



Original article

Correlation between asymptomatic gastroesophageal excessive transmural injury after pulmonary vein isolation and a bonus freeze protocol using the second-generation 28-mm cryoballoon for paroxysmal atrial fibrillation



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ABSTRACT

Background: Second-generation cryoballoon (2G-CB) ablation is highly effective for achieving pulmonary vein isolation (PVI) with a promising clinical outcome. However, the ideal freezing strategy for preventing gastroesophageal excessive transmural injury (ETI) remains under debate. This study aimed to clarify the correlation between gastroesophageal ETI and a bonus-freeze protocol after PVI using 2G-CBs.

Method: This study included 100 patients who underwent PVI using 2G-CB followed by an endoscopic examination. The freeze-cycle duration was set at 180 s. In the first 33 patients a 120 s bonus-freeze was applied after successful PVI (bonus group), while in the following 67 the bonus freeze was omitted (non-bonus group). Early freezing interruption was performed when the esophageal temperature reached 25 °C. Gastroesophageal ETI was defined as any injury that resulted from the PVI, including esophageal damage or periesophageal nerve injury.

Results: Gastroesophageal ETIs were observed in 9 (27.3%) and 6 (9.0%) patients and were all asymptomatic, esophageal damage in 3 and 0, and periesophageal nerve injury in the remaining 6 and 6 in the bonus group and non-bonus group, respectively ($p = 0.033$). In the multivariate analysis, the bonus freeze protocol (odds ratio 3.527; 95% confidence interval 1.110–11.208; $p = 0.033$) was the sole independent predictor of gastroesophageal ETI. During a one-year follow-up 26 of 33 bonus group patients (78.8%) and 52 of 67 (77.6%) non-bonus group patients remained in stable sinus rhythm without any differences between the groups.

Conclusions: In the patients with a bonus-freeze protocol using the 2G-CB, gastroesophageal ETIs were detected more often than in those with the non-bonus freeze protocol. In contrast, freedom from atrial fibrillation after the 2G-CB based PVI was comparable when applying either a bonus or non-bonus freeze protocol.

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Introduction

Pulmonary vein isolation (PVI) has become the cornerstone procedure for patients with drug-refractory, symptomatic atrial fibrillation (AF) [1]. The second-generation cryoballoon catheter (Arctic Front Advance, Medtronic, Inc., Minneapolis, MN, USA) is an anatomically based ablation device that allows for a simplified PVI with a favorable safety profile [2–4]. To date, second-generation cryoballoon ablation has become increasingly used to perform PVI as an alternative to a point-by-point radiofrequency ablation [5]. Esophagus-related complications can occur during not only a radiofrequency- but also cryoballoon-based PVI [6–8]. The development of esophageal-related collateral damage, such as esophageal injury and periesophageal vagal nerve injury, remains an important complication regardless of the energy source. However, the ideal freezing strategy is still under debate in order to prevent gastroesophageal excessive transmural injury (ETI). Current ablation strategies are commonly based on a fixed freeze-cycle duration of 180–240 s followed by a bonus freeze-cycle of the same duration following a successful PVI [9–11]. To prevent damage to extra-cardiac structures, shorter freeze-cycle durations and omitting the bonus freeze-cycle have been suggested [12,13]. However, there are few direct comparisons with regard to the incidence of gastroesophageal ETI associated with bonus and non-bonus freeze protocols. The first aim of this study was to clarify the correlation between gastroesophageal ETI and the bonus freeze protocol after the PVI using the second-generation 28-mm cryoballoon. The second aim was to demonstrate an equal clinical efficacy of omitting the bonus freeze as compared to the bonus freeze protocol.

Methods

Study population

One hundred consecutive patients with paroxysmal AF (63 males; 66 ± 10 years; range 39–83 years) underwent esophagogastroscope within 3 days of the index PVI using a second-generation 28-mm cryoballoon. A PVI using a cryoballoon was performed using single 3-min freeze applications. In the first consecutive 33 patients, a 2-min bonus freeze was applied after the vein isolation. In the subsequent 67 patients the bonus freeze application was omitted. Written informed consent for the AF ablation was obtained from all patients. The study protocol was approved by the institution's ethics committee.

All patients underwent a transesophageal echocardiogram to rule out any left atrial thrombi. All patients were administered an anticoagulant for at least >4 weeks before the procedure. Warfarin ($n = 17$) was controlled to maintain the prothrombin time-international normalized ratio at 2.0–2.5 before the procedure and was not interrupted before or after the procedure. Dabigatran ($n = 20$), rivaroxaban ($n = 18$), apixaban ($n = 43$), and edoxaban ($n = 2$) were skipped only on the morning of the procedure. Those anticoagulants were continued for at least 3 months after the ablation. All antiarrhythmic drugs were discontinued for at least 5 half-lives before the electrophysiological study and ablation procedure. All patients underwent an electrophysiological evaluation under sedation. Sedation was performed by a continuous infusion of propofol. Intravenous heparin was administered before the Brockenbrough puncture to maintain an activated clotting time between 300 and 400 s.

Cryoballoon ablation procedure

At the start of the procedure, an esophageal temperature probe (SensiTherm, St. Jude Medical, Inc., St Paul, MN, USA) was inserted

into the esophagus under fluoroscopic guidance. The position of the probe was repeatedly adjusted to match the balloon position during freezing. One multipolar 6Fr catheter was positioned in the coronary sinus via the right subclavian vein. After a single transseptal puncture (SL1; St Jude Medical, Inc.), a guidewire was advanced into the left superior PV, and the sheath was exchanged for a 14 French deflectable sheath (FlexCath Advance; Medtronic, Inc.). The second-generation 28-mm cryoballoon was advanced into the ostium of the PV with an Achieve catheter (20-mm diameter Achieve; Medtronic, Inc.). The cryoballoon was inflated proximal to the PV ostium followed by a gentle push aiming for complete sealing at the antral aspect of the PV. Contrast medium injected through the central lumen of the cryoballoon was used to verify the complete occlusion of the PV ostium. This was followed by a freeze cycle of 180 s with luminal esophageal temperature (LET) measurements. For left common PVs, we adapted a sequential ablation approach. The first superior branch of the left common PV was targeted, followed by ablation of the first inferior branch. After at least a 3 min application for each PV and their electrical isolation, we proceeded with the following steps. The PVI was either assessed continuously using the circular Achieve catheter during freezing or traditionally using a 20-polar Lasso-catheter after the application. If the PV remained connected, additional applications were delivered using different angulations. A Quadripolar catheter was positioned in the superior vena cava during the ablation of the right PV for continuous pacing of the right phrenic nerve to monitor the diaphragmatic function. In the case of weakening of the right hemidiaphragm contractions, a balloon nadir temperature of $< -60^\circ\text{C}$, or LET $< 25^\circ\text{C}$, the freezing was immediately stopped. After a successful PVI one additional bonus freeze-cycle of a 120-s duration was applied in the first 33 patients, and the bonus freeze was omitted in the following 67 patients. In the case of residual LA to PV conduction after two applications for each PV, additional ablation was carried out using the cryocatheter (Freezor MAX, Medtronic, Inc.) according to the segment of the conduction on the circular mapping catheter. Additional ablation was performed until the complete abolition of the PV potentials was seen. The procedural endpoint was the absence or dissociation of all PV potentials as confirmed by the endoluminal spiral mapping catheter after a waiting period of 60 min.

Esophagogastroscope

All patients underwent esophagogastroscope within 3 days of the procedure. Esophagogastroscope was performed by experienced operators. The endoscope was inserted orally under pharyngeal anesthesia without sedation. Particular attention was paid to visualize the region of the mid-esophagus adjacent to the pulsating heart where ablation-related thermal injury would be expected to occur. Esophageal thermal lesions (ETLs) were defined as erythemas (focal redness of the mucosal surface), erosions (shallow mucosal defect), or ulcerations (deep mucosal defect) based on their macroscopic appearance (Fig. 1A and B) [12]. Gastroparesis was defined as gastric hypomotility and retained food on esophagogastroscope despite overnight fasting (at least a >16-h fasting state) (Fig. 1C). Gastroesophageal ETI was defined as any injury that resulted from the PVI, including esophageal damage or periesophageal nerve injury. Repeat esophagogastroscope was performed 1–3 months after the procedure in patients with any abnormal findings to evaluate the association between the ablation procedure and findings. All patients were administered proton-pump inhibitors for 3 months after the procedure. A gastric sodium alginate colloidal solution was prescribed in patients with ablation-related esophageal lesions for 1 week.

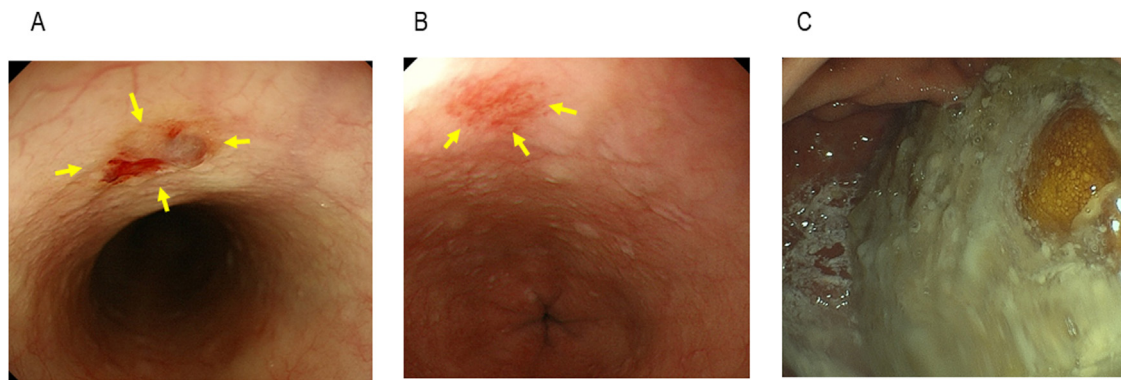


Fig. 1. Representative cases with esophageal erosion (A), esophageal erythema (B), and gastric paresis (C) on esophagogastroscopy one day after the cryoballoon pulmonary vein isolation are shown. The arrows indicate the lesions.

Multidetector computed tomography measurements

Pre-procedural cardiac enhanced multidetector computed tomography (MDCT) was performed with a 320-row scanner. All images were reviewed independently by experienced radiologists and cardiologists. The distance between the esophagus and left inferior PV (LIPV) ostium, and between the esophagus and right inferior PV (RIPV) ostium was measured. The esophageal location at the LIPV level was divided into three groups: right-sided, central, and left-sided esophagus.

Post-ablation management and clinical follow-up

In all the patients the anti-arrhythmic drugs were discontinued after the procedure. For three days after the procedure, electrocardiographic (ECG) monitoring was performed. The ECG and Holter ECG recordings were repeated at 1, 3, 6, and 12 months after the procedure. If the patients complained of symptoms suggestive of an arrhythmia recurrence, an event monitor was provided. Long-term success was defined as the absence of any sustained (>30 s) atrial arrhythmias. The indication for a repeat procedure was left to the discretion of the physician.

Statistical analysis

Categorical variables are expressed as absolute and relative frequencies. Continuous variables are expressed as the mean $\pm$ standard deviation or median and interquartile range as appropriate. For 2-sample comparisons of the continuous variables, a Student *t* test was used to determine the statistically significant interactions. Categorical variables were compared using a chi-square test or Fisher's exact test. All parameters with a significance of <0.20 in the univariate analysis were entered into a multiple logistic regression analysis. Survival curves were generated with the Kaplan–Meier technique and compared by the log-rank test. A two-sided $p < 0.05$ was considered to indicate statistical significance.

Results

Clinical characteristics

The baseline characteristics of the patient population are presented in Table 1. Fifty-two (52.0%) patients had hypertension and 5 (5.0%) had structural heart diseases. Among the 100 patients, 69 (69.0%) had left-sided, 27 (27.0%) central, and the remaining 4

(4.0%) right-sided esophageal locations. The patient characteristics did not differ between the two groups.

Second-generation 28-mm cryoballoon PVI

In 33 patients with a bonus freeze protocol a total number of 132 PVs were identified. After the initial and second cryo-applications, an acute PVI was achieved in 101 of 132 (76.5%) PVs and in 26 of 31 (83.9%) PVs. In 5 RIPVs, 5 focal lesions were placed with the spot cryocatheter to achieve an acute isolation. In 67 patients with a non-bonus freeze protocol a total number of 265 PVs including 3 left common PVs were identified. After the initial and second cryo-applications, an acute PVI was achieved in 190 of 265 (71.7%) PVs and in 70 of 75 (93.3%) PVs. In 5 RIPVs, 5 focal lesions were placed with the spot cryocatheter to achieve an acute isolation. At the termination of the index ablation procedure, an acute PVI was demonstrated in 100% of the ablated PVs (397 PVs) in both groups. Table 2 lists the characteristics of the second-generation 28-mm cryoballoon procedures used in this study. The mean total freezing time was 240.3 ± 92.0 , 233.8 ± 103.1 , 228.4 ± 81.8 , and 283.5 ± 86.8 s for the left superior PV (LSPV), LIPV, right superior PV (RSPV), and RIPV, respectively. The typical freeze time was 180 s, with a shorter duration representing freeze terminations based on an ultracold balloon nadir temperature ($<-60^\circ\text{C}$) or an attempt to avoid collateral tissue freezing (e.g. phrenic nerve and esophagus). The total freezing time of all PVs was longer in the patients with a bonus freeze than in those without a bonus freeze. The mean nadir balloon temperatures were -53.3 ± 4.3 , -46.4 ± 4.2 , -55.0 ± 5.1 , and $-49.4 \pm 6.7^\circ\text{C}$ for the LSPV, LIPV, RSPV, and RIPV, respectively. The nadir balloon temperatures recorded at the LIPV and RIPV were lower in the patients with a bonus freeze than in those without a bonus freeze. The mean nadir LETs were 31.1 ± 4.4 , 26.8 ± 5.4 , 35.2 ± 1.5 , and $35.1 \pm 1.9^\circ\text{C}$ for the LSPV, LIPV, RSPV, and RIPV, respectively. The nadir LET for all PVs did not differ between the patients with and without bonus freezes. An early freezing interruption due to an LET $<25^\circ\text{C}$ was performed in 16 of 33 patients (48.5%) (2 at the LSPV and 14 at the LIPV) with a bonus freeze protocol and in 45 of 67 patients (67.2%) (11 at the LSPV, 33 at the LIPV and 1 at the RIPV) with a non-bonus freeze protocol. Table 3 lists a comparison of the characteristics of the second-generation 28-mm cryoballoon procedures for achieving a PVI between the bonus and non-bonus freeze protocol groups. There were no significant differences in the parameters of the cryoballoon ablation for achieving a PVI, such as the freezing time, nadir balloon temperature, nadir LET, and early freezing interruption due to an LET, between the two groups.

Table 1

Patient characteristics.

	Total (n = 100)	Bonus Freeze Protocol (n = 33)	Non-Bonus Freeze Protocol (n = 67)	p-Value
Age, years	65.9 ± 9.5	67.5 ± 8.3	65.1 ± 10.0	0.228
Female, n (%)	37 (37.0)	10 (30.3)	27 (42.0)	0.383
Weight, kg	61.8 ± 10.2	62.0 ± 11.0	61.7 ± 9.9	0.886
Body mass index, kg/m ²	23.3 ± 2.7	23.1 ± 2.9	23.4 ± 2.7	0.654
Categorized body mass index, n (%)				0.964
Under weight (<18.5 kg/m ²)	3 (3.0)	1 (3.0)	2 (3.0)	
Normal (18.5–24.9 kg/m ²)	73 (73.0)	24 (72.7)	49 (73.1)	
Overweight (25–29.9 kg/m ²)	22 (22.0)	7 (21.2)	15 (22.4)	
Obese (≥30 kg/m ²)	2 (2.0)	1 (3.0)	1 (1.5)	
Duration of an AF history, months	47 (1–280)	36 (6–72)	24 (5–48)	0.221
Hypertension, n (%)	52 (52.0)	17 (51.5)	35 (52.2)	>0.999
Organic heart disease, n (%)				
CAD, n (%)	1 (1.0)	1 (3.0)	0 (0)	0.330
HCM, n (%)	3 (3.0)	1 (3.0)	2 (3.0)	>0.999
DCM, n (%)	1 (1.0)	1 (3.0)	0 (0)	0.330
CHADS ₂ score	1.1 ± 1.0	1.1 ± 1.0	1.1 ± 1.1	0.895
HAS-BLED score	1.3 ± 1.1	1.2 ± 0.9	1.4 ± 1.2	0.492
Echocardiographic parameters				
LA diameter, mm	38.9 ± 5.6	38.7 ± 5.5	39.0 ± 5.6	0.751
LV ejection fraction, %	66.2 ± 7.6	67.4 ± 6.7	65.7 ± 8.0	0.277
Esophageal location, n (%)				0.330
Left	69 (69.0)	26 (78.8)	43 (64.2)	
Central	27 (27.0)	6 (18.2)	21 (31.3)	
Right	4 (4.0)	1 (3.0)	3 (4.5)	
Esophagus-RPV os distance, mm	23.0 ± 10.0	23.0 ± 10.7	22.9 ± 9.7	0.970
Esophagus-LPV os distance, mm	3.7 ± 5.4	3.4 ± 6.0	3.9 ± 5.2	0.649
Esophagus-PV os distance, mm	2.8 ± 3.5	2.3 ± 3.2	3.1 ± 3.6	0.304

AF, atrial fibrillation; CAD, coronary artery disease; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; LA, left atrium; LV, left ventricle; RPV, right pulmonary vein; LPV, left pulmonary vein; PV, pulmonary vein; os, ostium.

Table 2

Procedural characteristics of the cryoballoon PVI.

	Total (n = 100)	Bonus freeze protocol (n = 33)	Non-bonus freeze protocol (n = 67)	p-Value
Total freezing time (s)				
LSPV	240.3 ± 92.0	324.1 ± 75.0	199.0 ± 68.7	<0.001
LIPV	233.8 ± 103.1	307.6 ± 88.6	197.5 ± 89.8	<0.001
RSPV	228.4 ± 81.8	282.3 ± 70.6	201.8 ± 73.9	<0.001
RIPV	283.5 ± 86.8	313.6 ± 73.4	268.7 ± 89.6	0.009
Nadir balloon temperature (°C)				
LSPV	−53.3 ± 4.3	−53.3 ± 4.4	−53.3 ± 4.3	0.978
LIPV	−46.4 ± 4.2	−47.8 ± 3.9	−45.7 ± 4.2	0.019
RSPV	−55.0 ± 5.1	−55.7 ± 5.4	−54.7 ± 4.9	0.358
RIPV	−49.4 ± 6.7	−51.4 ± 7.0	−48.4 ± 6.4	0.036
Nadir LET (°C)				
LSPV	31.1 ± 4.4	31.4 ± 4.1	30.9 ± 4.5	0.561
LIPV	26.8 ± 5.4	26.5 ± 5.0	27.0 ± 5.6	0.658
RSPV	35.2 ± 1.5	34.9 ± 1.6	35.4 ± 1.5	0.110
RIPV	35.1 ± 1.9	35.1 ± 0.7	35.0 ± 2.3	0.996
Early freezing interruption due to LET, n (%)				
LSPV	13 (13.0)	2 (6.1)	11 (16.4)	0.210
LIPV	47 (47.0)	14 (42.4)	33 (49.3)	0.532
RSPV	0 (0)	0 (0)	0 (0)	>0.999
RIPV	1 (1.0)	0 (0)	1 (1.5)	>0.999

PVI, pulmonary vein isolation; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; LET, luminal esophageal temperature.

Esophagogastroscopy findings

Esophagogastroscopy was performed in all patients at a mean of 1.4 ± 0.5 days after the procedure. In the patients with a bonus freeze protocol, gastroesophageal ETI was observed in 9 of 33 patients (27.3%) (1 with erosion, 2 with erythema, and 6 with gastric hypomotility). In the patients with a non-bonus freeze protocol, gastroesophageal ETI was observed in 6 of 67 patients (9.0%) (6 with gastric hypomotility). All patients with gastroesophageal ETI were asymptomatic, and the gastroesophageal ETI

in all patients resolved on the repeat esophagogastroscopy at a mean of 2 ± 1 months after the procedure.

Predictors of gastroesophageal ETI

Table 4 shows the clinical characteristics of the patients with and without gastroesophageal ETI. The minimum distance from esophagus to PV ostium was closer in patients with gastroesophageal ETI than those without gastroesophageal ETI (1.4 ± 1.8 mm vs. 3.1 ± 3.6 mm; $p = 0.008$). Gastroesophageal ETI was observed more

Table 3

Procedural characteristics of cryoballoon PVI for achieving a PVI.

	Total (n = 100)	Bonus freeze protocol (n = 33)	Non-bonus freeze protocol (n = 67)	p-Value
Total freezing time (s)				
LSPV	201.2 ± 70.2	205.6 ± 74.0	199.0 ± 68.7	0.663
LIPV	195.3 ± 87.5	191.0 ± 83.7	197.5 ± 89.8	0.728
RSPV	194.4 ± 68.2	179.4 ± 52.8	201.8 ± 73.9	0.086
RIPV	258.4 ± 84.9	237.5 ± 71.1	268.7 ± 89.6	0.062
Nadir balloon temperature (°C)				
LSPV	53.0 ± 4.6	52.3 ± 5.2	53.3 ± 4.3	0.315
LIPV	45.9 ± 4.2	46.4 ± 4.2	45.7 ± 4.2	0.447
RSPV	54.9 ± 5.1	55.4 ± 5.5	54.7 ± 4.9	0.523
RIPV	49.0 ± 6.8	50.2 ± 7.3	48.4 ± 6.4	0.210
Nadir LET (°C)				
LSPV	31.2 ± 4.4	31.7 ± 4.1	30.9 ± 4.5	0.387
LIPV	26.9 ± 5.4	26.7 ± 5.2	27.0 ± 5.6	0.827
RSPV	35.2 ± 1.5	34.9 ± 1.6	35.4 ± 1.5	0.112
RIPV	35.1 ± 1.9	35.1 ± 0.6	35.0 ± 2.3	0.918
Early freezing interruption due to LET, n (%)				
LSPV	13 (13.0)	2 (6.1)	11 (16.4)	0.210
LIPV	47 (47.0)	14 (42.4)	33 (49.3)	0.532
RSPV	0 (0)	0 (0)	0 (0)	>0.999
RIPV	1 (1.0)	0 (0)	1 (1.5)	>0.999

PVI, pulmonary vein isolation; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; LET, luminal esophageal temperature.

Table 4

Clinical characteristics of the patients with and without gastroesophageal ETI.

	Total (n = 100)	GE ETI (n = 15)	No GE ETI (n = 85)	p-Value
Age, years	65.9 ± 9.5	69.0 ± 8.7	65.3 ± 9.6	0.169
Female, n (%)	37 (37.0)	5 (33.3)	32 (37.6)	>0.999
Weight, kg	61.8 ± 10.2	61.2 ± 9.7	61.9 ± 10.4	0.800
Body mass index, kg/m ²	23.3 ± 2.7	23.7 ± 2.4	23.2 ± 2.8	0.550
Categorized body mass index, n (%)				0.787
Under weight (<18.5 kg/m ²)	3 (3.0)	0 (0)	3 (3.5)	
Normal (18.5–24.9 kg/m ²)	73 (73.0)	11 (73.3)	62 (72.9)	
Overweight (25–29.9 kg/m ²)	22 (22.0)	4 (26.7)	18 (21.2)	
Obese (≥30 kg/m ²)	2 (2.0)	0 (0)	2 (2.4)	
Duration of AF history, months	47 (1–280)	20.0 (7.5–54)	24.0 (6–60)	0.431
Hypertension, n (%)	52 (52.0)	9 (60.0)	43 (50.6)	0.582
Organic heart disease, n (%)				
CAD, n (%)	1 (1.0)	0 (0.0)	1 (1.2)	>0.999
HCM, n (%)	3 (3.0)	1 (6.7)	2 (2.4)	0.389
DCM, n (%)	1 (1.0)	0 (0.0)	1 (1.2)	>0.999
Ecocardiographic parameters				
LA diameter, mm	38.7 ± 6.6	38.9 ± 5.5	38.9 ± 5.6	0.992
LV ejection fraction, %	66.1 ± 7.8	64.3 ± 7.7	66.6 ± 7.6	0.278
Esophageal location				
Esophagus-RPV os distance, mm	23.0 ± 10.0	24.7 ± 12.7	22.6 ± 9.5	0.453
Esophagus-LPV os distance, mm	3.7 ± 5.4	3.0 ± 7.1	3.9 ± 5.1	0.565
Esophagus-PV os distance, mm	2.8 ± 3.5	1.4 ± 1.8	3.1 ± 3.6	0.008
Ablation protocol				
Bonus freeze protocol	33 (33.0)	9 (27.3)	24 (27.7)	0.033
Non-bonus freeze protocol	67 (67.0)	6 (9.0)	61 (91.0)	

GE, gastroesophageal; ETI, esophageal thermal injury; AF, atrial fibrillation; CAD, coronary artery disease; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; LA, left atrium; LV, left ventricle; RPV, right pulmonary vein; LPV, left pulmonary vein; PV, pulmonary vein; os, ostium.

often in patients (27.3%) with a bonus freeze protocol than in those without a bonus freeze protocol (9.0%) ($p = 0.033$). In the multivariate analysis, the bonus freeze protocol [odds ratio 3.527; 95% confidence interval (CI) 1.110–11.208; $p = 0.033$] was the sole independent predictor of gastroesophageal ETI (Table 5).

Follow-up

During the follow-up period of 12 months, 26 out of 33 patients (78.8%) in the bonus freeze protocol group and 51 out of 67 patients (76.1%) in the non-bonus freeze protocol group were in sinus rhythm without any antiarrhythmic drugs. There was no signifi-

cant difference between the two groups (log-rank test $p = 0.753$) (Fig. 2). The recurrent arrhythmia was paroxysmal AF in all patients. Complications occurred in 2 patients (6.1%) in the bonus freeze protocol group and in 4 (6.0%) in the non-bonus protocol group ($p > 0.999$). Temporary phrenic nerve paralysis occurred in one patient (3.0%) in the bonus freeze protocol group and 2 (3.0%) in the non-bonus protocol group. Phrenic nerve paralysis resolved in all patients after 3 months. Transient ischemic attacks occurred in one patient in the non-bonus freeze protocol group. A hematoma occurred in one patient in each group. No pulmonary vein stenosis, cerebral infarctions, atri-esophageal fistulae, or cardiac tamponade occurred in any patients.

Table 5
Multivariate analysis for identifying predictors of gastroesophageal ETI.

Variable	OR	p	95% CI
Age, years	0.987	0.741	0.910–1.069
Esophagus–PV os distance, mm	1.166	0.232	0.906–1.501
Bonus freeze protocol	3.527	0.033	1.110–11.208

ETI, excessive transmural injury; OR, odds ratio; CI, confidence interval; PV, pulmonary vein.

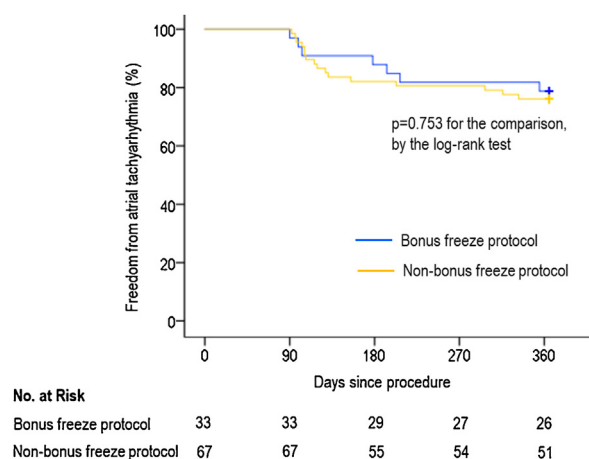


Fig. 2. Kaplan–Meier curve showing the cumulative freedom from all atrial tachyarrhythmias after the second-generation cryoballoon ablation of paroxysmal atrial fibrillation in the patients with and without a bonus freeze protocol. The freedom from all recurrent atrial tachyarrhythmias did not differ between the two groups when compared by log-rank testing ($p = 0.753$).

Discussion

Our study produced the following three results: (1) an LET guided second-generation cryoballoon ablation with and without a bonus freeze protocol carries the risk of an asymptomatic ETI; (2) gastroesophageal ETI after a cryoballoon PVI was more frequent in patients with a bonus freeze protocol than in those without; and (3) the freedom from AF after the second-generation cryoballoon PVI was comparable between a bonus- and non-bonus freeze protocol.

Esophageal thermal lesions and gastric hypomotility after a cryoballoon PVI

The systematic postprocedural esophagogastrosocopy results after a second-generation cryoballoon PVI have been reported in several studies [6,7,14–16]. Collectively, those studies reported that ETLs were observed in 12–19% of patients without an early interruption due to an LET after 2×240 s cryoballoon applications. Additionally, Fuernkranz et al. [15] reported that an LET-guided second-generation cryoballoon PVI reduces the incidence of ETL and interrupting the cryoablation at an LET of 15°C is associated with the lowest incidence of ETL. Gastroparesis after a second-generation cryoballoon PVI was reported by Miyazaki et al. [16]. In their report, gastroparesis and ETL were detected in 17.3% and 8.7% of patients after a single 3-min cryoapplication technique.

The present study compared the incidence of ETL and gastroparesis between the patients with and without a bonus freeze protocol added to the 3-min cryoapplication. Furthermore, we interrupted the cryoapplications when the LET reached 25°C , that is the strictest cut-off value previously reported for an interruption due to the LET, because delayed esophageal temperature drops of a maximum of 6.4°C after interruption of the cryoballoon application have been reported [17]. Despite the strict cut-off value for an early

interruption due to the LET, the ETL could not be completely suppressed in patients with a bonus freeze protocol. In the non-bonus freeze protocol group, ETL did not appear, but gastroparesis appeared in 9% of patients with a combination of a strict cut-off value for an early interruption due to the LET. These findings suggested that the combination with a non-bonus freeze protocol and strict cut-off value for an early interruption due to the LET could prevent ETL such as esophageal ulcers or erosions. In the present study, gastroparesis could not be completely suppressed despite the combination with a non-bonus protocol and strict cut-off value for an early interruption due to the LET. Recently, it has been reported that an individualized dosing strategy based on the time to the PVI results in shorter freeze-cycle applications and an arrhythmia-free survival comparable to a conventional protocol [18–20]. It is expected that an individualized dosing strategy based on the time to the PVI may reduce the excessive application time and incidence of both ETLs and gastroparesis.

Optimal freeze cycle for the second-generation cryoballoon ablation

PVI using the second-generation cryoballoon has demonstrated a high rate of a PVI durability because of the improved cooling effect compared to the first-generation cryoballoon [21,22]. The PVI using the second-generation cryoballoon has exhibited more reproducible results and reduced procedural times than the conventional radiofrequency catheter ablation [8,11,22,23]. However, the ideal freezing strategy is still under debate. Regardless of the balloon inflation times of 3 or 4 min with and without a bonus freeze protocol, the sinus rhythm maintenance rate after one year from the cryoballoon PVI is about 70–80% [8,12,13,24]. Heeger et al. reported that the freedom from AF after the second-generation cryoballoon based PVI is comparable between the 4-min bonus- and non-bonus freeze protocols [25]. Miyamoto et al. also reported that no benefit was found in patients receiving additional 3-min freeze cycles after a complete PVI with the second-generation cryoballoon [26]. In the present study, the freedom from AF after the second-generation cryoballoon based PVI did not differ between the patients with a 2-min bonus freeze protocol and those with a non-bonus freeze protocol. This result was in line with the previous reports. Therefore, an insurance freeze after achieving a PVI with the second-generation cryoballoon may be unnecessary from the viewpoint of the clinical effect.

Previous reports described that there were no differences in the periprocedural complications identified between patients with and without a bonus freeze [25,26]. However, the number of freeze cycles and freeze time were considered to be associated with the thermal injury of the extracardiac structures, such as the phrenic nerve, esophagus, and bronchial tree [27–29]. In this study, omitting the bonus freeze reduced the ETLs and gastroparesis as compared to that in the patients with a bonus freeze. To the best of our knowledge, this is the first report to compare the incidence of ETLs and gastric hypomotility on esophagogastrosocopy between patients with and without a bonus freeze. As insight from the present study, a bonus freeze protocol using the second-generation cryoballoon may not only consume procedure and fluoroscopic time, but also increase the risk of gastroesophageal ETI.

Study limitations

First, the presented findings are based on a single-center experience enrolling only a limited number of patients in a non-randomized fashion. However, the baseline characteristics in the current study are not different between the groups. Second, the first 33 patients underwent PVI with bonus freeze protocol and the following 67 patients were applied non-bonus freeze protocol. Although such study design may result in technical bias, cryoballoon PVI is a technically less biased procedure.

Conclusion

The freedom from AF after a second-generation cryoballoon-based PVI was comparable between the bonus and non-bonus freeze protocols. However, gastroesophageal ETIs were detected more often in the patients with a bonus freeze protocol than in those with a non-bonus freeze protocol. These findings suggest that a bonus freeze application may not only be unnecessary but also increase the risk of esophageal complications.

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Conflict of interest

All authors have no conflict of interest.

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