sheaths (SL1 and SR0, St Jude Medical; St Paul, MN, USA) were advanced via the right femoral vein into the LA. After transseptal catheterization, intravenous heparin was administered to maintain an activated clotting time of 250–300 s. The transseptal sheaths were continuously flushed with heparinized saline (20 ml/h) in order to avoid thrombus formation and air embolism. Catheter ablation targeting the following sites was performed in a double sequence. First, we performed circumferential PV ablation guided by 3-D LA mapping, which has been described previously in detail[9,10] Procedural endpoints were completeness of continuous circular lesions and electrical isolation of all PVs. Then, RFCA was performed to target complex fractionated atrial electrograms at the PV ostial and antral areas, various regions of the LA and the CS until AF was terminated or all identified complex fractionated atrial electrograms were eliminated![11] If typical atrial flutter was documented before the procedure, or a macro-reentrant atrial tachycardia spontaneously occurred during ablation, the critical isthmus responsible was identified and ablated (Fig 1).

Postprocedural Management and Follow-up

After the procedure, all patients received AADs (either 200 mg/day amiodarone orally, 150 mg propafenone orally t.i.d., or 80 mg sotalol orally b.i.d.). If ERAF did not occur after 2 months the drug was discontinued. Low-molecular heparin (enoxaparin, 1 mg/kg) and warfarin were administered during the first 3 days after the procedure. Warfarin was maintained for at least 3 months with an international normalized ratio in the range of 1.8–2.5 and withdrawn later

if no AF was detected. All asymptomatic patients were followed up with 12-lead electrocardiogram (ECG) and 24-h Holter recordings before discharge and at 1, 3, 6 and 12 months after the ablative procedure. If the patient was symptomatic, a new ECG was recorded. Additionally, telephone interviews were conducted monthly by a physician for all patients. ERAF was defined as symptomatic AF that recurred within 1 month, and delayed cure was defined as AF disappearing despite ERAF during subsequent followup and stable SR maintained for 2 months off any AADs.

Statistical Analysis

Continuous variables are expressed as mean±SD. Factors related to ERAF or delayed cure after ablation were determined by univariate and multivariate analyses. In the univariate model, t-test was used for continuous variables analysis and χ^2 or Fisher's exact test for discrete variables analysis. A stepwise logistic regression analysis was used for multivariate analysis. Variables selected to be tested in multivariate analysis were those with p<0.05 in the univariate model. A value of p<0.05 was considered statistically significant. Analyses were performed using SPSS statistical software (Version 13.0; Chicago, IL, USA).

Results

Outcome of RFCA

In 34.8% (32/92) of patients, AF termination occurred during ablation without the use of AADs or DC cardioversion. Among these 32 patients, AF converted to SR in 11 and to atrial flutter in 21 (Fig 2). ERAF occurred in 48.9% (45/92) of patients during follow-up. Among the 47 patients without ERAF, although some experienced a late recurrence, there were 41 who were ultimately remained free of symptomatic AF without AADs during a period of 12±11 months follow-up. Overall, it seemed that patients with ERAF had less probability of long-term freedom from recurrent AF than patients without ERAF (p<0.001). A total of 53 (57.6%) patients had long-term success after a single ablation. Asymptomatic recurrence of AF was infrequent in our study; only 9.8% (9/92) asymptomatic recurrences of AF were discovered based on Holter monitoring alone.

ERAF

ERAF occurred in 48.9% (45/92) of patients during follow-up. Among 7 variables evaluated (age, male sex,
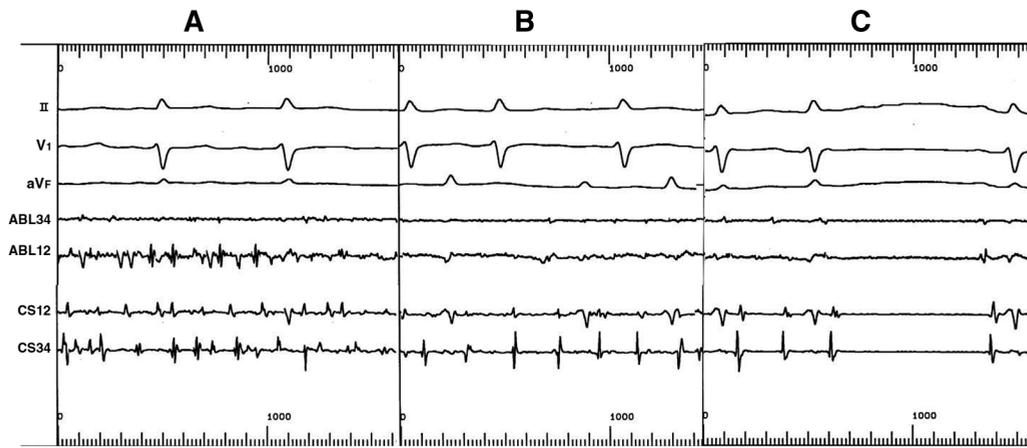
Fig 2.   Termination of atrial fibrillation (AF) during radiofrequency ablation. After ablation of CFAEs in or near the left and right superior pulmonary veins, CFAEs were targeted in the left atrium. AF (A) first organized into atrial flutter (B), then converted to sinus rhythm (C). Shown are electrocardiogram leads II, aVF and V1.

Table 2   Univariate Analysis of Predictors of ERAF

	ERAF (n=45)	No ERAF (n=47)	p value
Male (n)	33 (73.3%)	37 (78.7%)	0.62
Age (years)	59.2±6.9	57.3±6.7	0.18
Case history (years)	5.9±3.9	5.4±3.1	0.49
Structural heart diseases (n)	23 (51.1%)	11 (23.4%)	0.009
LA (mm)	44±7.3	40±6.9	0.008
LVEDD (mm)	53±4.7	50±5.6	0.06
LVEF (%)	59±6.3	61±6.1	0.12
Without AF termination(n)	36 (80%)	24 (51%)	0.004

ERAF, early recurrence of AF; LA, left atrium. Other abbreviations see in Table 1.

Table 3   Univariate Analysis of Predictors of Delayed Cure

	Delayed cure (n=16)	No delayed cure (n=29)	p value
Male (%)	12 (75%)	23 (79.3%)	0.85
Age (years)	57.6±5.6	60.6±5.9	0.10
Case history (years)	5.1±3.2	5.6±4.1	0.63
Structural heart diseases (%)	8 (50%)	16 (55.1%)	0.76
LA (mm)	41±5.6	44±5.9	0.03
LVEDD (mm)	53±6.1	51±4.8	0.23
LVEF (%)	56±7.2	57±7.8	0.67
AF termination	8 (50%)	4 (13.8%)	0.01

Abbreviations see in Tables 1,2.

duration of AF, presence of SHD, LA size, left ventricular end-diastolic diameter, left ventricular ejection fraction and without AF termination), the following were related to ERAF after ablation by univariate analysis: presence of SHD (p=0.009); LA size (p=0.008); without AF termination during ablation (p=0.004) (Table 2). Of the 34 patients with associated SHD, 23 had ERAF (67.6%); however, only 22 (37.9%) of the 58 patients without associated SHD had ERAF. ERAF developed in 29 (64.4%) of the 45 patients with LA enlargement, and in only 16 (34.0%) of the 47 patients without LA enlargement. ERAF was more commonly observed in the group of patients without AF termination by RFCA: 38 of 60 (63.3%) vs 7 of 32 (21.9%), respectively (p=0.002). Furthermore, multivariate analysis demonstrated that only 'without AF termination' could predict ERAF (odd ratio (OR) 0.95; 95% confidence interval

(CI) 0.84–1.13; p=0.02).

Delayed Cure

During the follow-up period (12±11 months, ≤25 months), the 45 patients with ERAF were treated with AADs for a period of 10–12 weeks (mean 10±1.4 weeks). After the AADs were withdrawn, delayed cure occurred in 16 (35.6%) patients with ERAF during subsequent follow-up. Patients with ERAF were then divided in 2 groups according to the presence of delayed cure. The results revealed that AF termination (p=0.01) and LA size (p=0.03) were significantly related to delayed cure (Table 3). AF termination was the only independent predictor of delayed cure (OR 1.47; 95% CI 1.05–1.87; p=0.02). There was no difference in the duration of follow-up between those with and without delayed cure (12±10 vs 13±11 months; p=0.76).

Complications

Procedure-related complications occurred in 5 (5.4%) of the 92 patients. Asymptomatic single PV stenosis (defined as >50% reduction in diameter), which was confirmed by spiral CT at 6 months after the procedure, occurred in 2 patients. Hematoma complicating femoral venous access occurred in 3 patients. No other severe complications, such as pericardial tamponade, occurred during the ablation procedure.

Discussion

Main Findings

In the present study, ERAF was common after RFCA for patients with chronic AF, occurring in approximately 48.9% of patients. Patients who had ERAF were significantly less likely to have long-term freedom from recurrent AF than patients without ERAF. Nevertheless, approximately 35.6% of patients with ERAF were free from recurrent episodes of symptomatic AF in the absence of AAD therapy during long-term follow-up. In this study demonstrate 'without AF termination' was the only independent predictor of ERAF for patients with chronic AF. Among the patients with ERAF, those with AF termination and smaller LA had a higher probability of delayed cure. AF termination could independently predict delayed cure.

ERAF

Oral et al reported that 35.4% (39/110) of patients had ERAF in the 2 weeks after ablation.[9] Dong et al also reported that the rate of ERAF was 33.8% (23/68).[7] In our study, ERAF occurred in 48.9% (45/92) of chronic AF patients after a single ablation. It is associated with a significantly higher recurrence rate in patients with chronic AF. The mechanisms of post-ablation ERAF have not been elucidated. Among the possible causes are: (1) transient stimulatory effect of RFCA secondary to the inflammatory response developing after thermal injury and/or pericarditis;[12,13] (2) recovery of electrical conduction between the LA and PVs;[14,15] and (3) transient imbalance of the autonomic nervous system ultimately acting as an arrhythmia trigger.[16,17]

Our study demonstrated that LA size, presence of SHD and 'without AF termination' were significantly related to the occurrence of ERAF, and 'without AF termination' was the only independent predictor. Haissaguerre et al found that early arrhythmia recurrence was more commonly observed in the group of patients without AF termination by RFCA.[18] Anisotropism is more prominent when the LA is enlarged, which makes it more susceptible to ectopic activity. One important fact is that shortening of the atrial effective refractory period and delaying conduction in different regions facilitate the onset and perpetuation of atrial arrhythmias when the LA is dilated.[19] The presence of SHD is also significantly related to ERAF. An anatomically remodeled LA requires more time after ablation to reverse the vulnerablity to AF triggers[20] and it is more susceptible to early relapses of AF. The mechanism has not been elucidated for the relatively high rate of ERAF in patients without AF termination, but it maybe that elimination of the PV triggers and reversal of the substrate for AF by RFCA is not complete.

Delayed Cure After Ablation

For patients with ERAF, either early re-ablation or late re-ablation after a period of follow-up was considered as a further treatment strategy. With increasing awareness of delayed cure after transcatheter ablation in patients with AF, late re-ablation after a period of follow-up has been proposed in an increasing number of centers to avoid unnecessary repeat procedures and save medical resources. Patients with ERAF are overall less likely to have long-term freedom from AF recurrence than patients without ERAF. However, ERAF does not necessarily mean failure of the ablation procedure because AF may disappear during subsequent follow-up. Our results yielded from a sample of 92 patients including only chronic AF patients, demonstrated that AF termination during ablation and LA size were significantly related to delayed cure, and AF termination could independently predict delayed cure.

The mechanism responsible for delayed cure remains unclear. We postulate that tissue necrosis and the inflammatory reaction caused by ablation could partly explain it. Generally, these changes take approximately 2 weeks to resolve. On the other hand, electrical remodeling of the LA does take time to return to normal after the LA substrate has been modified.[21] According to Jiang et al, patients with less P-wave dispersion and smaller LA diameter have a higher probability of delayed cure.[22] P-wave dispersion can independently predict delayed cure. It is reasonable that LA diameter and P-wave dispersion reflect the degree of structural and electrical remodeling, which requires more time after ablation to reverse the vulnerability to AF triggers[23] But for chronic AF patients, our finding of a correlation between AF termination and delayed cure sheds light on the significance AF termination during RFCA.

Study Limitations

Our results and conclusions should be interpreted in the light of the retrospective nature of the study. One limitation is that CFAEs were identified simply by visual inspection and not by spectral analysis or automated signal analysis algorithms. It is possible that a rigorous quantitative analysis of CFAEs would have resulted in more precise identification of suitable ablation sites. However, in a prior study that achieved an efficacy of 77% in patients with chronic AF, CFAEs were also identified only by visual inspection.[11] Asymptomatic recurrence may have had a potential effect on our results: 10% (9/92) asymptomatic recurrence of AF were detected by Holter monitoring alone.

Conclusions

ERAF occurred in 48.9% patients and was associated with a lower long-term success rate. However, approximately 35.6% of patients with ERAF had no further episodes of symptomatic AF during long-term follow-up. Among patients with ERAF, those with smaller LA and AF termination have a higher probability of delayed cure. AF termination can independently predict delayed cure. AF termination and LA size can be used for patient selection and prognostic evaluation for RFCA.

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