Introduction

Pulmonary vein (PV) isolation is presently the cornerstone of percutaneous transcatheter ablation of drug-refractory paroxysmal atrial fibrillation (PAF)\(^1\). In recent years, cryoballoon (CB) ablation has emerged as a valid alternative to radiofrequency (RF) ablation\(^2\). Recently, the second-generation cryoballoon has been released with technical development resulting in a larger and more homogeneous zone of freezing on the balloon surface, leading to significant improvements in procedural and clinical outcome as compared to its predecessor\(^3–5\). CB ablation in patients with persistent atrial fibrillation (PerAF) was also demonstrated to be associated with favorable outcomes with a 67% sinus rhythm rate at a mean follow-up duration of 10.6 months\(^6\). Previous studies on RF ablation showed that a significant proportion of patients experience an early recurrence of atrial fibrillation (AF)/tachycardia (ERAF) within the first few months of ablation\(^7–9\). Although relatively common, the long-term clinical significance of these early recurrences remains controversial, given the fact that a significant number of patients remain free of recurrent arrhythmias after the initial period\(^11–14\). The consensus document on catheter and surgical ablation of AF suggests the use of a uniform “blanking period of 3 months”\(^15\). However, recent reports have shown that ERAF is strongly associated with late recurrences of AF/atrial tachycardia (LRAF), especially if ERAF occurs within the last part of the blanking period\(^9,10,16\). There is limited evidence regarding the prognostic significance of VERAF and ERRAF after CB ablation\(^17–20\). The present study aimed to assess the role of ERAF in predicting LRAF in a single center study of patients with PAF and PerAF who had undergone CB ablation.

Methods

Study patients

This study consisted of 90 patients (mean age, 63.2 ± 9.9 y/o; male: 63) scheduled for their first catheter ablation of AF who underwent second-generation cryoballoon catheter ablation for PAF (AF lasting less than 7 days, n = 58) and PerAF (AF lasting more than 7 days, n = 32) between September 2014 and May 2016. Adequate oral

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**The Impact of Very Early Recurrence of Atrial Fibrillation after Cryoablation on the One-Year Clinical Outcome**

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Background: Recurrences within 3 months after radiofrequency catheter ablation of atrial fibrillation (AF) have been reported to be associated with the onset of recurrence after 3 months. Although very early recurrence of AF (VERAF) and early recurrence of AF (ERAF) after cryoballoon (CB) ablation are sometimes observed, little is known about their impact on recurrence beyond a recovery period of 3 months. This study aimed to clarify the characteristics of the VERA and ERAF of AF after CB ablation.

Methods and Results: Ninety patients with PAF (n = 58) and PerAF (n = 32), with a median AF duration since the first diagnosis of 2.5 (5, 48) months, underwent CB-based pulmonary vein isolation (PVI). The freeze cycle duration was set at 180 sec, and an additional freeze cycle of 120 sec was applied. The ECG monitor was recorded during hospitalization, and at the outpatient clinic visits at 2 weeks and 1, 3, 6, and 12 months, including Holter electrocardiograms and ambulatory event electrocardiograms. VERA (within 3 days) and ERAF (< 3 months) were observed in 14 (16%) and 12 (13%) patients, respectively. Nine patients with VERA and six with ERAF were AF free during a mean follow-up period of 12 months.

Conclusion: While very early recurrence of AF after cryoballoon-based PVI did not correlate with the clinical outcome, early recurrence of AF after cryoballoon-based PVI correlated with a worse clinical outcome.

Key words: cryoballoon ablation, very early recurrence, early recurrence, late recurrence, AF-free survival

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The patient characteristics and echocardiographic features are shown in Table 1. Patients with VERAF tended to be older, had a longer AF duration and larger left atrial diameter, but it did not reach a statistical significance. No significant differences were found in the other clinical and echocardiographic parameters (Table 1). The body mass index, prevalence of heart failure, left atrial dimension, and left atrial volume were higher in the PerAF patients.

Comparison of PAF and Per AF regarding the incidence of VERAF, ERAF, and LRAF

There were no significant differences in the incidence of VERAF, ERAF, and LRAF between PAF and PerAF (Table 2). Class I antiarrhythmic use did not differ between PAF and PerAF, but the class III antiarrhythmic drug, bepridil, was used more frequently in PerAF patients (Table 3).

| Table 1 Patient Characteristics |
|----------------------------------|
|                                | n = 90 |
| Age (years)                     | 63.2 ± 9.9 |
| Male                            | 63 (70%) |
| BMI (kg/m²)                     | 23.7 ± 3.9 |
| Paroxysmal AF                   | 58 (64%) |
| Hypertension                    | 48 (53%) |
| Diabetes Mellitus               | 17 (19%) |
| Hyperlipidemia                  | 47 (52%) |
| Heart Failure                   | 5 (6%) |
| AF duration (months)            | 12 [5, 48] |
| LVEF (%)                        | 67.0 ± 9.2 |
| LAD (mm)                        | 38.4 ± 6.2 |
| LAV (mL)                        | 45.3 ± 18 |

BMI: body mass index, AF: atrial fibrillation, LVEF: left ventricular ejection fraction, LAD: left atrial diameter, LAV: left atrial volume
showed that LRAF was observed in 18% after the CB low-up with a 92% freedom of AF recurrence during 1-year follow-up. ERAF patients exhibited a very good clinical outcome compared to those with ERAF (36% vs. 50%), and (3) no VERAF or LRAF was observed in 14 patients, LRAF in 5/14 (36%) of the ERAF patients, and LRAF was observed in 11/76 (14.5%) of the patients without ERAF. The reason that our results were slightly different from the previous study that the incidence of LRAF was lower in the no VERAF/ERAF patients (Fig. 3).

### Table 2  Patient Characteristics among the VERAF, ERAF, and No VERAF/ERAF Patients

| Age (years) | VERAF n = 14 | ERAF n = 12 | No VERAF & ERAF n = 64 | P value |
|------------|--------------|-------------|-------------------------|---------|
| 67.1 ± 9.8 | 57.8 ± 12.4  | 63.3 ± 9.2  | 0.0585                  |
| 8 (57%)    | 7 (54%)      | 48 (75%)    | 0.2669                  |
| 24.1 ± 3.7 | 22.8 ± 2.8   | 23.9 ± 4.1  | 0.6232                  |
| 9 (64%)    | 8 (62%)      | 41 (64%)    | 0.9851                  |
| 7 (50%)    | 4 (31%)      | 37 (53%)    | 0.2855                  |
| 5 (36%)    | 2 (15%)      | 10 (16%)    | 0.9645                  |
| 7 (50%)    | 6 (46%)      | 34 (53%)    | 0.8578                  |
| 0 (0%)     | 2 (15%)      | 3 (5%)      | 0.1542                  |
| 32 [6, 102]| 13 [2.3, 33]| 10.5 [5, 36]| 0.0929                  |
| 66.8 ± 6.3 | 64.4 ± 14.6  | 67.5 ± 8.6  | 0.5694                  |
| 40.1 ± 5.5 | 34.9 ± 4.5   | 38.7 ± 6.5  | 0.0815                  |
| 50.0 ± 17.2| 36.3 ± 16.6  | 45.7 ± 17.6 | 0.2380                  |

BMI: body mass index, AF: atrial fibrillation, LVEF: left ventricular ejection fraction, LAD: left atrial diameter, LAV: left atrial volume, VERAF: very early recurrence of atrial fibrillation, ERAF: early recurrence of atrial fibrillation. 

### Table 3  Comparison of the Clinical Outcome between Paroxysmal and Persistent Atrial Fibrillation

|                  | PAF n = 58 | PerAF n = 32 | P value |
|------------------|------------|--------------|---------|
| Very early recurrence AF | 9 (16%)    | 5 (16%)      | 0.8439  |
| Early recurrence AF | 8 (14%)    | 5 (16%)      | 0.6848  |
| Late recurrence AF | 10 (17%)   | 6 (19%)      | 0.8578  |
| Class I AAD use after ablation | 9 (16%)    | 4 (13%)      | 0.6967  |
| Bepridil use after ablation | 14 (24%)   | 23 (72%)     | < 0.0001|

PAF: paroxysmal atrial fibrillation, PerAF: persistent atrial fibrillation, AF: atrial fibrillation, AAD: antiarrhythmic drug.

### Relationship between VERAf, ERAf and LRAf

LRAF was observed in 16 (17.7%) patients. VERAf was observed in 14 patients, LRAF in 5/14 (36%) of the VERAf patients, and LRAF in 11/76 (14.5%) of the patients without VERAf (P = 0.0561). ERAF was observed in 12 patients, LRAF in 6/12 (50%) of the ERAF patients, and LRAF in 10/78 (12.8%) patients without ERAF (P = 0.00285) (Figs. 1 and 2). Kaplan-Meier curves showed that the recurrence of AF after 3 months was significantly lower in the no VERAF/ERAF patients (Fig. 3).

### Discussion

The main findings of the present study were as follows: (1) VERAf occurred in 15% and ERAF in 13% of our study population after the CB ablation procedure, (2) there were fewer LRAF patients with VERAf than those with ERAF (36% vs. 50%), and (3) no VERAF or ERAF patients exhibited a very good clinical outcome with a 92% freedom of AF recurrence during 1-year follow-up. The STOP AF trial showed that ERAF (during the first 3 months) was observed in 51.5%, and LRAF was significantly related to ERAF (55.5% LRAF with ERAF vs. 12.7% LRAF without ERAF). Irfan et al. also showed that LRAF was observed in 18% after the CB ablation, and 65% of the patients with ERAF presented with LRAF. Mungai et al. showed that ERAF occurred in 9/29 (31%) patients with ERAF, and 20/29 (69%) patients with ERAF also presented with LRAF, the highest prevalence of ERAF was observed in the first 2 weeks (55%) after the CB ablation, and all ERAF occurring 1.5 months after the CB ablation relapsed after 3 months.

Another human study showed that both energy sources in cryoablation compared to radiofrequency ablation resulted in a comparable rise in the markers of cell damage, platelet activation, and an inflammatory response.
Fig. 1 Schema showing the relationship of very early and early recurrence of atrial fibrillation (AF) on the late recurrence of atrial fibrillation after cryoballoon-based ablation.

Late recurrence in the VERAF group

| Group     | Late Recurrence (%) | P Value |
|-----------|---------------------|---------|
| VERAF+    | 5/14                | 0.0561  |
| VERAF-    | 11/76               |         |

Late recurrence in the ERAF group

| Group     | Late Recurrence (%) | P Value |
|-----------|---------------------|---------|
| ERAF+     | 6/12                | 0.00285 |
| ERAF-     | 10/78               |         |

Fig. 2 Relationship between very early recurrence of atrial fibrillation (VERAF) and early recurrence of atrial fibrillation (ERAF) on the late recurrence of atrial fibrillation.

Kaplan-Meier survival estimate

| Group                  | Number at risk | Follow-up period (months) |
|------------------------|----------------|---------------------------|
| ERAF                   | 12             | 30                        |
| VERAF                  | 14             | 30                        |
| no VERAF + no ERAF     | 64             | 30                        |

Log-rank p = 0.0002

Fig. 3 Kaplan-Meier curves showing the freedom from atrial fibrillation after 3 months in patients with very early recurrence of atrial fibrillation (VERAF), early recurrence of atrial fibrillation (ERAF), and no VERAF/ERAF.
Miyazaki et al. showed that the proportion of ERAF was comparable after RF and 2nd-generation CB ablation and that despite CB ablation exhibiting greater myocardial injury than RF ablation, the inflammatory responses were comparable between the groups, and the inflammatory response extent predicted an ERAF post-RF ablation but not post-CB ablation. We also demonstrated that CB ablation, in comparison to a point-by-point circumferential contact-based radiofrequency ablation, produced a larger PV-LA surface isolation area. Therefore, VERAF after CB ablation might be related to greater myocardial injury by the CB ablation, however, VERAF after the CB ablation might not predict LRAF.

**Study limitations**

Our study limitations should be considered. The study involved a relatively small number of patients with PAF and PerAF. The follow-up duration was relatively shorter and the use of the class III antiarrhythmic drug, bepridil, was significantly higher in the PAF patients than PAF patients (23 [72%] vs. 14 [24%], \( P < 0.0001 \)). Previous studies showed that the restoration of sinus rhythm by the use of the class III antiarrhythmic drug, bepridil, after ablation of PerAF might result in a favorable outcome after the ablation in PerAF patients. Therefore, a study with a longer follow-up off antiarrhythmic drugs is warranted in a larger number of patients.

**Conclusions**

VERAF after the cryoballoon-based PVI did not correlate with the clinical outcome, but early recurrence of AF after the cryoballoon-based PVI correlated with a worse clinical outcome.

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