



# Circulatory dynamics changes are an additional predictor of successful pulmonary vein isolation during cryoballoon ablation

Takatsugu Kajiyama<sup>1</sup> · Shinsuke Miyazaki<sup>2</sup> · Rikuta Hamaya<sup>1</sup> · Tomonori Watanabe<sup>1</sup> · Kazuya Yamao<sup>1</sup> · Shigeki Kusa<sup>1</sup> · Miyako Igarashi<sup>1</sup> · Hiroaki Nakamura<sup>1</sup> · Hitoshi Hachiya<sup>1</sup> · Yoshito Iesaka<sup>1</sup>

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## Abstract

The association between circulatory dynamics changes during cryoballoon applications and a successful pulmonary vein isolation (PVI) is unknown. Seventy atrial fibrillation patients who underwent PVI with 28-mm second-generation cryoballoons and single 3-min freezes were included. Intra-procedural parameters including circulatory dynamics changes during cryoapplications, were compared between 113 successful applications (30 left superior PVs[LSPVs], 30 left inferior PVs[LIPVs], 25 right superior PVs[RSPVs], and 28 right inferior PVs[RIPVs]) and 47 failed applications (10 LSPVs, 9 LIPVs, 8 RSPVs, and 20 RIPVs). In all individual PVs, lower nadir balloon temperatures (MinTemps) and longer thawing times (ThawTimes) significantly predicted a successful PVI. In addition, greater systolic blood pressure drops following releasing the PV occlusion (SBP-drops) significantly predicted a successful right PV PVI, and longer elapse times during SBP-drops significantly predicted a successful RIPV PVI. Composite parameters incorporating MinTemps and ThawTimes, SBP-drops, and ThawTimes showed the highest area under the curve to predict a successful left PV (0.876 for LSPVs, 0.851 for LIPVs) and right PV (0.927 for RSPVs, 0.980 for RIPVs) PVI, respectively. If the ThawTime ( $\geq 30$  s) and SBP-drop ( $\leq -21$  mmHg) cutoff values were achieved for the RIPVs, the positive predictive value was 100%. In contrast, if both criteria were not achieved for the RIPVs, the negative predictive value was 100%. In the second-generation cryoballoon PVI, the MinTemp and ThawTime were significantly associated with acute success for all four PVs. In addition, SBP-drops further improved the accuracy of predicting a successful right PV PVI, especially of the RIPV.

**Keywords** Cryoballoon · Pulmonary vein isolation · Atrial fibrillation · Catheter ablation · Physiology

## Introduction

Pulmonary vein isolation (PVI) is a fundamental curative therapy for paroxysmal atrial fibrillation (AF) [1, 2]. Although radiofrequency (RF) catheter ablation have been established as a standard procedure, the cryoballoon (CB) technology is becoming a major alternative thanks to a less-complicated technique, shorter procedure time, and higher durability of the PVI than RF-PVI [3–6]. There have been multiple studies reporting the non-inferiority of the

mid-term outcome after the CB-PVI when compared to RF-PVI [5].

One of the vital factors for a successful CB-PVI is the complete occlusion of the entire ostium of the PV, and freezing with a complete occlusion results in a significant impact on the balloon temperature and circulatory parameters [7–9]. In brief, the nadir balloon temperature is lower with successful than failed freezes [7, 8]. The blood pressure (BP) rises during freezing and sharply drops after releasing the PV occlusion during completely occluded cryoapplications [9]. This is presumably because freezing of atrial tissue might result in a BP elevation, and the peripheral circulation of dammed chilled blood in the distal PV might cause a sharp BP drop [9]. However, those intra-procedural parameters significantly differ among the 4 individual PVs due to the different PV anatomies and CB position during the applications. The purpose of the present study was to explore the intra-procedural parameters, including the circulatory

✉ Takatsugu Kajiyama  
tak4poincar@gmail.com

<sup>1</sup> Cardiology Division, Cardiovascular Center, Tsuchiura Kyodo Hospital, 4-1-1 Otsuno, Tsuchiura 300-0028, Ibaraki, Japan

<sup>2</sup> Department of Cardiovascular Medicine, Faculty of Medical Sciences, University of Fukui, Fukui, Japan

dynamics changes during the cryoapplication, predicting a successful CB-PVI of all 4 individual PVs.

## Methods

### Study population

We retrospectively enrolled 70 AF patients who underwent CB-PVI using second-generation CBs (Arctic Front Advance, Medtronic, Minneapolis, MN) in our institute between March and December 2016. The CB-PVI was performed with a single 3-min freeze strategy using exclusively 28-mm CBs. To calculate the optimal cutoff values for a successful CB-PVI, the study included 113 successful applications in 32 patients in whom all 4 PVs were successfully isolated by a single application (group A), and 47 failed applications in 38 patients who had at least one failed freezing (group B). Cryoapplications that were discontinued before 180 s were excluded from the analysis. All the patients gave written informed consent prior to the procedure. The study protocol was approved by the hospital's institutional review board. The study complied with the Declaration of Helsinki.

### Ablation procedure

All antiarrhythmic drugs were discontinued for at least five half-lives prior to the procedure. The surface electrocardiogram, bipolar intracardiac electrograms, and femoral intra-arterial BP were continuously monitored and stored on a computer-based digital recording system (LabSystem PRO, Bard Electrophysiology, Lowell, MA). The bipolar electrograms were filtered from 30 to 500 Hz. The procedure was performed under moderate sedation obtained with dexmedetomidine. A 100 IU/kg body weight of heparin was administered immediately following the venous access, and heparinized saline was additionally infused to maintain the activated clotting times at 300–350 s. A single transseptal puncture was performed using an RF needle (Baylis Medical., Montreal, QC) and 8-Fr long sheath (SL0, AF Division, SJM, Minneapolis, MN). The transseptal sheath was exchanged over a guidewire for a 15-Fr steerable sheath (Flexcath Advance, Medtronic). A 20-mm circular mapping catheter (Lasso, Biosense-Webster, Diamond Bar, CA) was used for mapping all PVs before and after the cryoablation to confirm an electrical isolation. A spiral mapping catheter (Achieve, Medtronic) was used to advance the CB into the PV for support and mapping the PV potentials. Following sealing at the PV antrum, a complete occlusion was confirmed by injecting contrast medium. This was followed by a freeze cycle of 180 s. No additional applications were performed after the isolation. Touch-up radiofrequency

ablation was applied in cases with residual PV potentials after a maximum of 3 cryoapplications. To avoid bilateral phrenic nerve injury, all CB applications were applied under diaphragmatic electromyography monitoring [10]. When the balloon nadir temperatures exceeded  $-60\text{ }^{\circ}\text{C}$  or phrenic nerve injury was suspected, the application was interrupted [11]. As the standard deflation technique, the intraballoon shaft was manually straightened when the intraballoon temperature reached  $15\text{ }^{\circ}\text{C}$  to rewrap the balloon prior to the balloon deflation. The procedural endpoint was defined as an electrical PVI.

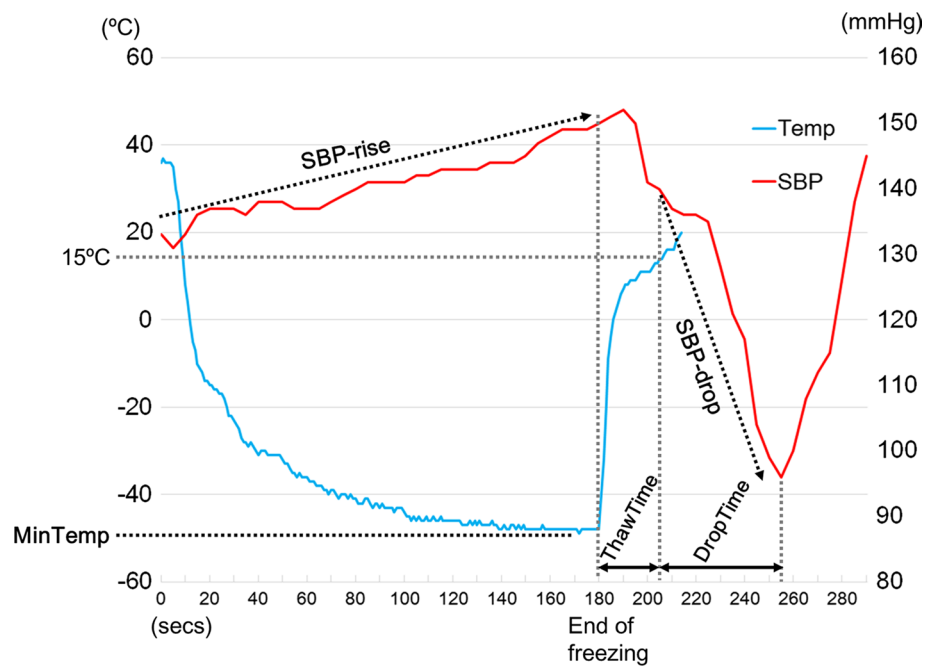
### Evaluation of the circulatory dynamics

The changes in the circulatory parameters were evaluated by comparing the systolic BP (SBP) at specific time points: (1) the beginning and the end of the 3-min freezing phase ( $T_{0\text{ min}}$  and  $T_{3\text{ min}}$ ), (2) at a balloon temperature of  $15\text{ }^{\circ}\text{C}$  during the thawing phase ( $T_{15\text{ }^{\circ}\text{C}}$ ), and (3) at the nadir of the BP after balloon deflation ( $T_{\text{nadir}}$ ). An interval thaw time at  $15\text{ }^{\circ}\text{C}$  was selected since that was generally the CB temperature limit at which the balloon was manually stretched by the operator on termination of the cryoballoon application. The nadir balloon temperature (MinTemp), rise in the SBP from  $T_{0\text{ min}}$  to  $T_{3\text{ min}}$  (SBP-rise), drop in the SBP after the  $T_{15\text{ }^{\circ}\text{C}}$  to  $T_{\text{nadir}}$  (SBP-drop), and elapsed time from  $T_{3\text{ min}}$  to  $T_{15\text{ }^{\circ}\text{C}}$  (ThawTime) and  $T_{15\text{ }^{\circ}\text{C}}$  to  $T_{\text{nadir}}$  (DropTime) were compared between the successful and failed freezes (Fig. 1). The parameters were also compared between the successful cryoapplications during AF and sinus rhythm. All the analyses were performed individually in the 4 PVs, including the left superior (LSPVs), left inferior (LIPVs), right superior (RSPVs), and right inferior PVs (RIPVs).

### Statistics

All statistical analyses were performed using R version 3.4.1 software [12]. The continuous variables are reported as mean values  $\pm$  standard deviations and were compared using a Student's *t* test. Differences between proportions were compared using Fisher's exact tests. Differences in the mean values between three or more groups were evaluated by a Welch's ANOVA. The changes in the circulatory parameters and intra-PV analyses of each predictor were compared by a paired *t* test. A receiver-operator characteristics (ROC) curve of each parameter was calculated to quantify the area under the curve (AUC). The ROC curves were exclusively calculated for the parameters that significantly differed between the successful and failed freezes. As for the composite predictors incorporating multiple parameters, the AUC of the ROC curve was also calculated. The numbers of the pretest probability of an acute success for all 4 PVs were quoted from the previous report [7]. All *p* values were

**Fig. 1** Transition of the SBP and in-balloon temperature during the freezing and thawing phases of the cryoapplications. In-procedural parameters were defined as follows: MinTemp: nadir in-balloon temperature; SBP-rise: rise in the systolic blood pressure during the freezing phase; SBP-drop: sharp drop of the systolic blood pressure after releasing the PV occlusion; ThawTime: thawing time (from the end of the freezing to a 15 °C balloon temperature); DropTime: elapsed time during the SBP-drop



two-sided, and statistical significance was established at a  $p < 0.05$ .

## Results

### Procedural results

The patient characteristics are shown in Table 1. In group A, among a total of 128 successful CB applications, 15 were interrupted during the 3-min freeze. The remaining 113 applications (30 LSPVs, 30 LIPVs, 25 RSPVs, and 28 RIPVs) in which a 3-min freeze was applied were further analyzed. In group B, a total of 47 failed freezes (10 LSPVs, 9 LIPVs, 8 RSPVs, 20 RIPVs) were analyzed.

### Nadir balloon temperature and thawing time

In group A, the mean MinTemp was  $-52.1 \pm 5.4$  °C, which significantly differed among the 4 PVs ( $p < 0.001$ ) (Table 2). In group B, the mean MinTemp was  $-44.0 \pm 6.0$  °C, and it was similar among the 4 PVs ( $p = 0.251$ ). The mean MinTemp was significantly lower in group A than group B ( $p < 0.0001$ ), and the results were consistent for the 4 individual PVs. The AUCs of the ROC curves and best cutoff values are noted in Table 3.

As for the time course, both the ThawTime ( $40.6 \pm 11.8$  vs.  $23.4 \pm 9.8$  s,  $p < 0.001$ ) and DropTime ( $21.5 \pm 7.5$  vs.  $15.7 \pm 9.2$  s,  $p < 0.001$ ) were significantly longer in group A than group B. The ThawTime significantly differed among the 4 PVs both in group A ( $p < 0.001$ ) and group B

**Table 1** Patient characteristics

	Group A	Group B	<i>p</i> value
Patients, <i>n</i>	32	38	
Female (%)	11 (34.4)	15 (38.5)	0.807
BMI (kg/m <sup>2</sup> )	24.6 ± 3.6	23.7 ± 4.1	0.331
Height (cm)	164.8 ± 9.9	163.7 ± 9.3	0.636
Weight (kg)	67.2 ± 13.5	63.4 ± 11.9	0.215
LAD (mm)	37.2 ± 5.2	37.4 ± 6.6	0.908
LAV (ml)	44.0 ± 12.4	45.1 ± 17.5	0.758
LVDD (mm)	45.1 ± 4.1	44.4 ± 5.1	0.546
LVEF (%)	67.3 ± 6.3	67.0 ± 6.9	0.832
PVs, <i>n</i>	113	47	
Freezing during AF, <i>n</i> (%)	23 (20.4)	17 (36.2)	0.045
Analyzed PVs, <i>n</i> (%)			
LS	30 (26.5)	10 (21.3)	
LI	30 (26.5)	9 (19.1)	
RS	25 (22.1)	8 (17.0)	
RI	28 (24.8)	20 (42.6)	

AF atrial fibrillation, BMI body mass index, LAD left atrial diameter, LAV left atrial volume, LI left inferior, LS left superior, LVDD diastolic left ventricular diameter, LVEF left ventricular ejection fraction, PV pulmonary vein, RI right inferior, RS right superior

( $p = 0.013$ ). The DropTime significantly differed among the 4 PVs in group B ( $p = 0.042$ ) but not in group A ( $p = 0.060$ ). The difference in the ThawTime between group A and group B was still significant for all 4 PVs (Table 2). The AUC of the ThawTime is shown in Table 3. In contrast, the difference in the DropTime between group A and group B was

**Table 2** Comparison of the in-procedural parameters between successful and failed freezes

		PVI	LSPV	LIPV	RSPV	RIPV
MinTemp (°C)	Success		$-52.2 \pm 4.6$	$-47.9 \pm 3.8$	$-55.3 \pm 4.4$	$-53.8 \pm 5.8$
	Failure		$-45.8 \pm 3.7$	$-43.0 \pm 7.9$	$-46.4 \pm 6.0$	$-42.5 \pm 5.8$
	<i>p</i> value		<0.001	0.015	<0.001	<0.001
SBP-drop (mmHg)	Success		$-46.7 \pm 22.4$	$-39.4 \pm 17.8$	$-43.5 \pm 20.5$	$-46.9 \pm 14.8$
	Failure		$-39.7 \pm 26.8$	$-30.9 \pm 12.1$	$-25.5 \pm 13.7$	$-18.3 \pm 12.7$
	<i>p</i> value		0.420	0.188	0.023	<0.001
ThawTime (secs)	Success		$44.1 \pm 13.3$	$33.8 \pm 8.5$	$48.2 \pm 9.2$	$37.5 \pm 10.3$
	Failure		$29.2 \pm 6.7$	$23.1 \pm 12.9$	$26.3 \pm 13.6$	$19.4 \pm 6.1$
	<i>p</i> value		0.002	0.006	<0.001	<0.001
DropTime (secs)	Success		$23.3 \pm 8.2$	$19.8 \pm 5.3$	$19.6 \pm 10.3$	$23.0 \pm 4.9$
	Failure		$20.6 \pm 13.0$	$17.9 \pm 6.7$	$17.4 \pm 8.3$	$11.6 \pm 7.0$
	<i>p</i> value		0.445	0.387	0.576	<0.001

*DropTime* elapsed time during SBP-drop, *LIPV* left inferior PV, *LSPV* left superior PV, *MinTemp* nadir in-balloon temperature, *RIPV* right inferior PV, *RSPV* right superior PV, *SBP-drop* drop of systolic blood pressure after releasing PV occlusion, *ThawTime* thawing time

**Table 3** Predictors of a successful cryoapplication

PV	Predictor	AUC	BCO	Sensitivity	Specificity	PPV	NPV
LSPV	MinTemp (°C)	0.873	$\leq -49$	0.700	0.900	0.968	0.413
	ThawTime (secs)	0.833	$\geq 37$	0.655	0.900	0.965	0.380
LIPV	MinTemp (°C)	0.780	$\leq -43$	0.933	0.778	0.941	0.755
	ThawTime (s)	0.828	$\geq 28$	0.897	0.778	0.938	0.668
RSPV	MinTemp (°C)	0.908	$\leq -53$	0.840	0.875	0.989	0.292
	SBP-drop (mmHg)	0.755	$\leq -37$	0.640	0.875	0.986	0.155
	ThawTime (s)	0.906	$\geq 35$	1.000	0.875	0.991	1.000
RIPV	MinTemp (°C)	0.914	$\leq -48$	0.857	0.800	0.931	0.639
	SBP-drop (mmHg)	0.931	$\leq -22$	1.000	0.750	0.927	1.000
	ThawTime (s)	0.941	$\geq 26$	0.926	0.850	0.951	0.784
	DropTime (s)	0.910	$\geq 17$	0.893	0.800	0.934	0.702

*AUC* area under the receiver-operating characteristic curve, *BCO* best cutoff value, *LIPV* left inferior PV, *LSPV* left superior PV, *NPV* negative predictive value, *PPV* positive predictive value, *RIPV* right inferior PV, *RSPV* right superior PV

significant only for the RIPVs (Table 2), and the AUC was 0.910 (Table 3).

### Circulatory dynamics during the freezing and thawing phases

The SBP significantly increased during the 3-min freeze phase from  $138.7 \pm 28.8$  to  $148.0 \pm 28.3$  mmHg in group A ( $p < 0.001$ ) and from  $144.9 \pm 33.0$  to  $152.0 \pm 31.2$  mmHg in group B ( $p < 0.001$ ). The magnitude of the SBP rise differed among the 4 PVs in group A ( $11.5 \pm 18.7$  in the LSPV,  $14.5 \pm 13.0$  in the LIPV,  $6.3 \pm 11.0$  in the RSPV, and  $3.8 \pm 12.6$  in the RIPV,  $p = 0.013$ ) but not in group B ( $p = 0.132$ ). The magnitude of the SBP rise was similar between group A and group B ( $9.2 \pm 14.7$  vs.  $7.1 \pm 13.6$ ,  $p = 0.403$ ).

After the balloon temperature reached 15 °C, the SBP significantly dropped from  $136.4 \pm 26.8$  to  $94.6 \pm 18.5$  mmHg in group A ( $p < 0.001$ ) and from  $138.1 \pm 27.7$  to  $102.2 \pm 27.9$  mmHg in group B ( $p < 0.001$ ). The magnitude of the SBP-drop was significantly greater in group A than group B ( $-44.1 \pm 19.1$  vs.  $-26.5 \pm 19.4$ ,  $p < 0.001$ ). The difference was significant for the right PVs but not the left PVs (Table 2). The AUC of the SBP-drop for a successful CB-PVI of the RSPVs and RIPVs was 0.755 and 0.931, respectively (Table 3).

### Impact of the rhythm on the procedural parameters

The MinTemp did not significantly differ during sinus rhythm and AF in the LSPVs ( $-52.5 \pm 4.6$  vs.  $-51.0 \pm 4.5$ ,  $p = 0.481$ ), LIPVs ( $-48.4 \pm 3.9$  vs.  $-45.7 \pm 2.9$ ,  $p = 0.119$ ),

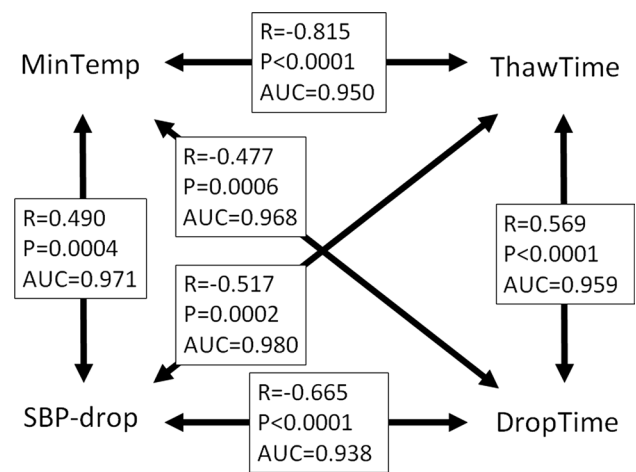
and RIPVs ( $-53.2 \pm 5.7$  vs.  $-55.3 \pm 6.1$ ,  $p = 0.427$ ), but significantly differed in the RSPVs ( $-56.2 \pm 3.1$  vs.  $-50.5 \pm 7.2$ ,  $p = 0.013$ ). The ThawTime did not significantly differ in the LSPVs ( $43.7 \pm 13.8$  vs.  $45.5 \pm 12.2$ ,  $p = 0.778$ ), LIPVs ( $33.9 \pm 9.1$  vs.  $33.0 \pm 4.8$ ,  $p = 0.830$ ), RSPVs ( $48.6 \pm 9.8$  vs.  $45.3 \pm 1.2$ ,  $p = 0.574$ ), and RIPVs ( $36.1 \pm 10.3$  vs.  $42.1 \pm 9.7$ ,  $p = 0.212$ ). The DropTime did not significantly differ in the LSPVs ( $24.7 \pm 7.8$  vs.  $17.7 \pm 8.0$ ,  $p = 0.060$ ), LIPVs ( $19.5 \pm 4.5$  vs.  $20.8 \pm 8.3$ ,  $p = 0.591$ ), RSPVs ( $19.9 \pm 6.9$  vs.  $18.5 \pm 22.9$ ,  $p = 0.814$ ), and RIPVs ( $22.3 \pm 4.9$  vs.  $25.1 \pm 4.7$ ,  $p = 0.191$ ). The SBP-drop did not significantly differ in the LSPVs ( $-48.9 \pm 23.5$  vs.  $38.0 \pm 16.1$ ,  $p = 0.296$ ), LIPVs ( $-42.5 \pm 18.1$  vs.  $-27.3 \pm 10.3$ ,  $p = 0.062$ ), RSPVs ( $-45.3 \pm 20.6$  vs.  $-34.0 \pm 19.9$ ,  $p = 0.324$ ), and RIPVs ( $-48.0 \pm 13.4$  vs.  $-43.6 \pm 19.3$ ,  $p = 0.500$ ).

### Comparison of the parameters predicting a successful PVI

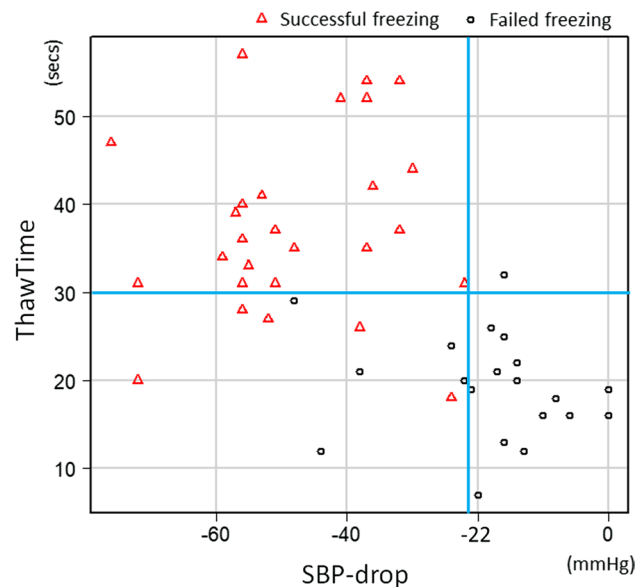
Table 3 summarizes the significant predictors and their best cutoff values with the sensitivities, specificities, positive predictive values (PPVs), and negative predictive values (NPVs). The MinTemp and ThawTime were both significant predictors for all PVs. These 2 parameters were significantly correlated ( $R = -0.715$ ,  $p < 0.001$ ), while the per-PV analyses still remained significant for the LSPVs ( $R = -0.755$ ,  $p < 0.001$ ), LIPVs ( $R = -0.638$ ,  $p < 0.001$ ), RSPVs ( $R = -0.768$ ,  $p < 0.001$ ), and RIPVs ( $R = -0.815$ ,  $p < 0.001$ ). The AUC of each significant parameter was statistically similar for each PV (LSPV:  $p = 0.339$ , LIPV:  $p = 0.578$ , RSPV:  $p = 0.100$ , RIPV:  $p = 0.324$ ).

For the individual PVs, we tried to build a composite predictor incorporating 2 different factors. In the univariate analysis for the left PVs, only the MinTemp and ThawTime were significant predictors. For the LSPVs and LIPVs, the AUC of the composite predictor was 0.876 and 0.851, respectively, which was not significantly better than the univariate models. As for the RSPVs, we calculated the composite predictors including any 2 of the MinTemp, ThawTime, and SBP-drop. The AUC of the composite predictor calculated from the MinTemp + ThawTime, MinTemp + SBP-drop, and ThawTime + SBP-drop was 0.917, 0.915, and 0.927, respectively.

As for the RIPVs, the AUC of the 4 parameters was equivalent over 0.9. The correlation coefficients between every 2 factors as well as the AUC of the composite predictors for the RIPVs are shown in Fig. 2. The highest correlation was observed between the MinTemp and ThawTime. The lowest correlation was between the MinTemp and DropTime. As for the ROC curve analyses, the highest AUC was obtained from the combination of the SBP-drop and ThawTime, while the lowest was the combination of the SBP-drop and DropTime. If the cutoff values of the



**Fig. 2** Correlation coefficient and AUC of the composite predictors incorporating every two parameters during freezes of the RIPVs. The highest and lowest correlations were observed with the combination of the MinTemp/ThawTime and MinTemp/DropTime, respectively. The highest and the lowest AUCs were obtained from the ThawTime/SBP-drop and SBP-drop/DropTime, respectively. AUC: area under the receiver operating characteristics curve, R: correlation coefficient. The other abbreviations are the same as in Fig. 1



**Fig. 3** Overlay of the best cutoff values of the ThawTime and SBP-drop on a scattered plot of all freezes for the RIPVs. If both the criteria were achieved, all freezes were found to be successful. If both the criteria were not achieved, all freezes turned out to be failures

ThawTime ( $\geq 30$  s) and SBP-drop ( $\leq -21$  mmHg) were achieved for the RIPVs, the positive predictive value was 100%. In contrast, if both the criteria were not achieved, the negative predictive value was 100% (Fig. 3).

## Discussion

To the best of our knowledge, this is the first report to explore the parameters, including the circulatory dynamics changes predicting a successful PVI in each individual PV, in the CB-PVI. We found that (1) both the MinTemp and ThawTime were significant parameters predicting a successful PVI of all 4 PVs, and (2) the SBP-drop was a significant parameter predicting a successful PVI of the right PVs, and a composite parameter incorporating the ThawTime and SBP-drop improved the diagnostic accuracy for the right PVs, especially the RIPV.

### Predictors of a successful PVI

When analyzing all PVs altogether, the MinTemp and ThawTime are already known to be predictors of successful cryoapplications for both the 1st-generation [13] and 2nd-generation CB ablation [7, 8]. Our study confirmed the results in an analysis of the 4 individual PVs, and also there was a strong correlation between the MinTemp and ThawTime. Moreover, we revealed that the magnitude of the SBP-drop could be an additional predictor of a successful freeze of the right PVs. A previous study showed a gradual rise in the SBP during the freezing phase and a recovery of the elevated SBP during the initial thawing phase followed by a sharp drop of the SBP after releasing the PV occlusion [9]. The present study clarified that the magnitude of the SBP rise was similar between a successful and failed application, while the magnitude of the SBP drop was more evident in a successful application. That was because a sharp SBP drop is provoked by peripheral circulation of dammed chilled blood [9], and the amount might be greater in a complete occlusion than an incomplete occlusion.

Although the magnitude of the SBP-drop was greater for successful than failed freezes of all 4 PVs, the utility of the SBP-drop for predicting a successful freeze was most prominent for the RIPV. We speculated that the greatest number of failed applications in the RIPV ablation increased the statistical power to prove the difference. For the left PVs, it might also be possible that inter-PV connections had an influence on the study results. The difference might also be explained by the (1) different anatomical location and surrounding tissue in each PV, which lead to a different atrial tissue distensibility and tissue contact area when the PVs were occluded, (2) different alignment from the trans-septal hole to each PV, which lead to a different balloon pushability and anatomical distortion, (3) different PV size and ostial area, which lead to a different amount of dammed blood, and (4) different occlusion technique (a complete occlusion is required in the LSPV,

but a small amount of contrast leakage is acceptable in the RSPV). In the RIPV ablation, the combination of the SBP-drop and ThawTime showed the highest AUC for predicting a successful application. Generally, RIPVs are the most challenging target among the 4 PVs during the CB-PVI due to the anatomical factors such as the proximity of the ostium to the interatrial septum, and frequent early branching with large oval ostia. Furthermore, the capability of real-time PV potential monitoring is the lowest for the RIPVs due to the short PV sleeve and procedural difficulty. Therefore, the knowledge of the factors predicting a successful RIPV application seems to be particularly important and useful.

### Limitations

First, this study was a single center, retrospective study concerning the outcome in the acute phase. Further investigation is needed to evaluate the durability of the PVI in the mid-term or long term. Second, the number of subjects was limited. Third, the operators cannot control the ThawTime and SBP-drop during freezing; however, that information might aid in evaluating the electrical isolation of the RIPV especially when solely using an Achieve mapping catheter. Fourth, the balloon temperature is not the tissue temperature and it is a measurement of the return gas temperature, which is influenced by several factors including the balloon–tissue contact area and collateral blood flow. Fifth, the BP might be influenced by the sedation level and alternation of the autonomic nervous system. However, we previously reported that the administration of atropine did not have an impact on the BP change, suggesting that the impact of the autonomic nervous system on the change in the BP seemed to be limited [9].

### Conclusions

In the second-generation CB-PVI, the longer thawing time and lower nadir in-balloon temperature significantly predicted a successful application for all 4 individual PVs. In addition, a greater magnitude of the SBP drop following releasing the PV occlusion significantly predicted a successful application for the right PVs, and a composite parameter incorporating the SBP drop and thawing time showed the highest accuracy in predicting a successful RIPV ablation.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

- Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quin-  
iou G, Garrigue S, Le Mouroux A, Le Métayer P, Clémenty J  
(1998) Spontaneous initiation of atrial fibrillation by ectopic beats  
originating in the pulmonary veins. *N Engl J Med* 339:659–666
- Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA,  
Crijns HJ, Damiano RJ, Davies DW, DiMarco J, Edgerton J, Ellen-  
bogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks  
G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim  
YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD,  
Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F,  
Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pap-  
pone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin  
RJ, Tsao HM, Wilber D, Heart Rhythm Society Task Force on  
Catheter, and Surgical Ablation of Atrial Fibrillation (2012) 2012  
HRS/EHRA/ECAS expert consensus statement on catheter and  
surgical ablation of atrial fibrillation: recommendations for patient  
selection, procedural techniques, patient management and follow-  
up, definitions, endpoints, and research trial design: a report of the  
Heart Rhythm Society (HRS) task force on catheter and surgical  
ablation of atrial fibrillation. *Heart Rhythm* 9(632–696):e21
- Kojodjojo P, O’Neill MD, Lim PB, Malcolm-Lawes L, Whinnett  
ZI, Salukhe TV, Linton NW, Lefroy D, Mason A, Wright I, Peters  
NS, Kanagaratnam P, Davies DW (2010) Pulmonary venous isola-  
tion by antral ablation with a large cryoballoon for treatment of  
paroxysmal and persistent atrial fibrillation: medium-term out-  
comes and non-randomised comparison with pulmonary venous  
isolation by radiofrequency ablation. *Heart* 96:1379–1384
- Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne  
J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG,  
Lehmann JW, Ruskin JN, Cryoablation Investigators STOPAF  
(2013) Cryoballoon ablation of pulmonary veins for paroxysmal  
atrial fibrillation: first results of the North American Arctic Front  
(STOP AF) pivotal trial. *J Am Coll Cardiol* 61:1713–1723
- Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun  
KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP,  
Tondo C, FIRE AND ICE investigators (2016) Cryoballoon or  
radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl  
J Med* 374:2235–2245
- Coulombe N, Paulin J, Su W (2013) Improved in vivo perfor-  
mance of second-generation cryoballoon for pulmonary vein iso-  
lation. *J Cardiovasc Electrophysiol* 24:919–925
- Kajiyama T, Miyazaki S, Matsuda J, Watanabe T, Niida T, Tak-  
agi T, Nakamura H, Taniguchi H, Hachiya H, Iesaka Y (2017)  
Anatomic parameters predicting procedural difficulty and bal-  
loon temperature predicting successful applications in individual  
pulmonary veins during 28-mm second-generation cryoballoon  
ablation. *JACC Clin Electrophysiol* 3:580–588
- Deubner N, Greiss H, Akkaya E, Zaltsberg S, Hain A, Berkow-  
itsch A, Guttler N, Kuniss M, Neumann T (2017) The slope of the  
initial temperature drop predicts acute pulmonary vein isolation  
using the second-generation cryoballoon. *Europace* 19:1470–1477
- Kajiyama T, Miyazaki S, Watanabe T, Yamao K, Kusa S, Igarashi  
M, Nakamura H, Hachiya H, Iesaka Y (2017) Circulatory dynam-  
ics during pulmonary vein isolation using the second-generation  
cryoballoon. *J Am Heart Assoc* 6:e006559
- Miyazaki S, Hachiya H, Taniguchi H, Nakamura H, Ichihara N,  
Usui E, Kuroi A, Takagi T, Iwasawa J, Hirao K, Iesaka Y (2015)  
Prospective evaluation of bilateral diaphragmatic electromyo-  
grams during cryoballoon ablation of atrial fibrillation. *J Cardio-  
vasc Electrophysiol* 26:622–628
- Su W, Kowal R, Kowalski M, Metzner A, Svinarich JT, Wheelan  
K, Wang P (2015) Best practice guide for cryoballoon ablation in  
atrial fibrillation: the compilation experience of more than 3000  
procedures. *Heart Rhythm* 12:1658–1666
- R Core Team (2017) R: A language and environment for statisti-  
cal computing. R Foundation for Statistical Computing, Vienna,  
Austria. <https://www.R-project.org/>
- Furnkranz A, Koster I, Chun KR, Metzner A, Mathew S, Konstan-  
tinidou M, Ouyang F, Kuck KH (2011) Cryoballoon temperature  
predicts acute pulmonary vein isolation. *Heart Rhythm* 8:821–825

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