

## Improved Resource Utilization With Similar Efficacy During Early Adoption of Cryoballoon Pulmonary Vein Isolation as Compared to Radiofrequency Ablation for Paroxysmal Atrial Fibrillation

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### Abstract

**Background:** Cryoballoon pulmonary vein isolation (PVI) is an alternative to radiofrequency (RF) PVI for the treatment of paroxysmal atrial fibrillation (AF). Treatment effect, complication rates, and hospital length of stay are not well established with early use of cryoballoon PVI as compared to more experienced performance of RF PVI.

**Methods:** We reviewed the early experience of cryoballoon PVIs for paroxysmal AF performed by 3 operators at our institution compared to their most recent RF PVIs. All repeat procedures were excluded. Patients were assessed for recurrence of AF at 6 months after the procedure, including a 3-month blanking period. Complications, procedure time, and hospital length of stay were recorded.

**Results:** Final analysis included 50 cryoballoon PVIs and 50 RF PVIs. There was no significant difference in baseline characteristics or percentage of patients wearing a home monitor (80% for cryoballoon vs 80% for RF). Symptomatic improvement was experienced by 96% of cryoballoon PVI as compared to 86% of RF PVI patients ( $p=0.08$ ). Freedom from AF at 6 months was similar between the two groups (70% for cryoballoon and 70% for RF,  $p=1$ ). Complications were seen in 6% of cryoballoon procedures as compared to 10% of RF procedures ( $p=0.46$ ). Hospital length of stay was significantly shorter in the cryoballoon group (1.6 vs 3.4 nights,  $p=0.003$ ).

**Conclusions:** At the time of its adoption, cryoballoon PVI is associated with shorter procedure times and hospital length of stay as compared to RF PVI in experienced operators while maintaining similar efficacy outcomes and complication rates.

### Introduction

It has been previously shown by Haisseguerre et al that the main trigger for paroxysmal atrial fibrillation (PAF) is ectopy arising from within the pulmonary veins.<sup>1</sup> Ablation therapy for PAF has therefore focused on the electrical isolation of the pulmonary veins.<sup>2</sup> This has traditionally been performed using radiofrequency (RF) catheter ablation with a point-by-point technique.<sup>3</sup> Cryoballoon ablation has more recently become available as a method to achieve pulmonary vein isolation (PVI) en bloc. The potential advantages of cryoballoon PVI include shorter procedure times and quicker learning curve, however the published experience is limited in this regard and it is not entirely clear if these potential gains are at the cost of efficacy. We therefore examined the comparative efficacy, complications, procedure time, and hospital length of stay of RF and cryoballoon for PVI during its initial adoption at our center.

**Disclosures:**  
None.

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### Material and Methods

Consecutive patients undergoing cryoballoon PVI procedures for symptomatic PAF by three operators at the University of Pittsburgh Medical Center were identified from August 2011 to March 2013 including the first cases in the learning curve of this procedure. As a comparison group, consecutive RF PVI procedures by the same operators were selected from June 2009 to August 2011. All patients had symptomatic PAF, which was defined as self-terminating atrial fibrillation lasting no longer than 7 days, and not having previously required cardioversion. Patients with persistent or permanent atrial fibrillation were excluded. Patients were also excluded with insufficient follow-up or if they had previously undergone pulmonary vein isolation by any technique. Patient follow-up was as per standard protocol with outpatient visits at 6 weeks, 3 months and 6 months post-ablation. Retrospective chart review was performed to assess clinical outcomes through 6 months post-procedure. Recurrence was defined as an episode of an atrial arrhythmia (atrial fibrillation, atrial tachycardia, atrial flutter) lasting > 30 seconds on event monitoring or a recurrence of typical symptoms, if not captured on monitoring. Persistent phrenic nerve injury (PNI) was defined as still present at the end of the procedure. Hospital length of stay (LOS) was defined as the number of nights the patient was hospitalized after

**Table 1: Baseline Patient Characteristics**

	Cryo	RF	p-value
Age (years)	58 ± 10	55 ± 11	0.24
Male	39 (78%)	34 (68%)	0.26
Hypertension	31 (62%)	26 (52%)	0.31
Heart Failure	0 (0%)	1 (2%)	0.31
Stroke/TIA	4 (8%)	0 (0%)	0.04
Diabetes	10 (20%)	4 (8%)	0.08
CHADS2	1.0 ± 0.9	0.6 ± 0.7	0.02
CHADS2-VASc	1.6 ± 1.3	1.3 ± 1.2	0.29
Ejection Fraction (%)	59 ± 2.8	58 ± 2.5	0.38
Left atrial size (cm)	4.1 ± 0.6	4.0 ± 0.7	0.52
AF duration (months)	38 ± 45	56 ± 78	0.16
# previous AADs	1.3 ± 0.7	1.4 ± 1.1	0.41
Prior AAD use	45 (90%)	45 (90%)	1.0
Prior amiodarone use	5 (10%)	6 (12%)	0.75
Warfarin use	17 (34%)	36 (72%)	<0.001

the procedure.

All patients underwent cardiac CT to assess the pulmonary vein anatomy as well as transesophageal echocardiogram to exclude the presence of left atrial thrombus either the day before or the morning of the procedure. Most patients underwent a follow-up transthoracic echocardiogram on the evening of the procedure or the next day. Periprocedural anticoagulation was managed as per physician discretion.

All ablation procedures were performed under general anesthesia and paralytics were avoided post induction during cryoballoon ablations to allow monitoring of phrenic nerve function. The cryoballoon pulmonary vein isolation procedure has been previously described in detail,<sup>4,5,6</sup> but will be briefly reviewed here. All cases were performed using the Arctic Front cryoballoon (Medtronic, Inc, Minneapolis, Minnesota). Single and double transseptal punctures were performed but after initial learning curve, most cryoballoon cases were performed with a single transseptal approach. For most cases, after occlusive venogram, two 240 second lesions were applied in each pulmonary vein and additional cryoballoon or RF lesions were applied if conduction persisted until isolation was confirmed by elimination or dissociation of pulmonary vein potentials and high output pacing within the pulmonary veins. For the right-sided pulmonary veins, high-output pacing was performed from the superior vena cava to monitor phrenic nerve function and ablation was immediately terminated with any decreased diaphragmatic excursion.

The radiofrequency pulmonary vein isolation has also been described previously in detail,<sup>7,8</sup> but the technique utilized is briefly summarized here. All procedures were performed utilizing jet ventilation. Double transseptal puncture was performed and a 3.5mm open irrigation ablation catheter (NaviStar Thermocool Irrigated Tip Catheter; Biosense Webster, Inc, Diamond Bar, California) was utilized with 3D electroanatomic mapping with the Carto system (Biosense Webster). A 9MHz intracardiac echocardiography catheter

was placed in the left atrium through the second transseptal site to allow continuous visualization of the ablation catheter position and tissue contact. RF energy was delivered at a maximum of 30W, and limited to 25W during applications in the posterior left atrial wall. Two encircling ablation lesion sets were created to isolate the left and right pulmonary venous vestibules, respectively. Electrical isolation was confirmed by high output pacing within the pulmonary veins. No additional left atrial lines or complex fractionated electrograms were targeted.

All continuous variables were reported as mean +/- standard deviation. Statistically significant differences between the two groups were defined as a p-value < 0.05. P-values for continuous variables were determined by the Student's t-test. For discrete variables, p-values were calculated using chi-square. Multivariate analysis using binary logistic regression was performed in the analysis of hospital length of stay. The primary endpoint of the study was occurrence of atrial fibrillation at 6 months post-procedure. The secondary endpoints were procedural complications, procedure time, fluoroscopy time, and hospital length of stay.

## Results

Patients were selected from a pool of 77 consecutive cryoballoon PVI and 62 RF PVI for PAF. Eight redo PVI were excluded from each group, as well as those with insufficient follow-up (N=19 cryoballoon PVI, 4 RF PVI), leading to 50 patients in each group. The baseline characteristics of the two groups are shown in Table 1.

CT revealed conventional pulmonary vein anatomy in 39/50 (78%) cryoballoon cases and 36/49 (73%) RF PVI cases. CT scan was not available in one RF PVI patient. A common left pulmonary vein trunk was found in 7 cryoballoon and 7 RF PVI cases. An accessory right pulmonary vein os was found in 3 cryoballoon and 3 RF PVI patients. One cryoballoon and 3 RF PVI patients had both a common left pulmonary vein trunk and an accessory right pulmonary vein os.

The first generation balloon was used in 66% of cryoballoon cases, while the remaining 34% of cases used the second generation balloon. Touch-up RFA was utilized in 6/33 (18%) cases with the first generation balloon and 2/17 (12%) cases with the second generation balloon. Cavo-tricuspid isthmus ablation for right atrial flutter was performed in 2 cases.

Pulmonary vein isolation was confirmed in 49 of 50 cryoballoon cases (98%). In the unconfirmed case, isolation was confirmed in all veins except the right inferior pulmonary vein. In this vein, transseptal access was lost after one 4-minute freeze cycle, and was not reestablished. PVI was confirmed in 48 of 50 RF cases (96%). In one case, isolation was confirmed in the left veins, however the patient developed tamponade, and the case was ended before any ablation of the right veins. In the other case, isolation was confirmed in the left veins, however there were significant technical challenges during ablation of the right veins, and the case was terminated after transseptal access was lost for a third time.

Procedural results are summarized in Table 2. Procedure time was available for 31/50 (62%) cryoballoon procedures and 32/50 (64%) RF procedures. Mean procedure time was 2.7 hours for cryoballoon PVI compared to 4.8 hours for RF PVI (p<0.001). The fluoroscopy time was available for 49/50 (98%) cryoballoon procedures and 49/50

**Table 2: Procedural Outcomes**

	Cryo (N=50)	RF (N=50)	p-value
Procedure Duration (hours)	2.7 ± 0.6	4.8 ± 1.3	< 0.001
Fluoroscopy Time (minutes)	46 ± 22.9	45 ± 24.9	0.84
Complications	3 (6%)	5 (10%)	0.46
Length of Stay (nights)	1.6 ± 1.0	3.4 ± 3.9	0.003
Freedom from AF at 6 months	35 (70%)	35 (70%)	1

(98%) RF procedures. The mean fluoroscopy time was 46 minutes for cryoballoon PVI and 45 minutes for RF PVI ( $p=0.84$ ). Contrast usage was available for 31/50 (62%) cryoballoon procedures, and an average of 49cc of contrast was used during cryoballoon PVI, while no contrast was used for RF PVI.

During the follow-up period, home monitors were worn by 40/50 (80%) patients after cryoballoon ablation, and 40/50 (80%) patients after radiofrequency ablation, including one patient in each group with a permanent pacemaker. An additional 3 patients in each group did not wear a monitor due to documented recurrence of AF on EKG. Therefore, 7 patients in each group (14%) did not wear a monitor to document the absence of recurrent AF. The patients wore the monitors for an average of 21 days in the cryoballoon group and 18 days in the RF group ( $p=0.3$ ). The monitors were placed an average of 165 days after cryoballoon PVI and 168 days after RF PVI ( $p=0.7$ ).

Freedom from atrial fibrillation at 6 months was achieved in 35/50 (70%) patients after cryoballoon PVI and 35/50 (70%) patients after RF PVI after a 3-month blanking period. Patient-reported symptomatic benefit was observed in 48/50 (96%) cryoballoon patients and 43/50 (86%) RF patients ( $p=0.08$ ). Patients undergoing cryoballoon PVI using the first generation cryoballoon had AF recurrence in 12/33 (36%) as compared to 3/17 (18%) for the second generation balloon ( $p=0.17$ ).

Following the procedure, 17/50 (34%) cryoballoon PVI and 10/50 (20%) RF PVI patients were not on antiarrhythmic medications (AADs) at any point during the follow-up period ( $p=0.11$ ). Patients were on AADs for an average of 9.4 weeks after cryoballoon PVI and 11.7 weeks after RF PVI ( $p=0.2$ ). At 6 months, 13/50 (26%) cryoballoon and 15/50 (30%) RF PVI patients were on AADs ( $p=0.7$ ). Amongst the patients who did not have any recurrence of AF, 6/35 (17%) cryoballoon and 6/35 (17%) RF PVI patients were on AADs at 6 months.

There were 3 (6%) complications in the cryoballoon group (one groin bleed and 2 persistent PNIs) and 5 (10%) complications in the RF group (right buttock hematoma, prolonged respiratory failure, femoral pseudoaneurysm, cardiac tamponade, and persistent PNI). There was no significant difference in the complication rate between the 2 procedures ( $p=0.46$ ). The two persistent PNIs following cryoballoon PVI resolved within two months after the procedure, although the one PNI after RF PVI persisted through the follow-up period.

The average LOS following cryoballoon PVI was 1.6 nights as compared to 3.4 nights after RF PVI ( $p=0.003$ ). Removing one outlier from the RF group (LOS = 29 days), the mean LOS after RF PVI decreases to 2.9 nights, which remained significantly greater

than for cryoballoon PVI ( $p<0.001$ ). Four out of 50 (8%) cryoballoon PVI patients spent more than 2 nights in the hospital post-procedure as compared to 24/50 (48%) RF PVI patients ( $p<0.001$ ). Fewer cryoballoon than RF PVI patients were anticoagulated with warfarin (34% vs 72%,  $p<0.001$ ). Using binary logistic regression, cryoballoon PVI was an independent predictor of having LOS  $\leq 2$  nights, even after correcting for the difference in warfarin use between the groups (HR=0.01, 95% CI 0.03-0.33,  $p<0.001$ ).

## Discussion

There remains no consensus on the optimal method of ablation to treat patients with paroxysmal atrial fibrillation. While RF is the most widely utilized technique, cryoballoon is increasing in popularity at our institution. In this retrospective review, there was no significant difference in baseline characteristics between the cryoballoon and RF patients. Despite inclusion of initial “learning curve” cases with the cryoballoon amongst 3 RF PVI experienced operators, no significant difference in 6-month efficacy was seen.

One of the most appealing features of cryoballoon PVI as compared to RF PVI is the possibility of shorter procedure times and decreased complexity. The idea of shorter procedure times was supported by some smaller studies,<sup>9,10,11,12</sup> although a recent German registry showed no difference in procedure time, and actually suggested longer fluoroscopy times and ablation time with the cryoballoon technique.<sup>13</sup> In our patient population, there was a significantly shorter procedure time for cryoballoon as compared to RF PVI procedures, while fluoroscopy times were similar. These results were also demonstrated in a recent multicenter European study.<sup>14</sup>

Our study demonstrated shorter hospital LOS following cryoballoon PVI as compared to RF PVI. As the RF PVIs were performed before the cryoballoon cases, there was more warfarin use in the RF patients. However, even after accounting for this difference, there was a significantly shorter hospital stay following the cryoballoon procedure. The shorter procedure times for the cryoballoon cases may have helped these patients recover faster. It is also possible that the use of JET ventilation for the RF cases contributed to a longer hospital length of stay. The combination of shorter procedure time and decreased hospital length of stay with the cryoballoon procedure could have significant health care utilization implications.

The recent COR trial<sup>15</sup> compared a reduced-complexity version of the cryoballoon PVI where 2 freeze cycles were utilized, but no further ablation was used to ensure PV isolation. This method proved to be less efficacious than RF PVI, which was performed until PV isolation was confirmed. In our study, we used the most common cryoballoon strategy, which involved cryoballoon ablation until PV isolation is confirmed, with the use of RF for touch-up if needed. Although this added step increases the procedural complexity, the majority of cases were able to achieve acute PVI without the use of RF. Most of the cases requiring touch-up RF were early in the learning curve, and with the use of the first generation balloon. Furthermore, those cases that utilized adjunctive touch-up RF in addition to the cryoballoon were no more or less likely to have freedom from AF at 6 months.

The primary endpoint of this study was freedom from AF at 6 months. Both cryoballoon and RF had a 70% freedom from AF at 6 months. This is in line with previously published data for these techniques separately, when a single procedure is used for paroxysmal atrial fibrillation.<sup>9,11,12,14,16</sup> It is also important to note that this is

the initial experience with cryoballoon ablation in these operators as compared to the RF procedures in those same operators, who are experienced in RF PVI. This would imply that either the success rate with cryoballoon would increase with experience, perhaps to surpass RF, or there is no significant learning curve for the cryoballoon procedure.

The complication rates for both the cryoballoon and RF PVI procedures were similar and in line with previously published series.<sup>9,11,12,14,16</sup> For the cryoballoon cases, there were two cases of PNI that persisted at the end of the case. Both cases of PNI occurred in the operator's first 7 cases, and resolved within 2 months after the procedure. However, if recent techniques such as compound motor action potentials<sup>17</sup> gain widespread acceptance, the incidence of PNI is likely to be further reduced in cryoballoon procedures. It was encouraging that the complication rate with the cryoballoon procedure was low and comparable to the RF cases. Moreover, there were no life-threatening complications with the cryoballoon procedure, even during initial adoption of the procedure.

There are some notable limitations to this study. First, patients were not continuously monitored for recurrence of atrial fibrillation, although 80% of patients wore a monitor during the follow-up period. Although it is possible that continuous monitoring may have revealed additional AF recurrences, the significance of the additional asymptomatic cases is uncertain. Additionally, data for procedure times was limited to ~60% in each group, although subsequent evaluation of our own database confirms the trend seen in this study.

As was mentioned previously, the cryoballoon cases represent the initial operator experiences. It is unknown if the results would be different if compared to more experienced use of the technique. During the time under consideration, the Arctic Front cryoballoon transitioned from a first to a second generation device, and some evidence does suggest that the second generation device may have greater ablation efficacy.<sup>18</sup> Our study showed a trend toward superiority of the second generation cryoballoon, although this did not reach statistical significance. However, in light of the results of other reports,<sup>19,20</sup> our findings would only underestimate the efficacy of cryoballoon given the widespread adoption of the second generation balloon.

In regards to the RF procedure, newer catheters which measure contact force and may impact procedural efficacy<sup>21</sup> were not in use during the time of this study. As the RF cases were performed before the adoption of cryoballoon, it is unknown if the difference in hospital length of stay would remain significant when comparing cases performed during the same time period. This was a retrospective study involving only 100 patients for a short follow-up such that the data cannot be utilized to make conclusions regarding long-term efficacy. Larger and randomized trials are ongoing which should provide more data as to confirm or refute these findings. Lastly, this study represents the results from 3 operators within one university-based health system, and it is uncertain how well this data can be generalized to other practices.

## Conclusion

In operators who are experienced in RF PVI, the cryoballoon cases immediately after the adoption of the technique were performed with a shorter procedure time and were associated with a shorter hospital length of stay. These advantages came while maintaining similar procedural efficacy, and without increased complication rates. Our results suggest cryoballoon ablation is a viable alternative to RF

ablation for paroxysmal atrial fibrillation ablation patients and has important implications regarding resource utilization.

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