


ORIGINAL ARTICLE

Influence of balloon temperature and time to pulmonary vein isolation on acute pulmonary vein reconnection and clinical outcomes after cryoballoon ablation of atrial fibrillation

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Abstract

Background: Limited data exist on indicators of durable pulmonary vein isolation (PVI) undergoing cryoballoon ablation (CBA) for atrial fibrillation (AF). We investigated whether balloon temperature and time to PVI can be used to predict early PV reconnection (EPVR), including residual PV conduction and adenosine triphosphate-induced dormant conduction and the relation between touch-up ablation of EPVR sites and mid-term recurrence of AF.

Methods: We obtained procedural and outcome data from the records of 130 consecutive patients who underwent CBA and followed up for 13.4 months.

Results: EPVR was identified in 86 (17%) PVs of 61 (47%) patients. Balloon temperatures during 30 seconds ($-27 \pm 5.7^\circ\text{C}$ vs $-31 \pm 5.5^\circ\text{C}$), 60 seconds ($-36 \pm 5.6^\circ\text{C}$ vs $-41 \pm 5.4^\circ\text{C}$), and at the nadir point ($-41 \pm 7.4^\circ\text{C}$ vs $-49 \pm 7.0^\circ\text{C}$) were significantly higher, and the time to PVI was longer (90 ± 50 seconds vs 52 ± 29 seconds) in PVs with EPVR than in those without ($P < 0.0001$ for all). Among PVs without EPVR, the time to PVI was longer and balloon temperature was lower for the left superior pulmonary vein/ right inferior pulmonary vein (LSPV/RIPV) than for the right superior pulmonary vein/left inferior pulmonary vein (RSPV/LIPV) (time: $60 \pm 25/73 \pm 37$ seconds vs $41 \pm 31/45 \pm 20$ seconds, $P < 0.0001$) (temp: $-39.2 \pm 11.3/-39.4 \pm 8.3^\circ\text{C}$ vs $-33.8 \pm 10.6/-33.6 \pm 6.8^\circ\text{C}$, $P = 0.0023$). AF recurrence rates were equivalent between patients with and without EPVR (13% [8/69] vs 15% [9/61], $P = 0.845$).

Conclusions: Cryoballoon temperature and time to PVI appear to be useful in predicting durable PVI, that is, prevention of EPVR, but the balloon temperature and time required for PVI differ between PVs. Although EPVR does not predict AF

recurrence, high success rates can be expected when touch-up ablation of EPVR sites is performed.

KEYWORDS

acute pulmonary vein reconnection, atrial fibrillation, cryoballoon ablation

1 | INTRODUCTION

Cryoballoon ablation (CBA) has emerged as an alternative to radiofrequency (RF) ablation of atrial fibrillation (AF).¹ Pulmonary vein isolation (PVI) performed with a second-generation cryoballoon has been highly successful in cases of paroxysmal AF and is comparable to PVI performed by point-by-point RF ablation²⁻⁶ or even contact force (CF)-guided RF ablation.^{7,8} However, despite efforts to properly position the cryoballoon to establish good balloon surface-tissue contact, some patients experience early PV reconnection (EPVR) in the form of residual PV potentials, spontaneous PV-left atrium (LA) reconnection, or adenosine triphosphate (ATP)-provoked dormant PV conduction (DC).⁹ Balloon temperature measured by the console at different time points, for example, at 30 and 60 seconds, and nadir point and the time to PVI during CBA have been shown to be useful in predicting successful PVI.¹⁰ However, the best predictor of durable PVI has not been established. Further, even when good balloon surface-tissue contact is achieved, the balloon temperature and time to PVI differ between patients and between PVs because of the different thicknesses of the PV wall and histologic characteristics of the myocardial sleeves.^{11,12} Thus, in the retrospective study described herein, we first investigated relations between the occurrence of EPVR after CBA and the following four variables: balloon temperature at different time points, time from the initial delivery of cryoenergy to completion of PVI, balloon temperature for each of the 4 PVs at during the PVI, and time to PVI for each of the four PVs.

A recent randomized clinical trial showed improved clinical outcomes after elimination of dormant PV conduction by delivery of additional RF energy to ATP-provoked DC sites,¹³ whereas other randomized trials showed no superiority of ATP- or adenosine-guided PVI over conventional PVI.^{14,15} Because it remains unclear whether additional delivery of RF energy to EPVR sites affects clinical outcomes of CBA, we also investigated the relation between additional RF ablation of EPVR sites and recurrence of AF after CBA.

2 | METHODS

2.1 | Study patients

Included in our study were 130 consecutive patients who had undergone cryoballoon-based PVI for drug-refractory AF (paroxysmal AF, $n = 84$; persistent AF, $n = 46$) at Nihon University Itabashi Hospital between September 2014 and June 2017. All patients had provided informed consent for use of their anonymized clinical data for

research purposes, and our access to the patient information was approved by the hospital's institutional review board.

2.2 | Cryoballoon ablation

Cryoballoon ablation was performed with a 28-mm second-generation Arctic Front Advance Cardiac CryoAblation Catheter System (Medtronic, Minneapolis, MN), as described previously.^{9,16} In brief, a single transeptal puncture was performed, and an 8-Fr long sheath (St. Jude Medical, Inc., St. Paul, MN) was inserted into the LA via the puncture hole. A 20-pole circular mapping catheter (Inquiry AFocus II EB; St. Jude Medical) was used to create an activation map of the LA and PVs and for 3-dimensional (3D) reconstruction with an EnSite NavX mapping system (St. Jude Medical). The SLO sheath was exchanged over a guidewire for a 15Fr deflectable sheath (Flexcath Advance, Medtronic). A cryoballoon with an inner lumen mapping catheter (Achieve, Medtronic) was placed in the LA through the 15Fr deflectable sheath. The balloon was then inflated and advanced successively to each PV ostium to establish optimal PV occlusion, determined by the absence of contrast leakage. To avoid overwedging of the balloon inside the PVs, we used the "proximal-seal" technique for all RSPVs and LSPVs; that is, we withdrew the inflated balloon until a small leak was observed and then repositioned the balloon slightly.⁹ Cryoenergy was delivered to each PV after occlusion was established. The freeze time for ablation of each PV antrum was 180 seconds. Whenever possible, the PV potentials were monitored by means of an inner lumen mapping catheter. To avoid phrenic nerve injury, the phrenic nerve was monitored continuously during ablation of the right superior and inferior PVs (RSPV and RIPV, respectively) by systematically pacing the right phrenic nerve from the superior vena cava.¹⁶ A 3D voltage map was created 30 minutes after CBA. Residual PV potentials or spontaneous early PV-LA reconnections were confirmed on the 3D voltage map and by the 20-pole circular mapping catheter. If residual PV potentials or spontaneous early PV-LA reconnections were evident, additional touch-up RF ablation was performed with an open irrigated 3.5-mm tip ablation catheter (FlexAblity, St. Jude Medical) to achieve PVI. Thereafter, a 30-mg bolus of ATP was injected to unmask any DC.⁹ If ATP-provoked DC was identified by the 20-pole circular mapping catheter, additional touch-up RF ablation was performed until no DC was provoked by repeat ATP injection. Any post-CBA residual PV potential, spontaneous early PV-LA reconnection, or DC was defined as EPVR. A cavotricuspid isthmus linear ablation was performed when typical atrial flutter was documented clinically. No additional ablation of the LA body was performed in this study.

2.3 | PV diameter measurements

We measured the PV ostial diameters using 3D CT images. The maximum and minimum diameters were measured at the PV ostium, which was defined based on the geometry obtained from 3D CT images.

2.4 | Ablation-related variables

Balloon temperature, measured by the console during CBA targeting each of the four PVs, was determined at 30 seconds, at 60 seconds, and the nadir point, and the thaw times to 0°C were also determined. When PV potentials were recorded during CBA, the balloon temperature and time from the first cryoenergy application to achievement of PVI, that is, to occurrence of dissociated PV conduction or to disappearance of the PV potential, were determined.

2.5 | Postablation follow-up

All antiarrhythmic drugs were resumed after ablation but then typically stopped after a 3-month blanking period. In some patients, antiarrhythmic drugs were continued beyond this point on the basis of physician and/or patient preference even in the absence of AF recurrence. All patients underwent routine follow-up examination at our outpatient clinic 2 weeks and 1 month after ablation and at 1-to-3-month intervals thereafter for at least 6 months. Twenty-four-hour Holter monitoring was performed at 3 to 6 and at 12 months after ablation. An electrocardiographic event recorder was used if patients reported any cardiac symptoms. Any AF episode lasting > 30 seconds and documented on a standard electrocardiogram, an event recorder, or 24-hour Holter monitor was considered AF recurrence.

2.6 | Statistical analysis

Continuous variables are expressed as mean \pm SD values or median values and interquartile ranges. Differences in the continuous variables between patients in whom EPVR occurred and those it did not were analyzed by unpaired *t* test or Mann-Whitney *U* test, as appropriate. Differences in categorical variables were analyzed by chi-square test. Stepwise multivariable analysis was performed to determine significant predictors of EPVR. Factors shown to be significant in univariate analysis were entered into the model. Pearson's correlation coefficients were used to assess the correlation between the PV ostial diameters and balloon temperatures at any time phase. Receiver operating characteristic (ROC) curves were drawn to determine the prognostic performance of variables for absence of EPVR. The prognostic performance of the balloon temperature at each time point was measured by the area under the curve (AUC). Freedom from arrhythmia was estimated by the Kaplan-Meier method, and differences between the patients with and without EPVR were analyzed by log-rank test. All statistical analyses were performed with JMP 11 software (SAS Institute, Cary, NC) or MedCalc for Windows version 13.1.2.0 (MedCalc Software, Mariakerke, Belgium), and $P < 0.05$ was accepted as statistically significant.

3 | RESULTS

3.1 | Patients' clinical characteristics and incidence of EPVR

Clinical characteristics of the study patients are shown in Table 1. The male/female ratio was 90/40, age was 64.2 ± 9.9 years, body mass index was 23.9 ± 4.2 kg/m², and CHADS2 and CHA2DS2-VASc scores were 1.2 ± 1.1 and 2.1 ± 1.5 , respectively. 35% had persistent AF. The ablation involved a total of 518 PVs (2 left common PVs) in the 130 patients. Balloon temperatures were accurately recorded for 502 of the 518 PVs. Reconduction occurred in 86 (17%) PVs in 61 (47%) patients (1.6 ± 0.7 PVs per patient): Residual PV potentials were recorded in 66 (13%) PVs in 40 (31%) patients, spontaneous early PV-LA reconnection in 13 (3%) PVs in 12 (1%) patients, and DC in 23 (5%) PVs in 21 (16%) patients. Touch-up RF ablation of the EPVR was more often required for the RIPV than other PVs (RIPV 32% [42/130] vs LSPV 11% [14/129], LIPV 18% [24/129], and RSPV 13% [17/130]; $P = 0.038$). The incidence of EPVR was greater among male patients than among female patients (78.7% [48/61] vs 60.9% [42/69], respectively; $P = 0.028$). The incidence of EPVR was more prevalent in patients < 65 years of age than in those aged 65 years or older (57% [35/61] vs 33% [23/69], respectively; $P = 0.006$). There were no differences in the other CHA2DS2-VASc score components such as hypertension and diabetes mellitus, between the patients with and without EPVR. A young age and male sex among patients with EPVR resulted in lower CHA2DS2-VASc scores than among those without EPVR (1.8 ± 0.2 vs 2.4 ± 0.2 , respectively; $P = 0.014$). The incidence of EPVR was also greater among patients with persistent AF than among those with paroxysmal AF (44.3% vs 27.5%, respectively; $P = 0.047$). LA diameter tended to be greater among patients with EPVR than among those without EPVR (39.8 ± 7.0 vs 37.7 ± 5.3 mL, respectively; $P = 0.053$). LA volume also tended to be greater among patients with EPVR (48.2 ± 19.1 vs 42.6 ± 14.9 mL, respectively; $P = 0.096$) (Table 1). Stepwise multivariable analysis showed age < 65 years to be a strong determinant of the occurrence of EPVR (odds ratio [OR] 2.69, 95% confidence interval [95% CI]: 1.13-5.56, $P = 0.0057$).

3.2 | Residual leak

Residual leaks were observed in 241 of the 518 PVs (46.5%). The prevalence of residual leaks increased gradually from 25/129 (19.4%) for the LSPV, to 53/130 (40.8%) for the RSPV, to 72/129 (55.8%) for the LIPV, and to 91/130 (70%) for the RIPV. For each PV except the LSPV (LSPV: 35.7% [5/14] vs 17.4% [20/115], respectively; $P = 0.100$), there was a significant association between the residual leak and EPVR (LIPV: 91.7% [22/24] vs 47.6% [50/105], respectively; $P < 0.0001$, RSPV: 64.7% [11/17] vs 37.2% [42/113], respectively; $P = 0.033$, RIPV: 83.3% [35/42] vs 63.6% [56/88], respectively; $P = 0.02$).

TABLE 1 Clinical characteristics and echocardiographic variables in patients with and without EPVR after cryoballoon ablation for AF

	Total (n = 130)	With EPVR (n = 61)	Without EPVR (n = 69)	P value ^a
Age (years)	64.2 ± 9.9	61.5 ± 10.7	66.6 ± 8.5	0.0032
Male sex	90 (70)	48 (79)	42 (61)	0.028
Persistent AF	46 (35)	27 (44)	19 (28)	0.047
Body mass index (kg/m ²)	23.9 ± 4.2	24.4 ± 3.9	23.5 ± 4.4	0.27
Congestive heart failure	9 (7)	5 (8)	4 (6)	0.59
Hypertension	77 (59)	33 (54)	44 (64)	0.26
Diabetes mellitus	25 (19)	9 (15)	16 (23)	0.22
Stroke/TIA	13 (10)	7 (11)	6 (9)	0.60
Vascular disease	8 (6)	2 (3)	6 (9)	0.20
CHADS ₂ score	1.2 ± 1.1	1.1 ± 1.1	1.2 ± 1.0	0.39
CHA ₂ DS ₂ -VASc score	2.1 ± 1.5	1.8 ± 0.2	2.4 ± 0.2	0.014
Ejection fraction (%)	67.0 ± 9.6	66.1 ± 1.2	67.7 ± 1.2	0.34
LA diameter (mm)	38.7 ± 6.3	39.8 ± 7.0	37.7 ± 5.3	0.053
LA volume (mL)	45.4 ± 17.3	48.2 ± 19.1	42.6 ± 14.9	0.096

Values are shown as mean ± SD or n (%).

EPVR, early pulmonary vein reconnection; AF, atrial fibrillation; TIA, transient ischemic attack; CHADS₂, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65-74 years, and sex category, LA left atrium.

^aby Student's *t* test, Mann-Whitney test, or chi-square test, as appropriate.

3.3 | PV diameter

The maximum LSPV and RIPV ostial diameters were significantly larger for the PVs with early reconnections than for those that without (LSPV 24 ± 5 mm vs 20 ± 3 mm, respectively; *P* = 0.001; RIPV 21 ± 3 mm vs 19 ± 4 mm, respectively; *P* = 0.001), while the maximum LIPV and RSPV ostial diameters were not (LIPV 18 ± 3 mm vs 17 ± 3 mm, respectively; *P* = 0.13; RSPV 21 ± 3 mm vs 21 ± 4 mm, respectively; *P* = 0.91). The maximum RSPV ostial diameter correlated negatively with the balloon temperatures at 60 seconds (*r* = -0.25, *P* = 0.007) and nadir point (*r* = -0.30, *P* = 0.001); however, the maximum PV ostial diameters of the other PVs did not correlate with the balloon temperatures during any time phase (*P* = *N.S.* for all). The minimum PV ostial diameters of all PVs did not have any association in terms of EPVR or the balloon temperatures.

3.4 | Balloon temperatures

Balloon temperatures at each time point were significantly higher for the PVs that had early reconnection than those that did not: 30 seconds (-27 ± 5.7°C vs -31 ± 5.5°C, respectively; *P* < 0.0001), 60 seconds (-36 ± 5.6°C vs -41 ± 5.4°C, respectively; *P* < 0.0001),

and the nadir point (-41 ± 7.4°C vs -49 ± 7.0°C, respectively; *P* < 0.0001). The interval thaw time to 0°C was significantly shorter in the PVs that showed early reconnection than in those that did not (5.8 ± 3.7 seconds vs 9.9 ± 4.9 seconds, respectively; *P* < 0.0001) (Table 2 and Figure 1A-D). ROC curves for balloon temperatures at each time point and the interval thaw time to 0°C for absence of EPVR are shown in Figure 2A-D. Predictive performance of the nadir balloon temperature for the absence of EPVR was better than that for the balloon temperatures at 30 and 60 seconds (AUC 0.79 [95% CI: 0.76-0.83] vs AUC 0.71 [95% CI: 0.67-0.75] and AUC 0.76 [95% CI: 0.72-0.79], respectively; *P* < 0.05 for each). The best cutoff for balloon temperature at 30 seconds for absence of EPVR was -27°C (sensitivity 53%, specificity 80%), -37°C (sensitivity 69%, specificity 75%), and at the nadir point was -44°C (sensitivity 75%, specificity 70%). The best cutoff for balloon temperature at the nadir point in the LSPV was -44°C (sensitivity 46%, specificity 90%), LIPV -43°C (sensitivity 81%, specificity 60%), RSPV -47°C (sensitivity 79%, specificity 79%), and RIPV -41°C (sensitivity 71%, specificity 75%), respectively. The best cutoff for the interval thaw time to 0°C for the absence of EPVR was 6 seconds (sensitivity 74%, specificity 70) (AUC 0.78 [95% CI: 0.74-0.81]).

3.5 | Time to PVI

The time to PVI was successfully recorded for 201 (40%) of the 502 PVs. EPVR was observed in 18 (9%) of these PVs and not in the other 183 (91%). The time to PVI was significantly longer for the PVs that showed early reconnection than for those that did not (90 ± 50 seconds vs 52 ± 29 seconds, respectively; *P* < 0.0001). The best cutoff for time to PVI for absence of EPVR was < 65 seconds (sensitivity 72%, specificity 67%) (AUC: 0.74 [95% CI: 0.67-0.80]) (Figure 2E). Balloon temperature at the time of achievement of PVI did not differ statistically between PVs that showed and did not show early reconnection (-40.4 ± 6.5°C vs -37.1 ± 8.9°C, respectively; *P* = 0.15). For PVs that did not show reconnection, the time to achievement of PVI was significantly longer and the balloon temperature to achievement of PVI tended to be lower for the LSPV and RIPV than for the RSPV and LIPV (Table 2). Among the PVs that showed reconnection, there was no difference in balloon temperature or time to PVI between the 4 PVs.

3.6 | Procedural complications and clinical outcomes

Transient phrenic nerve palsy occurred in 3 (2%) of 130 patients. No other major complications such as permanent phrenic nerve palsy, pericardial effusion, pericardial tamponade, symptomatic PV stenosis, cerebral embolism, or atrio-esophageal fistula were noted. During the median follow-up of 13.4 (7.1-25.0) months, AF recurred in 17 (13.1%) of the 130 patients. Clinical characteristics did not differ between patients with and without AF recurrence, with the exception of the use of Class I antiarrhythmic drugs (24% vs 8%, respectively; *P* = 0.046). Nadir balloon temperature also did not differ between these patients (Table 3). Freedom from AF was equivalent between

TABLE 2 Balloon temperature at each time point and balloon temperature/time to the PVI for PVs with and without early reconnection after cryoballoon ablation

		PVs with EPVR (n = 86)		PVs without EPVR (n = 416)	P value ^a
Balloon temperature (°C)					
At 30 s	n = 86	-27 ± 5.7	n = 416	-31 ± 5.5	<0.0001
At 60 s	n = 86	-36 ± 5.6	n = 416	-41 ± 5.4	<0.0001
At the nadir point	n = 86	-41 ± 7.4	n = 416	-49 ± 7.0	<0.0001
Thaw time to 0°C (s)	n = 86	5.8 ± 3.7	n = 416	9.9 ± 4.9	<0.0001
Time to PVI (s)					
LSPV	n = 5	74 ± 55	n = 75	60 ± 25 ^b	0.30
LIPV	n = 4	83 ± 60	n = 36	45 ± 20	0.007
RSPV	n = 4	93 ± 57	n = 55	41 ± 31	0.003
RIPV	n = 5	111 ± 37	n = 17	73 ± 37 ^b	0.05
P value ^c		0.6999		< 0.0001	
Temperature to PVI (°C)					
LSPV	n = 5	-41.2 ± 5.8	n = 72	-39.2 ± 11.3 ^b	0.78
LIPV	n = 3	-35 ± 5.2	n = 35	-33.6 ± 6.8	0.74
RSPV	n = 4	-39 ± 7.4	n = 52	-33.8 ± 10.6	0.34
RIPV	n = 4	-44.8 ± 3.1	n = 16	-39.4 ± 8.3	0.24
P value ^c		0.2606		0.0023	

Values are shown as mean ± SD or n (%).

EPVR, early pulmonary vein reconnection; PVI, pulmonary vein isolation; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein.

^aBy Student's *t* test.

^b*P* < 0.05 versus LIPV and RSPV by Tukey-Kramer post hoc test.

^cBy ANOVA.

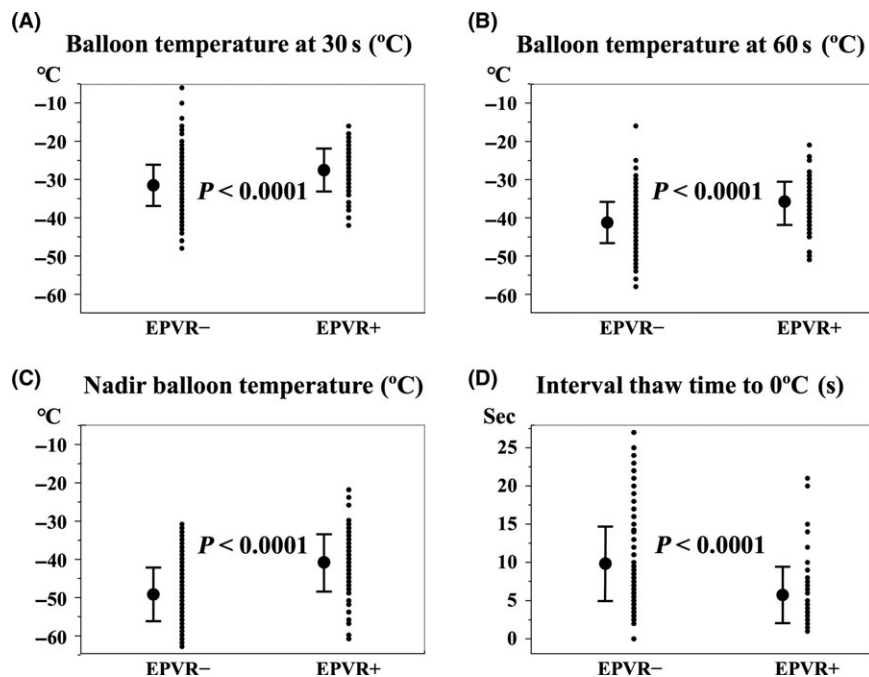


FIGURE 1 Scatter plot of balloon temperatures at 30 s (A), 60 s (B), and the nadir point (C), and the interval thaw time to 0°C (D) in relation to occurrence versus nonoccurrence of EPVR. Mean + SD values are shown at the left. *P* values were obtained by unpaired *t* test. EPVR, early pulmonary vein reconnection

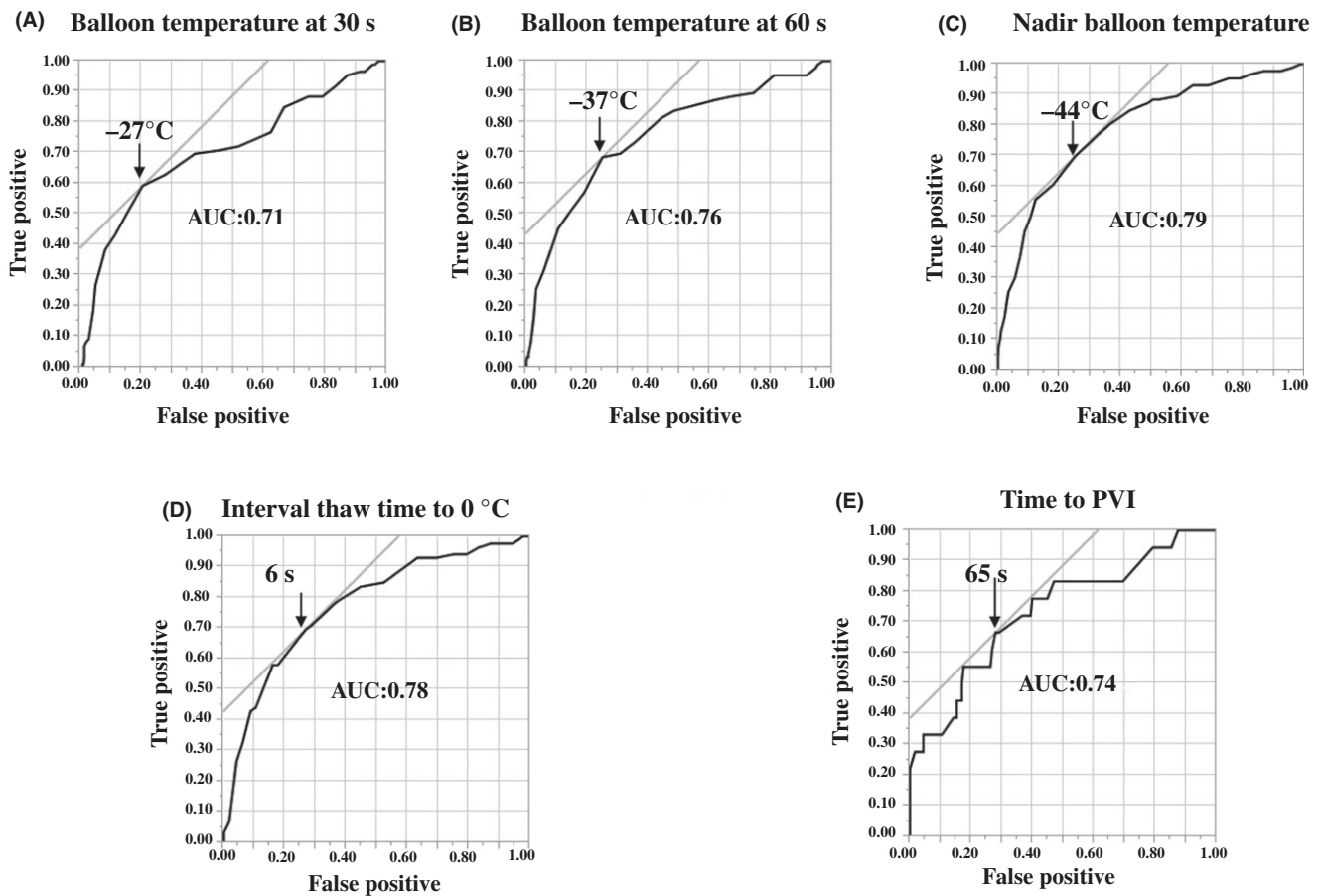


FIGURE 2 ROC curves for prediction of absence of EPVR according to cryoballoon temperature at 30 s (A), at 60 s (B), at the nadir point (C), interval thaw time to 0°C (D), and time to PVI (E). ROC, receiver operating characteristic; EPVR, early pulmonary vein reconnection; AUC, area under the curve; PVI, pulmonary vein isolation

patients with and without EPVR (8/69 [13%] vs 9/61 [15%], respectively; $P = 0.85$) ($P = 0.75$ by log-rank test, Figure 3). The AF recurrence rate was low among patients with persistent AF and equivalent to that among patients with paroxysmal AF (11% vs 14%, respectively; $P = 0.58$). However, the use of bepridil after ablation was significantly more prevalent among patients with persistent AF than among those with paroxysmal AF (57% vs 21%, respectively; $P < 0.0001$).

4 | DISCUSSION

Our main study findings were as follows: First, EPVR was related to male sex, younger age (age < 65 years), persistent AF, and a low CHA2DS2-VASC score. Second, residual leaks were more prevalent and the PV diameter longer for PVs with EPVR than for those without, but the association was not for all PVs. Third, although balloon temperatures at the different time points were higher and the time to PVI was longer for PVs showing reconnection than for those not showing reconnection, balloon temperature at the nadir point was shown to be particularly high, and the time to PVI differed between the 4 PVs. Fourth, no ablation-related variables, including balloon

temperatures and EPVR, were associated with AF recurrence, and the AF recurrence rate was very low, regardless of whether patients had paroxysmal AF or persistent AF.

4.1 | Balloon temperatures and EPVR

We found balloon temperature at 30 seconds, at 60 seconds, and at the nadir point to be significantly higher and the interval thaw time to 0°C to be significantly shorter in patients with EPVR than in those without EPVR. Touch-up ablation for residual PV potentials after CBA has been reported for 2%-17% of PVs.¹⁷⁻¹⁹ The need for touch-up ablation to achieve PVI reached 17% of our targeted PVs and affected 47% of our patients. Patients in most of the recently reported studies had paroxysmal AF, whereas persistent AF was quite prevalent among our study patients (35%). It might be that a balloon of 28 mm in diameter is too small for good balloon-tissue surface contact when the PV antrum is large, as in cases of persistent AF. Our patients with EPVR were likely to have persistent AF, and the LA diameter and LA volume were greater in these patients than in the other patients. According to our multivariable analysis, age > 65 years was the strongest predictor of EPVR. We speculate

TABLE 3 Clinical characteristics, echocardiographic variables, and balloon temperatures in patients with and without recurrence of AF after cryoballoon ablation

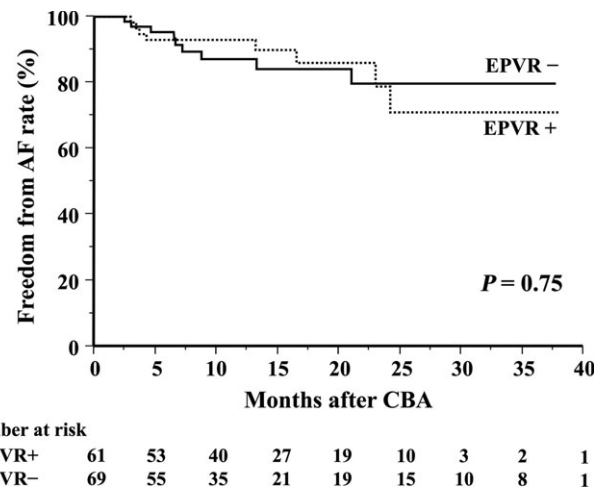
	AF recurrence (n = 17)	No AF recurrence (n = 113)	P value ^a
Age (y)	62.1 ± 8.6	64.5 ± 10.0	0.34
Male sex	10 (59)	80 (71)	0.32
Persistent AF	5 (29)	41 (36)	0.58
Body mass index	22.7 ± 2.8	24.1 ± 4.3	0.20
Congestive heart failure	1 (6)	8 (7)	0.86
Hypertension	9 (53)	68 (60)	0.57
Diabetes mellitus	3 (18)	22 (19)	0.86
Stroke/TIA	1 (6)	12 (11)	0.54
Vascular disease	0 (0)	8 (7)	0.26
CHADS2 score	0.9 ± 0.9	1.2 ± 1.1	0.24
CHA2DS2-VASc score	1.8 ± 1.1	2.1 ± 1.5	0.33
Ejection fraction (%)	70.1 ± 6.3	66.5 ± 10.0	0.16
LA diameter (mm)	37.3 ± 4.8	38.9 ± 6.4	0.33
LA volume (mL)	44.6 ± 5.0	45.5 ± 1.8	0.86
Presence of EPVR	8 (47)	53 (47)	0.99
Antiarrhythmic drugs used after CBA			
Class I	4 (24)	9 (8)	0.046
Bepridil	7 (41)	37 (33)	0.49
Nadir balloon temperature (°C)			
RSPV	−52.1 ± 6.5	−51.9 ± 6.9	0.89
RIPV	−41.2 ± 7.8	−44.3 ± 8.4	0.16
LSPV	−52.0 ± 5.9	−51.0 ± 6.0	0.52
LIPV	−43.4 ± 5.8	−44.5 ± 5.7	0.48
4 PVs (mean)	−47.3 ± 3.8	−47.9 ± 4.3	0.58

Values are shown as mean ± SD or n (%).

AF, atrial fibrillation; TIA, transient ischemic attack; CHADS₂, congestive heart failure; hypertension, age ≥ 75 years, diabetes mellitus, and stroke; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65–74 years, and sex category; LA, left atrium; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein.

^aBy Student's *t* test, Mann-Whitney test, or chi-square test, as appropriate.

that the tissue in young patients is healthier than that in older patients, thus requiring greater cryothermal energy to isolate the PVs, and this issue might be compounded by inadequate balloon-tissue surface contact if a young patient is being treated for persistent AF. Indeed, a larger maximum PV ostial diameter potentially leading to an inadequate balloon-tissue surface contact in such patients as persistent AF was strongly associated with EPVR. The association was prominent especially with the LSPV and RIPV. In most recently reported studies, PVI was assessed with an Achieve circular mapping catheter,^{18,20} and thus, the PV potentials were underestimated especially in the antral region.²¹ We searched meticulously for any residual PV potentials by means of 3D voltage remapping, and we looked

**FIGURE 3** Kaplan-Meier curve showing freedom from atrial fibrillation after cryoballoon ablation according to the presence or absence of EPVR. CBA, cryoballoon ablation; EPVR, early pulmonary vein reconduction

for potentials not only inside the PVs but also in the antral region. Thus, the characteristics of our patients and our procedure might account for the incidence of EPVR in our patient series.

Adequate balloon temperature following PV occlusion with good balloon-tissue surface contact is important for successful PVI. PV occlusion was generally established by contrast leakage. Our data showed the presence of a residual leak leads to the presence of EPVR, which is well in line with the other reports.^{3-10,17-20} We found that a balloon temperature less than −27°C at 30 seconds, less than −37°C at 60 seconds, and less than −44°C at the nadir point and that a >6-seconds interval thaw time to 0°C were all fairly accurate for predicting the absence of EPVR. Similarly, several reported studies of second-generation CBA have shown achievement of a balloon temperature of −40°C within the first 60 seconds of cryoenergy application to be an independent predictor of durable PVI.²² In previously reported studies, a minimal temperature of less than −51°C was shown to predict successful PVI without acute PV reconduction.^{10,18} In our study, the nadir balloon temperature also had the best prognostic performance for the absence of EPVR, but clinically, balloon temperature during the first 30 seconds or 60 seconds of CBA would be more important for early prediction of PV reconductions. For example, if the balloon temperature at 30 seconds is greater −27°C or at 60 seconds is greater than −37°C, it would be better to terminate the ablation and reposition the balloon so that a better temperature can be achieved. Further, in our study, < 65 seconds for the time to PVI was shown to be a good predictor for prevention of EPVR. A previous study showed 60 seconds to PVI to be predictive of sustained success (i.e., absence of reconduction).^{22,23}

Our study showed that, in addition to there being an optimum temperature to be reached at each of various time points, the optimum time to isolation varies between PVs. The optimum time to PVI appears to be significantly longer, and balloon temperature appears to be lower for the LSPV and RIPV than for the LIPV and RSPV. We

performed cryoballoon ablation sequentially first from the LSPV to the LIPV, then from the RIPV to the RSPV. It is possible that lesions created in the carina regions of the LSPV and RIPV overlapped the new ablation lesion sets around the LIPV and RSPV, and this might have shortened the time to isolation of the LIPV and RSPV. The time to PVI might also be explained in part by a thick LSPV or RIPV sleeve.¹² Therefore, the CBA time can be shortened if there is a potential risk of phrenic nerve injury or esophageal injury during ablation of the RSPV or LIPV located close to these collateral tissues. We also found an interesting finding that the maximum RSPV ostial diameter correlated negatively with balloon temperatures, but not for the other PVs. This suggests that the balloon is easily moved to the distal PV when the operators place the balloon in an enlarged RSPV ostium to establish appropriate balloon-tissue surface contact. Thus, careful balloon manipulation to prevent phrenic nerve injury or PV stenosis will be needed especially for cases in whom the PV ostium in the RSPV is large.

4.2 | Clinical outcomes after CBA

Clinical AF recurrence at a median follow-up of 13.4 months was detected in only 17 (13%) of 130 study patients. Recent studies comparing CF-guided RF ablation with CBA have shown statistical equivalence between the two technologies.^{7,8} In our study, the use of class I antiarrhythmic drugs was associated with AF recurrence, because those were often administered due to AF recurrence. Other than that, we did not find any predictors of AF recurrence, including the presence of EPVR or the nadir balloon temperature. In standard RF-based PVI, spontaneous PV reconnection and DC have been reported to predict PV reconnection or AF recurrence despite additional touch-up RF application to the involved sites.²⁴⁻²⁶ We observed spontaneous early PV-LA reconnection and DC in 3% and 5% of PVs in 1% and 16% of patients, respectively, rates lower than those reported for spontaneous PV reconnection or DC when RF-based PVI is performed.^{27,28} This was possibly because CBA, in comparison with RF-based ablation, produces wider and thus more durable lesions around the PV ostium.⁹ The durability of CBA-based PV lesions may have lessened the possibility of AF recurrence that would have arisen from PV reconnections. PVI is the only established strategy for both persistent AF and paroxysmal AF.^{29,30} Interestingly, in our patient series, the AF recurrence rate among patients with persistent AF was very low (only 10.9%) and equivalent to that among the patients with paroxysmal AF. Although the use of bepridil was more prevalent among our patients with persistent AF than among those with paroxysmal AF, the wide, durable PV lesions created by CBA and the touch-up RF ablation to EPVR sites identified by 3D remapping may, in part, confer favorable outcomes even in patients with persistent AF.

4.3 | Study limitations

Our study was limited by the size of the patient groups. Nonetheless, the acute and chronic post-CBA outcomes, including AF

recurrence, were similar to those reported by other investigators. We did not analyze the CBA lesions and PV reconnection sites in the chronic phase in patients in whom AF recurred, and therefore, it remains unclear whether the recurrence was due to PV reconnections, non-PV triggers, or a remodeled LA substrate. Finally, time to PVI can be used only when PV potentials are recorded by the circular mapping catheter during the CBA, but unfortunately, PV potentials were not always recorded in the inferior PVs that frequently had an EPVR. Nonetheless, time to PVI will be useful in cases in whom PV potentials can be recorded in the inferior PVs. Even in cases in whom PV potentials are not recorded, we can use alternative indicators of balloon temperatures for predicting an absence of EPVR.

5 | CONCLUSIONS

We found the nadir cryoballoon temperature to have the best predictive performance for absence of EPVR after ablation for AF. Time to PVI < 65 seconds may be a useful variable predictive of durable PVI when a real-time recording of PV potentials is obtained, but both the balloon temperature and time to PVI differ between the 4 PVs. Procedural data can be used to determine whether CBA is performed safely and effectively. Even though inappropriate nadir balloon temperatures leading to the EPVR are observed, high and equivalent success rates can be expected for patients with paroxysmal and those with persistent AF if touch-up RF ablation of EPVR sites identified by 3D voltage mapping is performed.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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