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ORIGINAL RESEARCH

Supplemental Radiofrequency Ablation After Acutely Unsuccessful Cryoballoon Pulmonary Vein Isolation is Associated With Increased Risk of Recurrent Atrial Fibrillation

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BACKGROUND: Cryoballoon (CB) ablation is widely performed for pulmonary vein isolation (PVI) in patients with atrial fibrillation (AF). Anatomic variations in patient pulmonary vein (PV) anatomy are believed to impact short- and long-term procedural success of CB PVI.

METHODS AND RESULTS: We hypothesized that failure of initial PV isolation with a standard technique (ie, requiring >2 freeze cycles per PV and/or radiofrequency ablation [RFA] to achieve PV isolation) during index CB PVI procedures would be associated with decreased freedom from AF. We examined a cohort of 177 consecutive patients with drug-refractory AF who underwent CB PVI with a 28-mm balloon second-generation CB device. Mean follow-up time was 19±9 months. Forty-three patients had AF recurrence after the 90-day blanking period after ablation. In 40 patients, acute isolation of one or more PVs could not be achieved by CB ablation with the standard technique (single freeze with or without bonus freeze). To obtain complete acute PVI, 15 patients received extra freeze applications, 20 required supplemental RFA, and 5 received both extra freeze applications and supplemental RFA. Multivariate regression analysis revealed supplemental RFA use during index CB PVI procedures was independently associated with a threefold increased risk of AF recurrence (adjusted hazard ratio, 3.01; 1.45–10.87; *P*=0.003).

CONCLUSIONS: Use of supplemental RFA during CB PVI procedures to assist with isolation of one or more PVs was independently associated with increased risk of AF recurrence. Use of additional freezes to achieve PVI did not increase the risk for recurrent AF.

Key Words: acute reconnection ■ atrial fibrillation ■ cryoballoon ■ pulmonary vein isolation ■ supplemental radiofrequency ablation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice and its prevalence is expected to increase worldwide. Pulmonary vein isolation (PVI) has become the cornerstone approach for treatment of patients with drug-refractory symptomatic AF. The most commonly performed percutaneous modalities for PVI in clinical practice are radiofrequency ablation (RFA) using point-by-point lesion delivery and cryoballoon (CB) ablation. A significant advantage of CB PVI is the potential for nonselective "single-shot" circumferential pulmonary vein (PV) antral isolation, resulting in reduced procedure times and simplified operator learning curves.[1]

The standard technique (ST) for CB ablation generally includes delivery of up to two freeze applications (ie, single freeze with or without bonus freeze) per PV.[2] Recent studies suggest that a single freeze may be sufficient to achieve durable isolation of PVs if time to PVI (TT-PVI) is short.[3,4] Conversely, longer time to PV isolation with CB ablation has been

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CLINICAL PERSPECTIVE

What Is New?

- We identified 177 consecutive patients who underwent cryoballoon pulmonary vein isolation and examined whether delivery of at least one bonus freeze per pulmonary vein or use of supplemental radiofrequency ablation was associated with atrial fibrillation recurrence.
- In the cohort, we found additional ablation to achieve pulmonary vein isolation was associated with lower freedom from atrial fibrillation; use of supplemental radiofrequency ablation to isolate at least one pulmonary vein after cryoablation was independently associated with atrial fibrillation recurrence.
- In a subset of patients, elliptical right inferior pulmonary vein ostium shape identified by computed tomography imaging and use of supplemental radiofrequency ablation were associated with higher atrial fibrillation recurrence.

What Are the Clinical Implications?

- Preprocedure imaging may be useful for stratifying patients with difficult pulmonary vein anatomy when deciding on modality to use for atrial fibrillation ablation.
- When the standard cryoballoon technique is unsuccessful, additional freeze attempts after balloon repositioning should be considered before using a supplemental radiofrequency ablation approach.
- If supplemental radiofrequency ablation is needed to assist with pulmonary vein isolation, then a wide empiric lesion set may be preferred over a focal ablation strategy targeting electrocardiograms given unclear demarcation between tissue destined for necrosis and tissue with acute reversible injury after cryoballoon ablation.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
CB	cryoballoon
PV	pulmonary vein
PVI	pulmonary vein isolation
RFA	radiofrequency ablation
ST	standard technique

independently correlated with occurrence of late PV reconnection.[5] For some patients, isolation of all targeted PVs can only be achieved after delivery of additional freezes or supplemental radiofrequency (RF) energy delivery. This is occurs most often when PV anatomy is unfavorable.[6–8]

We sought to determine whether the need for delivery of more than one bonus freeze per PV (ie, more than two total freezes) or supplemental RF to achieve acute PVI during index CB procedures would be associated with increased long-term AF recurrence postablation.

METHODS

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Objective

We hypothesized that failure of initial PV isolation with the ST (requiring more than one bonus freeze per PV and/or RFA to achieve PV isolation) during index CB PVI procedures would be associated with decreased intermediate- and long-term freedom from AF.

Study Population

The study population consisted of 177 consecutive patients at a large, urban tertiary center who underwent CB PVI for 12-lead verified, symptomatic, and drug-refractory paroxysmal or persistent AF. Patients who had AF episodes that self-terminated within 7 days were designated as having paroxysmal AF. Patients with continuous episodes of AF >7 days were designated as having persistent AF. No patients with long-standing persistent (>1 year of continuous AF) were included in this study. All patients had at least 6 months of follow-up after their index ablation procedures. The study was approved by the institutional review board of Rush University Medical Center. Informed consent was not obtained due to the retrospective nature of the study.

CB PVI procedures were performed by five experienced electrophysiologists. Written informed consent was obtained and presence of left atrial thrombus was excluded by transesophageal echocardiography or computed tomography before each procedure. All patients were therapeutically anticoagulated with either warfarin to maintain an international normalized ratio of 2 to 3 or a direct oral anticoagulant for at least 4 weeks before their index procedure. Warfarin was not intentionally interrupted before the procedure. The procedures were performed if international normalized ratio was ≥2 and ≤3.0. Direct oral anticoagulant medication was held on the morning of the procedure. Antiarrhythmic drugs were discontinued at least four half-lives before the index procedure.

Ablation Procedure

Procedures were performed under general anesthesia. After positioning a diagnostic decapolar catheter for (pacing and recording) into the coronary sinus, single transseptal access was obtained using an SL1 long sheath and Baylis transseptal needle system. Intravenous heparin was administered at time of transseptal puncture followed by an infusion to maintain activated clotting time of 300 to 400 seconds. All ablation procedures were performed using a second-generation 28-mm CB catheter (Arctic Front Advance; Medtronic, St Paul, MN) inserted through a 12F steerable sheath (FlexCath Advance Steerable Sheath; Medtronic).

The CB catheter was guided to each PV over a circular inner lumen mapping catheter (Achieve; Medtronic). Before delivery of each freeze, PV angiography was performed to assess venous occlusion. During freeze applications, attempts were made to record TT-PVI. A single-freeze application (TT-PVI+120 seconds) was applied to a PV if the TT-PVI was <60 seconds. When the TT-PVI was >60 seconds, a bonus freeze application of 120 seconds was administered. If TT-PVI was not measurable due to absence of PV recordings, an empiric 180-second freeze application was delivered followed by a single bonus freeze of 90–120 seconds. If PV isolation was not obtained after delivery of two freeze applications, then the CB catheter was repositioned and additional bonus freezes were performed with the CB until PVI was obtained.

In general, freeze applications were stopped when the CB temperature fell below −65°C, and the balloon was repositioned before the next freeze was performed. Luminal esophageal temperature monitoring was performed during cryoablation and freeze applications were stopped if temperature fell below 15°C. During cryoablation of the right PVs, a decapolar catheter was positioned in the superior vena cava and high-output phrenic nerve stimulation was performed while monitoring for loss of capture or attenuation of diaphragmatic compound motor action potential amplitude.

If isolation of all PVs could not be achieved despite repositioning of the CB catheter or due to risk of extracardiac injury, point-by-point RFA with an irrigated, force-sensing ablation catheter (Thermocool Smarttouch SF or Thermacool Smarttouch, Biosense Webster, Irving, CA) was employed to achieve acute PVI at the operator's discretion. Optimal location of RF lesion delivery was guided by electrocardiographic interpretation and activation mapping along the PV antrum using a three-dimensional mapping system (Carto 3; Biosense Webster) to identify gaps in conduction block. Care was taken to avoid delivery of RFA energy applications within the tubular portion of any PV. The goal of RFA was to target and abolish all remaining local electrocardiograms on the PV antrum. Once electrical isolation of the targeted PV was achieved with RFA, lesion delivery was stopped without additional empiric RFA unless acute PV reconnection was observed later in the study.

Postprocedural Evaluation

Intracardiac echocardiography or transthoracic echocardiography was performed immediately after the procedure to exclude the presence of a pericardial effusion. Patients were discharged the next day provided that their clinical status was considered stable. Oral anticoagulation was initiated in the evening on the day of ablation, unless a pericardial effusion was detected, and was continued uninterrupted at least 3 months after the procedure. Previous antiarrhythmic drug treatment was also continued for at least 3 months.

Study End Points

The procedural end points of the study were acute isolation of all PVs and whether at least bonus freeze or supplemental RFA was needed to achieve isolation of one or more PV(s). The primary clinical end point was freedom from an episode of AF after a 3-month blanking period after the index ablation procedure. The secondary end point was need for redo ablation procedures.

Recurrence was defined as any symptomatic or asymptomatic episode of AF lasting ≥30 seconds (recorded on 12-lead electrocardiogram or ambulatory monitoring). Any recurrence taking place in the first 3 months after the index ablation procedure was classified as an early recurrence and any recurrence after this period was a late recurrence. Very late recurrence was indicated if first recurrent AF episode occurred >2 years after index ablation.

Patients with AF recurrence after the blanking period were offered the opportunity to undergo a redo ablation procedure to evaluate the cause of recurrence. Preparatory steps were employed, similar to those performed during the index procedure. A multipolar diagnostic catheter was used to evaluate the status of isolation or reconnection of each PV.

Study Follow-Up

Follow-up started after the index PVI procedure. Regular follow-up intervals consisted of outpatient clinic visits at 1, 3, 6, and 12 months after the procedure and included a detailed history for arrhythmia-related symptoms (palpitations, chest discomfort, fatigue, and dizziness), physical examination, 12-lead

electrocardiogram, and 14-day ambulatory monitoring. The need for further oral anticoagulation was evaluated on the month 3 visit based on the Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/transient ischemic attack (2 points); VASc vascular disease, and sex category (CHA_2DS_2-VASc) score.

Statistical Analysis

Baseline characteristics were compared using a chi-square test for dichotomous variables. The two-sample *t* test was used for normally distributed continuous variables, and a two-sample Wilcoxon rank sum test was used for variables not normally distributed. The associations between clinical and procedural covariates and the end point were examined using Kaplan-Meier survival curves and the log-rank statistic *P* value. The Cox proportional hazards regression model was used to evaluate the independent contribution of baseline clinical factors and procedural covariates for the development of end points. Stepwise elimination and backward selections were used to select the most parsimonious set of predictive variables.

Multivariate analysis was performed using the Cox proportional hazards regression model. Stepwise selection was used to identify clinical predictors, and $P>0.10$ was used for removing a variable in constructing the baseline clinical model. The variables evaluated in the proportional hazard regression stepwise selection model predicting end points included: age, type of AF (paroxysmal vs persistent), female sex, hypertension, type 2 diabetes mellitus and history of ischemic heart disease. History of hypertension was the only variable that made a significant contribution to the model.

Stattistical analyses were performed using Minitab version 14. A two-sided $P<0.05$ was considered statistically significant.

RESULTS

A total of 177 consecutive patients who underwent a first CB PVI procedure for symptomatic AF were included in the study. The study population's baseline characteristics are detailed in Table 1. In our cohort, patients with recurrence of AF after the blanking period were more likely to have history of ischemic heart disease. Differences in age at the time of ablation, female sex, type of AF (paroxysmal vs persistent), hypertension, diabetes mellitus, left ventricular ejection fraction, history of obstructive sleep apnea, left atrial volume index as determined by transthoracic echocardiography, or use of antiarrhythmic medications were not statistically significant predictors of recurrence.

Table 1. Baseline and Procedure Characteristics of Patients Without Recurrence of AF and Patients With Recurrence of AF During Follow-Up

Variable	No Recurrence (N=134)	Recurrence (N=43)
Age, y	62±11	63±10
Follow-up time	560±360	273±208
Male sex	83 (62%)	28 (65%)
Body mass index	32±8	31±7
Paroxysmal AF, n (%)	101 (75%)	28 (65%)
Hypertension	83 (62%)	33 (77%)
Type 2 DM, n (%)	21 (16%)	3 (7%)
Ischemic heart disease, n (%)	19 (14%)	13 (30%)
Stroke or TIA, n (%)	15 (11%)	4 (9%)
Obstructive sleep apnea	16 (12%)	2 (5%)
Baseline LVEF, %	55±11	54±14
Left atrial volume index, mL/m^2	36±14	34±13
Antiarrhythmic drug, after ablation, n (%)	74 (55%)	26 (60%)
β-Blocker, n (%)	102 (76%)	32 (74%)
Anticoagulant use, n (%)	134 (100%)	43 (100%)
Procedure time, minutes	97±17	109±33
TT-PVI recorded	391 (72%)	109 (65%)
TT-PVI, seconds	49±14	54±17
Any additional ablation required to achieve PVI, n (%)	30 (22%)	21 (49%)
Extra freeze applications used to achieve PVI, n (%)	27 (20%)	11 (26%)
Supplemental RFA to achieve PVI, n (%)	5 (3.7%)	11 (26%)

AF indicates atrial fibrillation; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; RFA, radiofrequency ablation; TIA, transient ischemic attack; and TT, time to.

Procedural Outcomes

Complete acute PVI was achieved in 176 of 177 patients (99.4%) during the index ablation procedure. Mean procedure time was longer in patients who had recurrent AF ($P=0.003$). There was no statistical difference in TT-PVI between patients with and without recurrent AF ($P=0.09$) (Table 1). Forty patients (22.6%) had at least one PV that was not isolated after cryoablation with the ST (single freeze with or without bonus freeze). To obtain isolation of all PVs, 15 patients (8.4%) required delivery of extra bonus freezes, 20 (11.3%) required supplemental RFA, and 5 required both more than one bonus freeze and supplemental RFA. For delivery of supplemental RF, operators used irrigated contact force catheters (Thermocool Smarttouch SF and Thermocool Smarttouch) and a focal ablation approach (number of RF lesions per PV: 2.7±1.1; lesion duration: 25.6±7.5 seconds; power setting: 26.8±5.5 Watts).

Table 2 shows, by PV location, the percentage of time isolation was achieved using the standard

Table 2. Method of Ablation Used for Acute Isolation by PV Location

	Standard Technique Only	More Than 1 Bonus Freeze	Supplemental RFA
Left superior, n (%)	152/166 (91.6%)	11/166 (6.6%)	3/166 (1.8%)
Left inferior, n (%)	150/166 (90.3%)	10/166 (5.6%)	6/166 (2.4%)
Left common, n (%)	7/11 (63.6%)	3/11 (2.7%)	2/11 (18.1%)
Left middle, n (%)	3/3 (100%)	0/3 (0%)	0/3 (0%)
Right superior, n (%)	147/175 (80.5%)	20/175 (11.4%)	8/175 (4.6%)
Right inferior, n (%)	145/175 (82.9%)	21/175 (12.0%)	10/175 (5.7%)
Right common, n (%)	2/2 (100%)	0/2 (0%)	0/2 (0%)
Right middle, n (%)	12/12 (100%)	0/12 (0%)	0/12 (0%)

PV indicates pulmonary vein; RFA radiofrequency ablation.

technique vs only after additional bonus freezes or supplemental RFA. The right PVs more frequently required extra bonus freezes to achieve isolation than the left PVs (11.7% vs 6.3%; *P*=0.01). The right inferior pulmonary vein (RIPV) (17.7%) most commonly required supplemental ablation (either cryoablation or RF) to assist in achieving isolation among patients with normal PV anatomy. Among patients with left common vein variant PV anatomy, 18% required supplemental RF to achieve isolation after CB ablation.

Clinical End Points for Study

During a mean follow-up of 560±268 days, there were 43 recurrences of AF after the 3-month blanking period. All patients in the study had at least 6 months of follow-up. For the overall cohort, freedom from AF was 76% during the follow-up period. Freedom from AF was 83% when PVI was achieved using only the ST as compared with 59% when additional ablation (bonus freezes or RFA) was needed to accomplish PVI. Cumulative risk of AF recurrence was higher after index CB PVI procedures when there was deviation (additional bonus freezes or RF application) from the ST (*P*=0.0001) (Figure 1A). In the multivariate Cox regression model, risk of AF recurrence was significantly lower when PVI was accomplished using the ST alone (hazard ratio [HR], 0.34; 95% CI, 0.18–0.66; *P*=0.02) (Table 3).

When specifically analyzed by mode of additional ablation, we found no significant difference in cumulative risk of AF recurrence (*P*=0.08) or need for redo ablation procedures (*P*=0.8) when additional bonus freezes were required for PVI vs standard technique alone (Figure 2A and 2B). Conversely, patients who required supplemental RFA of at least one PV during CB PVI procedures had a significantly higher risk for AF recurrence (*P*=0.0001) (Figure 2C and Table 4). In the multivariate Cox regression model, use of supplemental RFA during index CB PVI was independently associated with threefold increased risk in recurrent AF after the blanking period (Table 3). Four of the 20 patients (20%) who required supplemental RFA during index CB PVI procedures underwent subsequent redo ablation procedures. Sites of acute reconnection where focal RFA was performed during index ablation procedures correlated highly with successful locations of ablation for long-term PV reconnection during redo procedures (Figure 3).

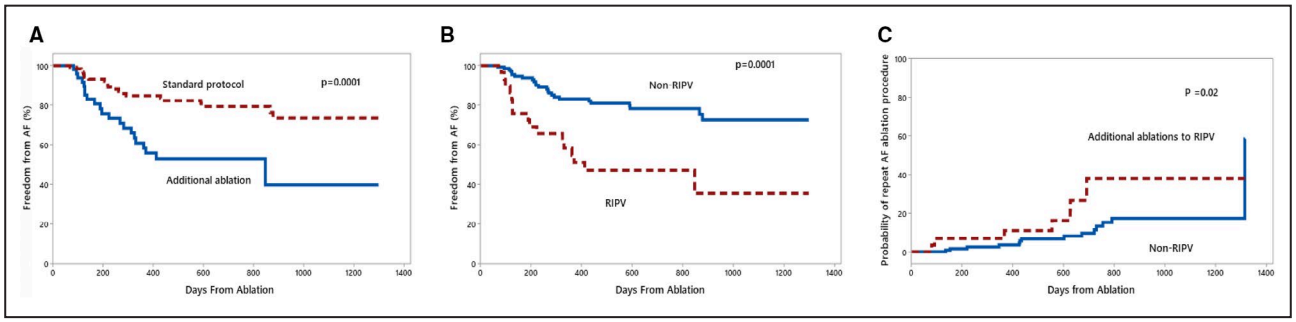


Figure 1. Freedom from atrial fibrillation and probability of undergoing repeat (primary analysis).
A, Probability of long-term freedom from AF after cryoballoon ablation with the standard technique vs requiring additional ablation of any modality (RFA, cryoablation, or both) to achieve acute PVI. **B**, Probability of freedom from AF when additional ablation was required to achieve acute isolation of RIPV vs non-RIPV locations. **C**, Probability of undergoing repeat ablation procedure when additional ablation was required to achieve acute isolation of RIPV vs non-RIPV vein locations. AF indicates atrial fibrillation; CB, cryoballoon; PVI, pulmonary vein isolation; RFA, radiofrequency ablation; and RIPV, right inferior pulmonary vein.

Table 3. Multivariate Cox Regression Models 1, 2 and 3

	Hazard Ratios	95% CI	*P* Value
Model 1: Risk of deviation from standard cryoablation technique			
Standard techniques (vs any additional ablations)	0.34	0.18 to 0.66	0.02
Model 2: Risk of any RFA (with or without additional cryoablation)			
Any additional RFA (vs additional cryoablation only and standard technique)	2.92	1.45 to 5.87	0.003
Model 3: Risk of RFA only and additional cryoablation (with or without RFA)			
Additional RFA only	3.01	1.45 to 10.87	0.003
Additional cryoablation and RFA (vs additional cryoablation only and standard technique)	2.40	0.53 to 10.87	0.3

Models adjusted for history of ischemic heart disease. RFA indicates radiofrequency ablation.

Interestingly, we also found that patients who required additional ablation to achieve isolation of the RIPV were at significantly increased risk of recurrent AF (*P*=0.0001) and there was a greater need for redo ablation procedures (*P*=0.02) compared with patients for whom additional ablation of only non-RIPVs was required (Figure 1B and 1C).

There were no procedure-related deaths during the study period. The most common procedure-related complication was phrenic nerve palsy, but all 5 of these patients had full recovery of phrenic nerve function by 6 weeks.

PV Anatomy on Contrast Tomography Imaging

We performed a subanalysis of the 97 patients in the study who had contrast computed tomography imaging before their ablation procedures to evaluate whether PV size parameters or PV shape (circular vs elliptical [ie, noncircular] shape) was associated with AF recurrence or operator use of supplemental RFA. Circularity index was calculated by short-axis dimension divided by long-axis dimensions measured from a plane perpendicular to the center line of the PV. Elliptical (noncircular)

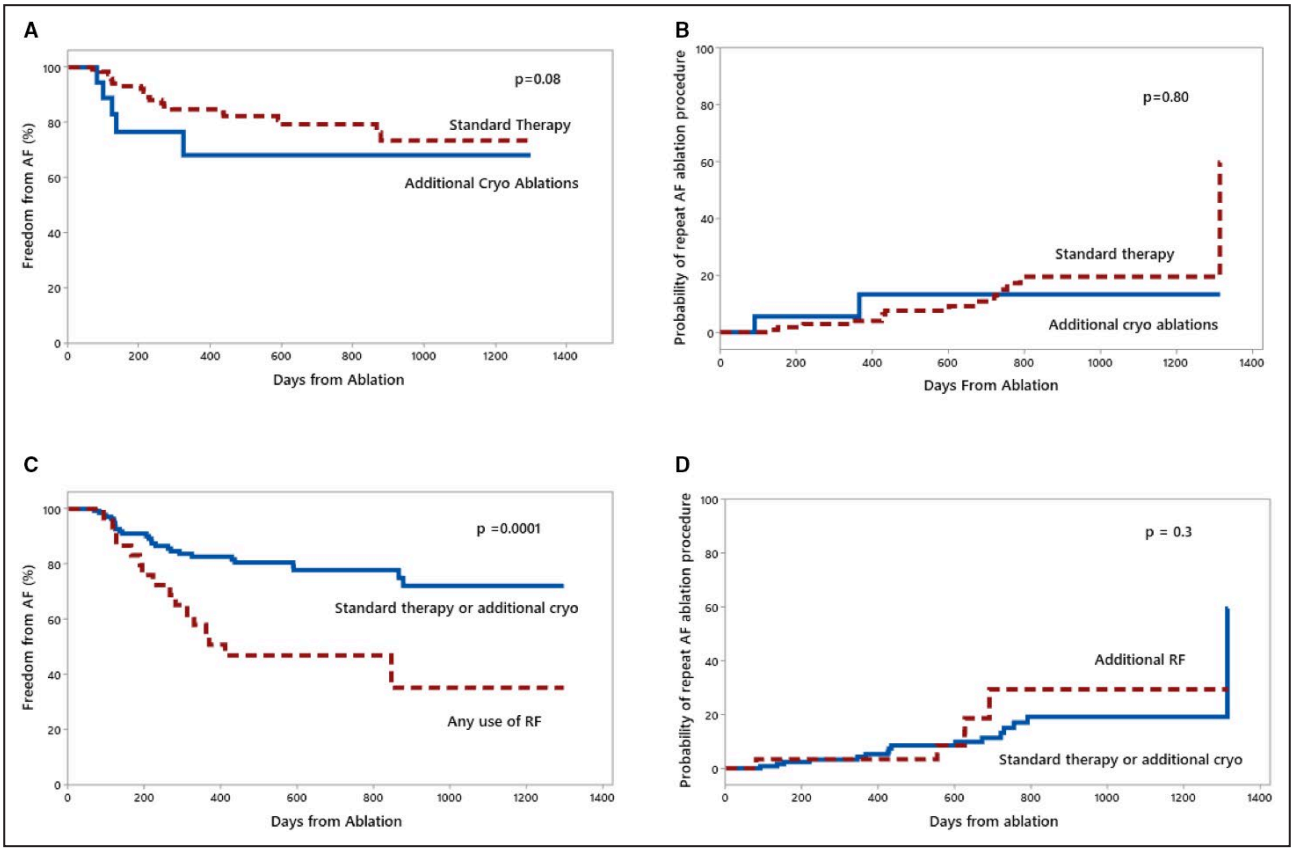


Figure 2. Freedom from atrial fibrillation and probability of undergoing repeat ablation (subanalysis).
A, Probability of long-term freedom from AF after CB ablation with the standard technique vs extra bonus freezes to achieve acute PVI. **B**, Probability of undergoing redo ablation procedure after CB ablation with the standard technique vs extra bonus freezes to achieve acute PVI. **C**, Probability of long-term freedom from AF after CB ablation with the standard technique vs supplemental RFA to achieve acute PVI. **D**, The probability of undergoing a redo ablation procedure after CB ablation with the standard technique vs supplemental RFA to achieve acute PVI. AF indicates atrial fibrillation; CB, cryoballoon; PVI, pulmonary vein isolation; and RFA, radiofrequency ablation.

Table 4. Baseline and Procedure Characteristics of Patients Without Supplemental RF and With Supplemental RF During Cryoablation Procedures

Variable	No Supplemental RF (N=152)	Supplemental RF (N=25)	*P* Value
Age, y	62±11	67±11	0.06
Follow-up time	495±351	444±355	0.5
AF recurrence	29 (19%)	14 (56%)	0.0001
Male sex	97 (64%)	14 (56%)	0.4
Body mass index	31±7	30±8	0.4
HTN, %	96 (63%)	19 (76%)	0.2
Paroxysmal	114 (75%)	15 (60%)	0.1
Type 2 DM, n (%)	20 (13%)	4 (16%)	0.7
Ischemic heart disease, n (%)	25 (16%)	7 (28%)	0.2
Stroke or TIA, n (%)	16 (11%)	3 (12%)	0.8
Obstructive sleep apnea	16(11%)	2 (8%)	0.7
Baseline LVEF, %	54±11	54±11	0.9
Left atrial volume index, mL/m^2	35±14	39±13	0.1

AF indicates atrial fibrillation; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; PVI, pulmonary vein isolation; RFA, radiofrequency ablation; TIA, transient ischemic attack; and TT, time to.

PV shape was defined as circularity index ≤0.7. No significant differences in PV sizes were observed between patients who had recurrent AF or required additional ablation and the rest of the cohort, except for larger size of RIPV (2.2±0.4 vs 1.9± 0.5 cm; *P*=0.03) for patients in whom operators chose to use supplemental RFA to assist with completing PVI. In the subanalysis, presence of elliptical RIPV ostium shape and use of RFA on an elliptical-shaped RIPV were associated with increased risk of AF (Figure 4) In the multivariate Cox regression model adjusted for history of ischemic heart disease, elliptical RIPV ostium shape (HR, 3.25; 95% CI, 1.25–8.41; *P*=0.02) and use of RFA on an elliptical-shaped RIPV (HR, 5.74; 95% CI, 2.05–16.23; *P*=0.001) were independently associated with multifold increase in risk of recurrent AF. An elliptical RIPV ostium shape was associated with higher use of supplemental RFA than circular RIPV shape (60.0% vs 33.3%; *P*=0.05), although there was no significant interaction between use of RF and elliptical RIPV shape when tested in the Cox regression model, possibly due to the sample size (n=97).

DISCUSSION

This is the first study to examine whether deviation from the standard CB ablation technique, a marker of challenging PV anatomy, has an impact on medium- and long-term outcomes after acutely successful CB PVI. In our single-center experience, we found no significant difference in risk of recurrent AF after index CB ablation procedures when more than one bonus freeze was required to achieve electrical isolation of all targeted PVs. However, the use of focal RFA during CB PVI procedures to achieve PVI was independently associated with recurrence of AF after the blanking period, suggesting poor lesion durability and potentially increased need for redo procedures when using this method.

Percutaneous PVI has become the cornerstone approach for treatment of patients with AF who have failed management with antiarrhythmic drug (AAD) therapy.[9] Regardless of ablation modality, the primary procedural objective of catheter PVI ablation is to create cellular necrosis and a durable circumferential line of conduction block between the atrial tissue and the PV musculature, which is known to harbor triggers for AF.[10] To broaden adoption of catheter ablation therapy for AF, the CB technique was designed to be a single-step approach for PVI intended to produce more homogeneous myocardial energy delivery than point-by-point RFA and reduce the total number of energy applications required to achieve acute, durable PVI. The second-generation cryoballoon (CB2; Artic Front Advance, Medtronic, Minneapolis, MN) provides improved uniform cooling on the distal hemisphere of its balloon compared with the first-generation device (CB1; Artic Front, Medtronic, Minneapolis, MN). In the Fire and Ice trial,[1] safety and freedom from AF with CB PVI was shown to be noninferior to RF PVI with comparatively shorter procedure times. CB ablation has become widely adopted as a preferred method for catheter PVI in clinical practice.[2] Recent data also suggest that, when short isolation time is achieved, only a single application is likely to be necessary for CB ablation to be clinically effective.[3,4]

Although techniques for CB ablation have been refined with increased user experience,[2] anatomic variables remain a significant obstacle to achieving effective energy transfer during lesion delivery and are predictive of long-term failure of CB PVI.[7,8] Several studies have identified anatomic variants associated with reduced success after CB PVI, including presence of a narrow ridge between the left superior pulmonary vein and left atrial appendage, a sharp carina between the left superior pulmonary vein and left inferior pulmonary vein, perpendicular angulation between the axis of the RIPV and its ostium, and early branching of the RIPV.[7,8,11] We found that difficulty achieving RIPV isolation, in particular, was a predictor of increased AF recurrence and need for redo ablation procedures, even after eventual RIPV isolation during the index procedure. In a subanalysis of 97 patients

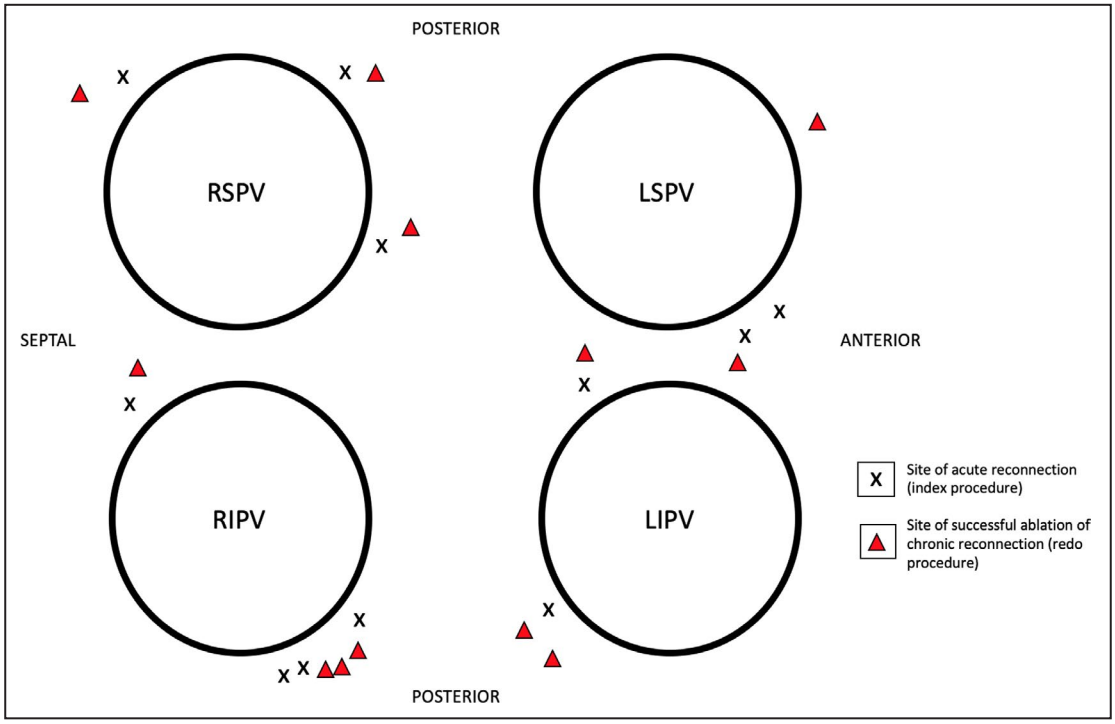


Figure 3. Locations of acute reconnections requiring supplemental radiofrequency ablation for PV isolation during index cryoablation procedures and successful sites of radiofrequency ablation for chronic reconnection in redo ablation procedures (n=4).
LIPV indicates left inferior pulmonary vein; LSPV, left superior pulmonary vein; RIPV, right inferior pulmonary vein; and RSPV, right superior pulmonary vein.

with preprocedure computed tomography imaging, presence of elliptical shape of the RIPV ostium was associated with use of supplemental RFA and higher risk of AF recurrence. These findings may suggest that ostial PV shape (particularly for the right PVs) may be an important anatomic consideration when deciding on which ablation modality to use for PVI.

Due to the fixed balloon size of the CB catheter, balloon/PV size mismatch is another challenge encountered during CB PVI, particularly for large ovoid PVs and common ostium PV variants.[11] For these reasons, the 28-mm CB catheter is more frequently used in clinical practice than the smaller balloon.[2] However, PV stenosis remains a concern, even with the CB2 device[12] so use of the "proximal seal" technique is recommended to avoid inadvertent ablation deep within or inside the tubular portion of large vessels. For PV ostia larger than the 28-mm balloon, this technique involves a segmental ablation approach, where balloon angulation is adjusted before each subsequent freeze to the PV ostium.[2] However, hemispheric balloon contact and convective heating due to moving blood caused by an incomplete seal may increase the chance of uneven or suboptimal tissue injury after freeze applications, perhaps even in multiple areas (Figure 5A). Also, due to the fluoroscopic nature of lesion delivery and absence of electroanatomic mapping correlation, the proximal segmental approach may be difficult for large PVs and targeting "gaps" on the antrum of acutely reconnected PVs.

In this study we found that the need for extra bonus freezes was not associated with increased AF recurrence. However, caution should still be applied toward unnecessary delivery of freeze applications, as reports have suggested a high number of freezes and total duration of freeze time may be associated with increased risk of complications, such as phrenic nerve injury and damage to esophageal or bronchial tissues.[13] Therefore, minimizing the number of freeze cycles remains prudent from a safety standpoint to reduce the chances of thermal injury to adjacent extracardiac structures. In situations where external injury is a concern during CB ablation, or if patient-specific risk factors are present,[13,14] then a pragmatic decision must be made between continuing further freeze attempts, switching to a supplemental RFA approach to accomplish acute isolation, or terminating the procedure without isolation of all PVs.

In our cohort, RFA was utilized in 11.3% of index CB ablation procedures to complete PVI. These results are consistent with the findings from other studies, which reported use of supplemental focal RFA in 9%–32% of cryo PVI procedures to achieve acute PVI.[6,7,15,16] In a study of 30 patients, Yasuoka et al[16] reported focal RFA was most commonly needed for isolation of RIPVs and left inferior pulmonary veins with low take-offs

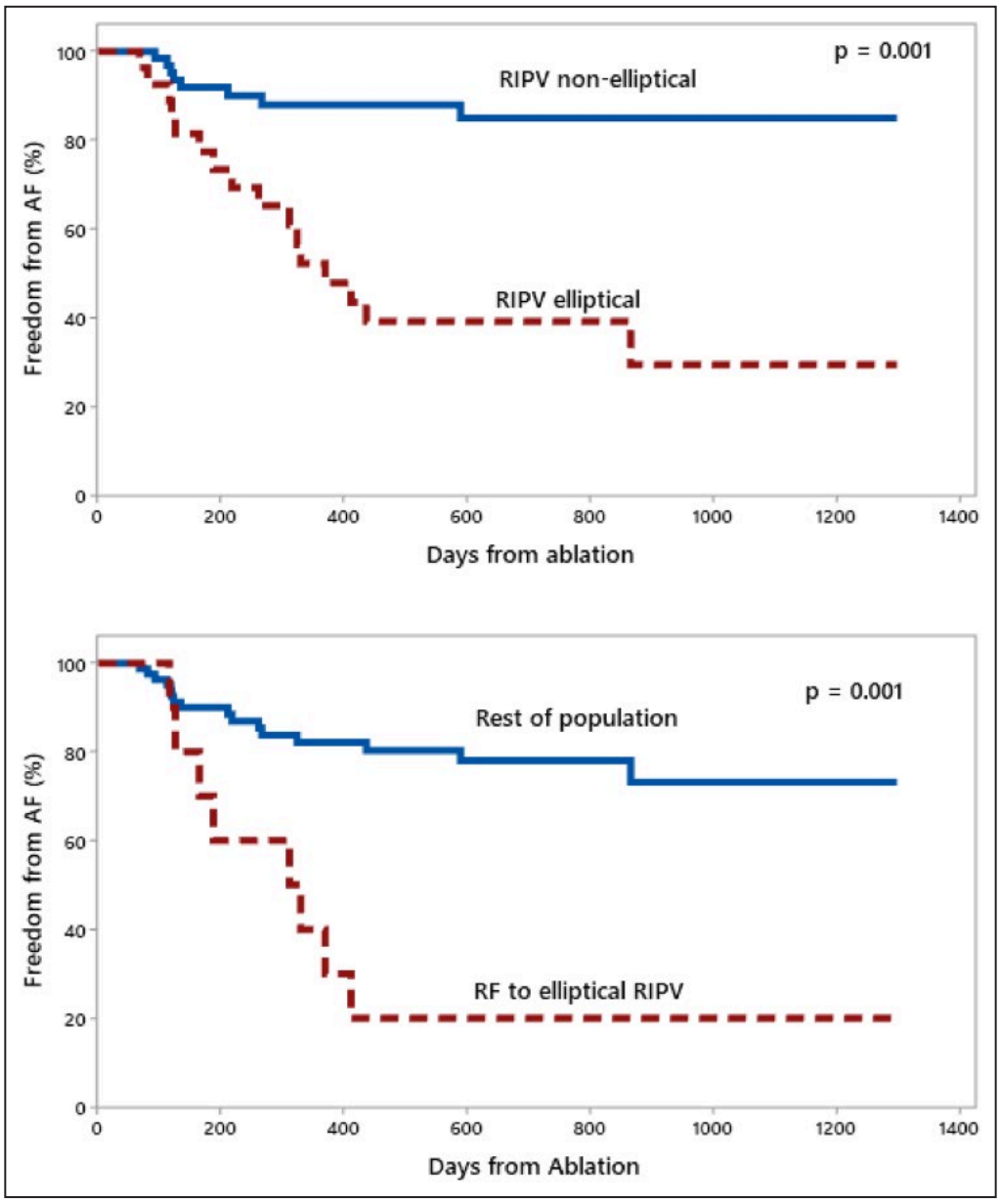


Figure 4. Freedom from atrial fibrillation based on shape of pulmonary vein ostium.
A, Probability of long-term freedom from AF based on elliptical RIPV ostium shape (regardless of need for additional ablation). **B**, Probability of long-term freedom from AF after RF to elliptically shaped RIPV ostium. AF indicates atrial fibrillation; RF, radiofrequency; and RIPV, right inferior pulmonary vein.

(23.3% vs 6.7% in the superior veins, respectively) after attempts at CB ablation were unsuccessful. A novel finding of the current study is that use of supplemental RFA (but not extra bonus freezes) was independently associated with increased risk of late recurrence of AF postablation. Although it is known that accomplishing acute PVI does not necessarily correlate well with durable circumferential necrosis,[17] these findings are nevertheless surprising and suggest that the combination of cryoablation and RF energy delivery may be less clinically effective, or (less likely) that there was a deficiency in the technique in which RFA was deployed.

We postulate two plausible explanations for this clinical observation. First, epicardial fibers are known to connect the PV musculature to other parts of the left atrial, muscle bundles within the ligament of Marshall, Bachman's bundle, superior vena cava, right atrium, and even between contiguous PVs. The presence of epicardial fibers is believed to reduce the likelihood of short- and long-term success during both PVI and left atrial ablation.[18–20] In an animal model, it was demonstrated that presence of epicardial fibers sometimes prevented successful PVI, even with repeated freeze applications targeting gaps identified by EAM. The

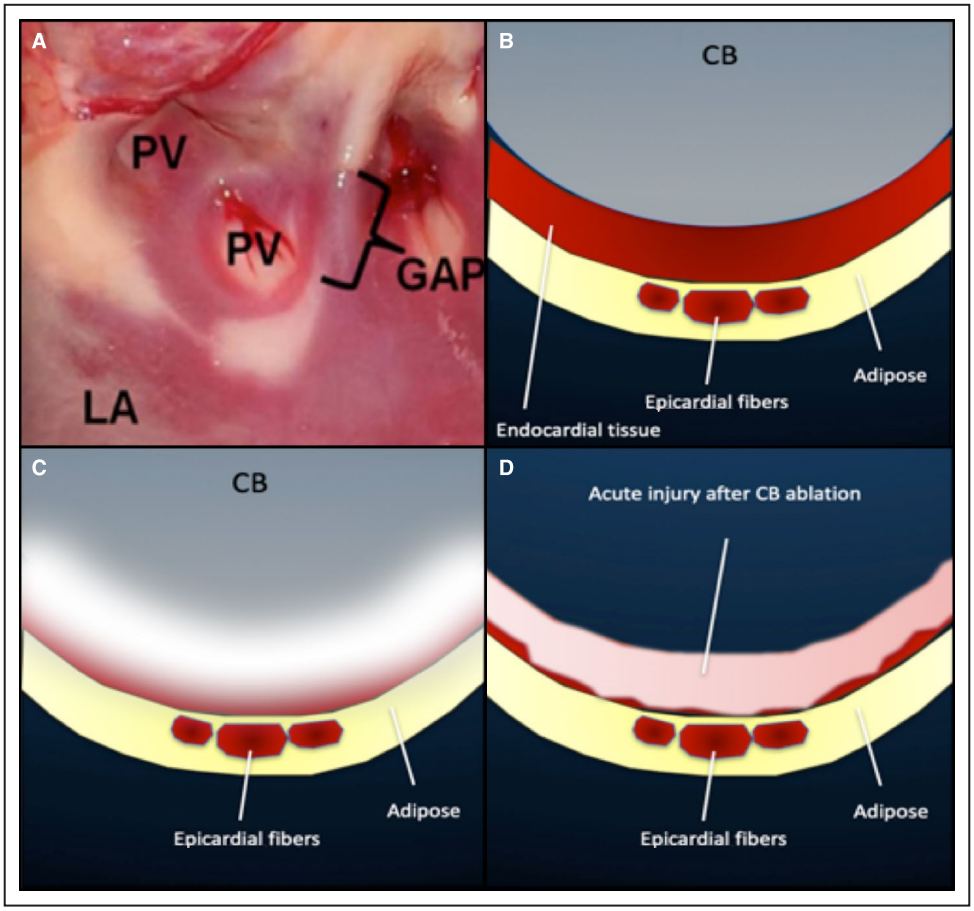
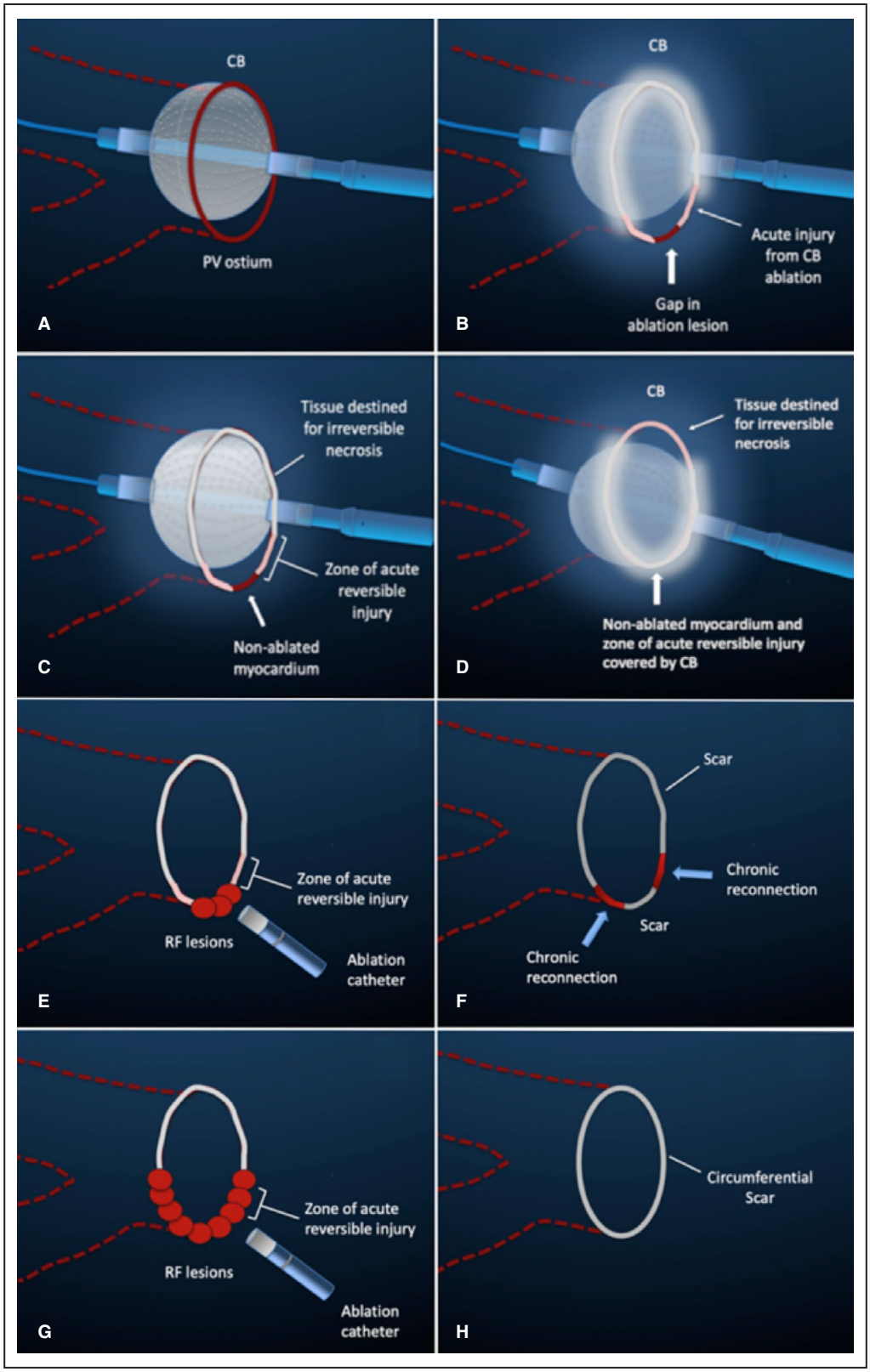


Figure 5. Failure of circumferential pulmonary vein isolation due to inadequate tissue depth during ablation.
A, Macroscopic findings at the left atrial–pulmonary vein junction. The pulmonary vein is reconnected due to presence of a gap after ablation. Another segment with thin, nontransmural lesion is visualized along the antrum. **B**, CB positioned on the PV ostium with optimum contact and seal. **C**, Delivery of cryothermal energy during the freeze cycle fails to reach subepicardial tissue and epicardial fibers due to thick myocardium or presence of epicardial fibers insulated by surrounding adipose tissue in the epicardium. **D**, Gap in conduction block after CB ablation due to absence of injury to epicardial fibers along the PV antrum. CB indicates cryoballoon; LA, left atrium; and PV, pulmonary vein. Reproduced from Takami et al[21] with permission. Copyright 2014 American Heart Association, Inc.

authors postulated that failure of targeted endocardial cryoablation was likely due to the presence of fat-insulating epicardial tissue or the coronary sinus itself acting as a thermal sink preventing effective heat transfer and transmural lesion formation.[20] Thus, it is plausible that, even with optimal positioning and

Figure 6. Addressing acute pulmonary vein reconnection due to balloon size mismatch with supplemental ablation.
CB ablation of a large ovoid-shaped PV using a segmental proximal ablation approach with the 28-mm second-generation CB catheter. **A**, Balloon/PV size mismatch results in a gap between the equatorial surface of the CB and the inferior and posterior portions of the PV antrum. **B**, Despite incomplete PV occlusion, delivery of cryothermal energy results in acute injury to most of the PV antrum except for a small gap on the inferior portion of the PV. However, heat transfer from myocardial tissue to CB during freeze application is lessened in areas not in contact with the balloon. **C**, Although there is a large area of acute injury after CB ablation, only the zones in direct contact with the balloon go on to develop necrosis, whereas areas of acute injury nearby unablated myocardium sustain only reversible injury. **D**, Repositioning of the CB inferiorly results in ablation of both the gap area and surrounding zone of reversible injury, resulting in durable PV isolation. **E**, Focal approach: RF lesions are delivered targeting electrocardiograms on the PV antrum. Once electrical isolation of the target PV is achieved with RF ablation, no further lesions are delivered. **F**, Tissue in the zone of acute reversible injury that was missed during focal RFA goes on to recover and form chronic reconnection between the PV and left atrium. **G**, Wide lesion set approach. Rather than stopping ablation after electrical isolation of the PV is achieved by targeting electrocardiograms on the PV antrum, additional empiric RFA is continued until a semicircumferential or circumferential lesion set is created along the PV antrum to ensure that tissue in the zone of acute reversible injury is adequately ablated. **H**, RFA using the wide lesion set approach results in circumferential scar around the PV antrum. CB indicates cryoballoon; PV, pulmonary vein; and RFA, radiofrequency ablation.

seal, cryoinjury may be insufficient to create the necessary depth of necrosis for long-term lesion durability (Figure 5A through 5C). Further, it is plausible that edema created from preceding CB ablation attempts may reduce the effectiveness of subsequent lesions (either cryoablation or RF) and could also result in insufficient lesion depth to reach thick tissue or epicardial fibers.



Another potential reason for reduced clinical efficacy observed in the RFA group may have been the ablation strategy employed by operators during the use of supplemental RFA to achieve PVI. To create a homogeneous lesion during cryoablation, circumferential balloon contact and seal is needed, otherwise ablation may lead only to reversible injury in some areas rather than intended necrosis and scar formation, potentially leading to long-term PV reconnection and clinical recurrence of AF (Figure 6A through 6C). In the current study, operators performed focal RF ablation to gaps identified after cryoablation by targeting discernible electrocardiograms along the PV antrum during lesion delivery (Figure 6E). Once PVI was achieved (as assessed by disappearance of PV electrocardiograms and demonstration of bidirectional electrical block), additional empiric ablation to extend the lesion set along the PV antrum was not performed unless there was further evidence of acute reconnection during the procedure. However, given the inability to distinguish between areas destined to develop irreversible necrosis from those with reversible injury after cryoablation, this focal RFA approach may have been insufficient to prevent late PV reconnection (Figure 4F). Conversely, when repositioning the CB and subsequent freeze attempts led to successful isolation, durable PVI may have been more likely because of the wide arc of ablation created by hemispheric balloon contact with the PV antrum (Figure 6D). Therefore, a surer approach for supplemental RFA when needed during CB PVI may be to empirically create a wider lesion set than necessary to simply achieve acute PVI, or consider deploying a partial or full circumferential lesion set around the target PV if the location of the gap is uncertain or multiple gaps are suspected (Figure 6G and 6H).

Although this study has confirmed that a single-modality approach is preferred for CB PVI, RFA is sometimes needed when PV anatomy is unfavorable, risk of injury to extracardiac structures is unacceptably high with CB ablation, and is more ideal than leaving intact electrical conduction of one or more PVs. In our cohort, overall freedom from AF was 76% after index CB PVI ablation procedures, commensurate with clinical outcomes of other studies.[1–4,15] Given supplemental RFA is sometimes required due to unfavorable PV anatomy or for procedural safety,[6,7,15,16] the findings of this study suggest that a revised supplemental RF ablation strategy may be needed to improve overall clinical efficacy and lesion durability for this subset of patients undergoing CB PVI.

CONCLUSIONS

Use of a supplemental RFA to achieve electrical isolation of one or more PVs after attempted CB ablation was independently associated with increased risk of AF recurrence despite accomplishing complete acute PVI. The use of extra bonus freezes to accomplish PVI was not associated with increased risk of AF recurrence.

STUDY LIMITATIONS

First, this was a moderate-sized study, and therefore our novel findings should be validated in a larger prospective cohort. Although this study was observational, the ablation protocol was consistent through the study period and the operators were blinded to the study aim and concept. Therefore, there is little treatment or selection bias in the main results of the study. Ablation was performed using the most contemporary technology for both modalities, including the second-generation cryoballoon device during CB ablation and contact force-sensing ablation catheters when RF ablation was employed.

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REFERENCES

1. Kuck KH, Brugada J, Fürnkranz A, Metzner A, Ouyan F, Chun J, Elvan A, Arentz T, Bestehorn K, Pocock SJ, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med*. 2016;374:2235–2245.
2. Su W, Kowal R, Kowalski M, Metzner A, Svinarich JT, Wheelan K, Wang P. Best practice guide for cryoballoon ablation in atrial fibrillation: the compilation experience of more than 3000 procedures. *Heart Rhythm*. 2015;12:1658–1666.
3. Aryana A, Kenigsberg DN, Kowalski M, Koo CH, Lim HW, O'Neil PG, Bowers MR, Hokanson RB; Ellenbogan, Cryo-DOSING investigators. Verification of a novel atrial fibrillation cryoablation dosing algorithm guided by time-to-pulmonary vein isolation: results from the Cryo-DOSING Study (Cryoballoon-ablation DOSING Based on the Assessment of Time-to-Effect and Pulmonary Vein Isolation Guidance). *Heart Rhythm*. 2017;14:1319–1325.
4. Ferrero-de-Loma-Osorio A, Garcia-Fernandez A, Castillo-Castillo J, Izquierdo-de-Francisco M, Ibanez-Criado A, Moreno-Arribas J, Martinez A, Bertomeu-Gonzalez V, Lopez-Mases P, Ajo-Ferrer M, et al. Time-to-effect-based dosing strategy for cryoballoon ablation in patients with paroxysmal atrial fibrillation: results of the plusone multicenter randomized controlled noninferiority trial. *Circ Arrhythm Electrophysiol*. 2017;10:e005318.
5. Ciconte G, Mugnai G, Sieira J, Velagic V, Saitoh Y, Irfan G, Hunuk B, Stroker E, Conte G, Di Giovanni G, et al. On the quest for the best freeze: predictors of late pulmonary vein reconnections after second-generation cryoballoon ablation. *Circ Arrhythm Electrophysiol*. 2015;8:1359–1365.
6. Miyamoto K, Doi A, Hasegawa K, Morita Y, Mishima T, Suzuki I, Kaseno K, Nakajima K, Kataoka N, Kamakura T, et al. Multicenter study of the validity of additional freeze cycles for cryoballoon ablation in patients with paroxysmal atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2019;12:e006989.

7. Knecht S, Kühne M, Altmann D, Amann P, Schaer B, Osswald S, Sticherling C. Anatomical predictors for acute and mid-term success of cryoballoon ablation of atrial fibrillation using the 28 mm balloon. *J Cardiovasc Electrophysiol*. 2013;24:132–138.
8. Huang SW, Jin Q, Zhang N, Ling TY, Pan WQ, Lin CJ, Luo Q, Han Y, Wu L. Impact of pulmonary vein anatomy on long-term outcome of cryoballoon ablation for atrial fibrillation. *Curr Med Sci*. 2018;38:259–267.
9. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2019;140:e125–e151.
10. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G, Garrigue S, Mouroux AL, Metayer PL, Clementy J. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339:659–666.
11. Sorgente A, Chierchia GB, de Asmundis C, Sarkozy A, Namdar M, Capulzini L, Yazaki Y, Muller-Burri S, Bayrak F, Brugada P. Pulmonary vein ostium shape and orientation as possible predictors of occlusion in patients with drug-refractory paroxysmal atrial fibrillation undergoing cryoballoon ablation. *Europace*. 2011;13:205–212.
12. Tokutake K, Tokuda M, Yamashita S, Sato H, Ikewaki H, Okajima E, Oseto H, Yokoyama M, Isogai R, Yokoyama K, et al. Anatomical and procedural factors of severe pulmonary vein stenosis after cryoballoon pulmonary vein ablation. *JACC Clin Electrophysiol*. 2019;5:1303–1315.
13. Canpolat U, Kocyigit D, Aytemir K. Complications of atrial fibrillation cryoablation. *J Atr Fibrillation*. 2017;10:1620.
14. Ichihara N, Miyazaki S, Iwasawa J, Matsuda J, Taniguchi H, Nakamura H, Hachiya H, Takagi T, Kuroi A, Iesaka Y. Prevalence and pre-procedural predictors associated with right phrenic nerve injury in electromyography-guided second-generation cryoballoon ablation. *JACC Clin Electrophysiol*. 2016;2:508514.
15. Defaye P, Kane A, Chaib A, Jacon P. Efficacy and safety of pulmonary veins isolation by cryoablation for the treatment of paroxysmal and persistent atrial fibrillation. *Europace*. 2011;13:789–795.
16. Yasuoka R, Kurita T, Kotake Y, Hashiguchi N, Motoki K, Iwanaga Y, Miyazaki S. Particular morphology of inferior pulmonary veins and difficulty of cryoballoon ablation in patients with paroxysmal atrial fibrillation. *Circ J*. 2017;81:668–674.
17. Arujuna A, Karim R, Caulfield D, Knowles B, Rhode K, Schaeffter T, Kato B, Rinaldi A, Cooklin M, Razavi R, et al. Acute pulmonary vein isolation is achieved by a combination of reversible and irreversible atrial injury after catheter ablation: evidence from magnetic resonance imaging. *Circ Arrhythm Electrophysiol*. 2012;5:691–700.
18. Ho SY, Sanchez-Quintana D, Cabrera JA, Anderson RH. Anatomy of the left atrium: implications for radiofrequency ablation of atrial fibrillation. *J Cardiovasc Electrophysiol*. 1999;10:1525–1533.
19. Yoshida K, Baba M, Shinoda Y, Harunari T, Tsumagari Y, Koda N, Hayashi K, Yaguchi T, Watabe H, Hasebe H, et al. Epicardial connection between the right-sided pulmonary venous carina and the right atrium in patients with atrial fibrillation: a possible mechanism for preclusion of pulmonary vein isolation without carina ablation. *Heart Rhythm*. 2019;16:671–678.
20. Jones DL, Guiraudon GM, Skanes AC, Guiraudon CM. Anatomical pitfalls during encircling cryoablation of the left atrium for atrial fibrillation therapy in the pig. *J Interv Card Electrophysiol*. 2008;21:187–193.
21. Takami M, Misiri J, Lehmann HI, Parker KD, Johnson SB, Sarmiento RI, Packer DL. Spatial and time-course thermodynamics during pulmonary vein isolation using the second-generation cryoballoon in a canine in vivo model. *Circ Arrhythm Electrophysiol*. 2015; 8:186–192.