

Incidence and Predictors of Complications During Cryoballoon Pulmonary Vein Isolation for Atrial Fibrillation

Emily N. Guhl, MD; Donald Siddoway, MD; Evan Adelstein, MD; Raveen Bazaz, MD; George S. Mendenhall, MD; Jan Nemec, MD; Samir Saba, MD; David Schwartzman, MD; Andrew Voigt, MD; Norman C. Wang, MD, MS; Sandeep K. Jain, MD

Background—Cryoballoon pulmonary vein isolation (PVI) has emerged as an alternative to radiofrequency PVI for atrial fibrillation (AF). Data are lacking to define the rates and predictors of complications, particularly phrenic nerve injury (PNI).

Methods and Results—We evaluated a single-center prospective registry of 450 consecutive patients undergoing cryoballoon PVI between 2011 and 2015. Patients were 59 ± 10 years old, 26% were women, 58% had hypertension, their mean CHA₂DS₂VASc score was 1.7 ± 1.3 , 30% had persistent atrial fibrillation, and 92% received a second-generation 28-mm balloon. Predefined major complications were persistent PNI, pericardial effusion, deep vein thrombosis, arteriovenous fistula, atrioesophageal fistula, bleeding requiring transfusion, stroke, and death. PNI was categorized as persistent if it persisted after discharge from the laboratory. Logistic regression was performed to identify predictors of complications and specifically PNI. We identified a major complication in 10 (2.2%) patients. In 49 (10.8%) patients, at least transient PNI was observed; only 5 persisted beyond the procedure (1.1%). All cases of PNI resolved eventually, with the longest time to resolution being 48 days. We also describe 2 cases of PNI manifesting after the index hospitalization. Regression analysis identified 23-mm balloon use (16.3% versus 5.2%, odds ratio 2.94, $P=0.011$) and increased age (62.8 ± 7.7 versus 58.7 ± 0.12 years, odds ratio 1.058, $P=0.014$) as independent significant predictors of PNI. There were no significant predictors of major complications.

Conclusions—In a large contemporary cohort, cryoballoon PVI is associated with low procedural risk, including lower rates of PNI than previously reported. Older age and 23-mm balloon use were associated with PNI. Our low rate of PNI may reflect more sensitive detection methods, including compound motor action potential monitoring and forced double-deflation. (*J Am Heart Assoc.* 2016;5:e003724 doi: 10.1161/JAHA.116.003724)

Key Words: ablation • atrial fibrillation • catheter ablation • complications

Cryoballoon pulmonary vein isolation (PVI) has emerged as an alternative to radiofrequency PVI in the treatment of drug-resistant atrial fibrillation (AF). Cryoballoon PVI, compared with radiofrequency PVI, offers potential advantages, including shorter procedure times,^{1–3} decreased hospital length of stay,¹ and decreased fluoroscopy time.³ The data

are limited that define the major complication rate of cryoballoon PVI. Additionally, previous literature identifies phrenic nerve injury (PNI) as the most frequent complication of cryoballoon PVI.^{4–9} Methods including monitoring diaphragmatic electromyographic signals with compound motor action potential (CMAP)^{10–14} and immediate balloon deflation¹⁵ have been described to help detect PNI and decrease its incidence and long-term persistence. Identifying predictors of major complications and PNI will assist in patient selection for this procedure.

Methods

Study Population

The study population included 450 consecutive patients undergoing cryoballoon PVI for AF at the University of Pittsburgh Medical Center between August 2011 and August 2015 as part of a prospective registry. Baseline clinical characteristics and detailed medical history, including specific AF history, were

From the Center for Atrial Fibrillation, Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA

Correspondence to: Sandeep K. Jain, MD, 200 Lothrop St, PUH B-535, Pittsburgh, PA 15312. E-mail: jainks@upmc.edu

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recorded for all patients. The University of Pittsburgh Institutional Review Board approved the study protocol.

All patients provided written informed consent for the ablation procedure. All patients underwent preprocedural cardiac computed tomography to assess pulmonary venous anatomy and transesophageal echocardiography to rule out intracardiac thrombus. Periprocedural anticoagulation was managed as per individual physician discretion.

Cryoballoon Ablation Procedure

The cryoballoon PVI procedure has been previously described in detail.^{16–18} In brief, all ablation procedures were performed with the patient under general anesthesia, avoiding paralytic agents after induction to allow monitoring of phrenic nerve function. All cases were performed by using the Arctic Front Cryoballoon (Medtronic) via a transeptal approach. For most cases, after confirming pulmonary vein occlusion via venography, two 180- to 240-second lesions were applied in each pulmonary vein and additional lesions were applied if conduction persisted. Isolation was confirmed through elimination or dissociation of pulmonary vein potentials, differential pacing maneuvers, and high output pacing within the pulmonary veins to confirm exit block. For the right-sided pulmonary veins, pacing was performed from the superior vena cava (SVC) to monitor phrenic nerve function, and ablation was immediately terminated with any decreased diaphragmatic excursion. CMAP monitoring^{10–14,19} and immediate balloon deflation¹⁵ were used in a subset of patients once these techniques were described. A quadripolar pacing catheter was used in the SVC to detect phrenic nerve injury. Anticoagulation during the procedure was with intravenous heparin to maintain an activated clotting time of 300 to 400 seconds. For patients on warfarin, the procedure was performed with an international normalized ratio 1.5 to 2.5 and for novel oral anticoagulants, the agent was held 1 to 2 days before the procedure and usually restarted 6 hours after the procedure.

Follow-Up

Patient follow-up was as per standard protocol with outpatient visits at 6 weeks, 3 months, 6 months, 1 year, and yearly thereafter postprocedure. At the time of the procedure, complications were noted and systematically recorded in the registry by the operator. In addition, retrospective chart review of all procedure notes, hospitalizations, office visits, and emergency department visits was performed to assess for additional complications postprocedure. Predefined major complications were persistent PNI, symptomatic pericardial effusion, deep vein thrombosis, arteriovenous fistula, atrioesophageal fistula, major bleeding, stroke, or death. Major

bleeding was defined as a bleed requiring transfusion. “Persistent PNI” was defined as PNI that persisted or occurred beyond discharge from the electrophysiology laboratory, while episodes of PNI that resolved before discharge from the laboratory without recurrence were termed “transient PNI.” “Long-term PNI” was defined as PNI lasting >6 months. Identification of complications was based on objective evidence of any of the predefined complications or after workup of new symptoms postprocedure.

Statistical Analysis

Statistical analysis was performed by using STATA (version 14.0, Statacorp LP). Continuous variables are presented as mean±SD. Categorical variables are presented as percentages and absolute frequencies. Logistic regression analyses were performed to identify predictors of PNI or major complications. Variables found to be associated with the outcomes in univariable analyses at $P<0.2$ were selected for multivariable analyses. The variables were analyzed separately for major complications and PNI. The criterion for statistical significance was set at $P<0.05$.

Results

Study Population

All 450 consecutive patients who underwent cryoballoon PVI between August 2011 and August 2015 were included in the final analysis. There were 9 physicians who performed the procedures described, with a mean of 56.4 ± 70.2 and median of 27 cryoballoon procedures per operator and a range of 2 to 170. The study population was a mean of 59 ± 9.9 years old, and 26% were women, with a mean CHA₂DS₂VASc score of 1.7 ± 1.3 and left atrial dimension of 4.3 ± 2.4 cm. Hypertension was present in 57.6% of the patients, persistent AF was present in 30% of the patients, and 75% had AF duration >1 year. The second-generation 28-mm cryoballoon was used in 92% of procedures. Additional baseline characteristics for the total study population, patients stratified by major complications, and patients with phrenic nerve injury are shown in Table 1.

Major Complications

Major complications occurred in 10 (2.2%) patients (Table 2). Major complications included 5 cases of persistent PNI, 3 episodes of symptomatic pericardial effusion, 1 deep vein thrombosis, and 1 arteriovenous fistula. There were no major bleeds, periprocedural strokes, atrioesophageal fistulas, or periprocedural deaths. The details of each individual major complication are outlined in Table 3.

Table 1. Baseline Characteristics

	Total Study Population (N=450)	Major Complications (n=10)
Age, y	59.1±9.9	61.2±10.9
Women	25.8% (n=116)	40% (n=4)
Duration of symptoms >1 y	74.6%	62.5%
Persistent AF	30.2% (n=136)	40% (n=4)
Previous AF ablation	11.1% (n=50)	0% (n=0)
Hypertension	57.6% (n=259)	60.0% (n=6)
Diabetes mellitus	13.3% (n=60)	10% (n=1)
Heart failure	12.0% (n=54)	20.0% (n=2)
Coronary artery disease	16.0% (n=72)	20.0% (n=2)
Left ventricular ejection fraction (%)	55±7	50±10
Left atrial size, mm	4.3±2.4	4.0±0.9
Body mass index, kg/m ²	31.3±6.0	30.5±4.7
Height, m	1.8±0.1	1.7±0.1
Weight, lb	215±50	198±36
CHA ₂ DS ₂ -VASc score	1.7±1.3	1.9±1.4
23-mm balloon use	6.4% (n=29)	20.0% (n=2)
Procedural time, min	136±49	130±37
Fluoroscopy time, min	33.0±17	28.4±6.1

AF indicates atrial fibrillation.

There were 3 symptomatic echocardiogram-confirmed pericardial effusions that presented during the postprocedural period; all resolved within 1 week without intervention. There

Table 2. Complication Rates

Complication	No.	(%) (N=450)
Major complications		
Total	10	2.2%
Persistent phrenic nerve injury	5	1.1%
Symptomatic pericardial effusion	3	0.67%
Deep vein thrombosis	1	0.22%
Arteriovenous fistula	1	0.22%
Bleed/hematoma requiring transfusion	0	0%
Stroke	0	0%
Death	0	0%
PNI	49	10.8%
Temporary phrenic nerve injury	44	9.7%
Persistent phrenic nerve injury	5	1.1%
Long-term phrenic nerve injury (>6 mo)	0	0%

PNI indicates phrenic nerve injury.

was 1 case of a right femoral pseudoaneurysm and arteriovenous fistula requiring surgical intervention. There was 1 right saphenous vein deep vein thrombosis that was discovered 6 days postprocedure.

Univariate logistic regression analysis did not reveal any significant potential predictors of major complications.

Phrenic Nerve Injury

In our study population, PNI (transient and persistent) was the most common complication, occurring in 49 (10.8%) procedures, of which PNI was persistent in 5 (1.1%) cases. Two of the persistent PNI cases were not detected in the laboratory during SVC pacing but rather discovered on chest radiography with right hemidiaphragm elevation during follow-up after the patients reported symptoms. Persistent PNI resolved in all cases at 2, 20, 30, 34, and 48 days postprocedure (Table 3). The distribution of veins for the cases of PNI was 73% right superior, 23% right inferior, and 4% right middle pulmonary veins.

Univariate analysis identified age (62.8±7.7 years versus 58.7±0.12 years, *P*=0.006) and use of the 23-mm balloon (16.3% versus 5.3%, *P*=0.005) as associated with PNI (Table 4). There was no significant difference between estimated vein orifice area for veins with PNI compared with right-sided veins without PNI (Table 4). Variables selected for multivariate analysis by using a cutoff of *P*<0.2 included redo procedures, age, hypertension, use of 23-mm balloon, CHA₂DS₂-VASc score, early procedures, and total fluoroscopy time. Multivariate analysis identified 23-mm balloon use (odds ratio 2.94, *P*=0.011) and age (odds ratio 1.058, *P*=0.014) as significant independent predictors for PNI.

Procedural characteristics, including cryoballoon temperature data, number of lesions, and freeze times, were available for 68.0% of patients. These procedural characteristics were compared for the right-sided veins with PNI and the right-sided veins without PNI (Table 5). Patients with PNI had a significantly shorter total freeze time (301±148 versus 404±117 seconds, *P*<0.001) and number of lesions per vein (1.9±0.7 versus 2.3±0.6, *P*=0.006). There were no significant differences in mean 30-second temperature or nadir temperature.

Discussion

The main findings of our study were that in our cohort of 450 consecutive cases, the major complication rate of cryoballoon PVI was 2.2%. We identified no predictors of major complications. Overall, the most frequent complication was PNI, which was usually transient and eventually resolved in all cases. We identified increased age and use of a 23-mm balloon as predictors of PNI.

Table 3. Major Complications

Complication	Summary
Persistent PNI	During isolation of RSPV diminished diaphragmatic excursion noted and cryoablation immediately terminated. At that time, improved within 10 min. CXR 1 day postoperatively with right hemidiaphragm elevation. Resolved by CXR 20 days postoperatively
Persistent PNI	During isolation of RSPV, diminished diaphragmatic excursion was noted and cryoablation was immediately terminated. Return of phrenic nerve function noted in 10 to 15 min, but diminished. CXR postoperatively revealed right hemidiaphragm elevation. Resolved within 48 d on CXR
Persistent PNI	No PNI detected during procedure. Patient called 6 days postoperatively with SOB, and CXR revealed right hemidiaphragm elevation. These symptoms resolved within 1 mo. CXR 30 days postoperatively revealed resolution of PNI
Persistent PNI	During isolation of RSPV, there was loss of phrenic nerve capture. Cryoablation was immediately terminated, and there was active deflation. There was ≈75% excursion recovery at 20 min. Symptomatically resolved by discharge on postoperatively day 2, and there was no evidence of hemidiaphragm elevation on CXR on postoperative day 1
Persistent PNI	No PNI detected during the procedure. At 15 days postprocedure, the patient presented to the ED with SOB, and CXR revealed right hemidiaphragm elevation. Symptoms improved and CXR 34 days postoperatively with resolution of diaphragm elevation
Right femoral arteriovenous fistula and pseudoaneurysm	Postprocedure, patient experienced prolonged bleeding from right groin puncture site. Arterial duplex studies revealed right femoral pseudoaneurysm and arteriovenous fistula that was repaired with vascular surgery 5 days postoperatively
Right saphenous vein deep vein thrombosis	At 6 days postoperative, developed swelling inferior to right groin insertion site; prompted to go to the ED, where he was noted to have a right saphenous deep vein thrombosis. Was found to be subtherapeutic on warfarin at the time and was bridged to therapeutic; at follow-up 2 months postprocedure, symptoms were noted to be resolved
Pericardial effusion	Patient developed pleuritic chest pain postoperatively; echocardiography revealed pericardial effusion that resolved over 4 days on repeat echocardiograms
Pericardial effusion	Pericardial effusion noted postoperatively with symptoms; resolved on repeat echocardiogram 7 days postoperatively
Pericardial effusion	Developed pleuritic chest pain during the admission and found to have pericardial effusion. Required monitoring in PACU overnight. On phone call 1 week postoperative, patient reported resolution of pain

CXR indicates chest radiograph; ED, emergency department; PACU, postanesthesia care unit; PNI, phrenic nerve injury; RSPV, right superior pulmonary vein; SOB, shortness of breath.

Our major complication rate is consistent with previously published rates of major complications: 2% to 5.1%.^{5,20–22} The lack of significant predictors for major complications is consistent with most previous studies⁵ and likely is limited by a lack of statistical power, given the low rate of complications (Table 6).^{5,6,9,15,16,20,23–26} A previous study has identified predictors that included female sex and procedures performed in July or August.²¹ Further research in larger cohorts may identify additional predictors of major complications. Alternatively, cryoballoon PVI may have such a low rate of major complications that no predictors will be identified for most specific complications.

The most common complication was PNI; the overwhelming majority of cases resolved before discharge from the electrophysiological laboratory, and the persistent cases resolved within 2 months. Other study populations have described long-term resolution of all or nearly all PNI cases.^{5–7,16} Despite the apparent temporary nature of phrenic nerve injury occurring during cryoballoon PVI, it is important to continue to use methods to reduce the incidence of PNI and identify predictors to aid in patient selection and guide estimation of risks and benefits of the procedure in individual patients. We found that

the use of the 23-mm balloon and increased age were associated with PNI. We have compared our study with other literature that reviewed complication rates, PNI rates, and predictors and found we had identified a similar or an improved PNI and major complication rate (Table 6).

We did identify 2 cases of persistent PNI that were not detected during the procedure but were discovered after discharge from the electrophysiological laboratory. Both cases were identified when the patients presented as outpatients with symptoms and confirmed with right hemidiaphragm elevation on chest radiography. These cases highlight the possibility of delayed PNI, which is currently not widely described. Both cases used SVC pacing but not CMAP monitoring. Possibilities include missed injury during the procedure (with SVC pacing below balloon position, which is unlikely given operator experience, and in 1 case, stored cine confirms appropriate position) versus a subtle injury not detected during the procedure with progression over the next several days. Delayed manifestation of PNI has not, to our knowledge, been described before.

Previous studies have established a decrease in CMAP of 30% to 35% as highly sensitive for detecting PNI, with a

Table 4. Comparison of Patients With PNI to Those Without

Characteristic	No PNI	PNI	Univariable		Multivariable	
	n=401	n=49	OR (95% CI)	P Value	OR (95% CI)	P Value
Redo	48 (12.0)	2 (4.1)	0.313 (0.074–1.330)	0.116	0.300 (0.069–1.310)	0.192
Age, y	58.7±10.1	62.8±7.7	1.050 (1.014–1.087)	0.006	1.058 (1.013–1.106)	0.014
CHF	45 (11.2)	7 (14.3)	1.219 (0.552–2.694)	0.628		
HTN	226 (56.4)	33 (67.3)	1.597 (0.852–2.995)	0.155	1.546 (0.705–3.394)	0.609
Female sex	104 (26.0)	12 (24.5)	0.926 (0.465–1.844)	0.820		
Height, mm	1.77±0.1	1.75±0.1	0.157 (0.009–2.893)	0.213		
23-mm balloon use	21 (5.2)	8 (16.3)	3.531 (1.471–8.476)	0.005	2.938 (1.118–7.723)	0.011
CHA ₂ DS ₂ -VASc score	1.65±1.3	1.92±1.3	1.157 (0.934–1.433)	0.183	0.855 (0.618–1.184)	0.832
Persistent AF	122 (30.4)	14 (28.6)	0.915 (0.475–1.762)	0.760		
Body mass index, kg/m ²	31.1±5.9	31.2±6.6	0.996 (0.948–1.047)	0.882		
Early (first third of procedures)	129 (32.2)	21 (42.8)	1.581 (0.865–2.891)	0.137	1.482 (0.756–2.906)	0.624
Total procedure time, min	136±51	321±36	0.998 (0.991–1.005)	0.613		
Total fluoroscopy time, min	32.4±16	37.4±19	1.016 (0.999–1.033)	0.065	1.014 (0.993–1.035)	0.203

Values are presented as mean±SD or n (%). AF indicates atrial fibrillation; CHF, congestive heart failure; HTN, hypertension; PNI, phrenic nerve injury.

decrease in 30% correlating with a c-statistic of 0.965.^{11,14} It is unclear if CMAP would have detected subtle injury in these cases. Regardless, our findings emphasize the importance of follow-up and monitoring for complications after the index cryoballoon procedure.

In our cohort, there was increased 23-mm balloon use for patients with PNI which has been reported in previous studies.^{15,16,26} An increased risk of PNI is likely when the balloon is positioned distal toward the vein, which occurs more frequently with the 23-mm balloon compared with the 28-mm balloon given its smaller size.^{16,20,26,27} Another hypothesis may be that the 28-mm balloon represents later cases in which the operator has gained experience; however, even when we controlled for early versus late cases, the effect of the 23-mm balloon was seen.

We saw that the patients who had PNI were older than patients without PNI, which is also a novel finding. This may

be a result of deeper tissue penetration in advanced age because of changes in extracellular matrix or possible age-related shifts in relative position of the phrenic nerve relative to the right pulmonary veins.^{28,29} While PVI has been shown to be effective and safe when evaluating major complications in elderly populations,³⁰ this slight increase in incidence of PNI is important to note when offering cryoballoon PVI to elderly patients.

We did not see an increase in vein size for cases with PNI. Given that there were no differences in maximum negative temperature or average 30-second temperature for patients with PNI, it is unlikely that more aggressive freezing contributed to PNI. In fact, the patients with PNI had lower total freezing duration and number of lesions, which is likely a result of no further ablation performed after PNI was detected. These data suggest that nerve anatomy is the determinant of likelihood of PNI.

Since the adoption of cryoballoon PVI for AF, methods to reduce the incidence of PNI have emerged. Monitoring using surface electrodes during phrenic nerve pacing to detect a 30% to 35% reduction in diaphragmatic CMAP has decreased the incidence of PNI by allowing for early detection.^{14,19} Additionally, double deflation or rapid balloon deflation, which leads to more rapid tissue rewarming, reduces the risk of persistent PNI.¹⁵

Limitations

Our study has several potential limitations. It is a retrospective observational study of a prospective registry involving

Table 5. Comparison of Procedural Characteristics by PNI

	Veins With PNI	Right-Sided Veins Without PNI	P Value
Maximal negative temperature, °C	-50.6±5.4	-52.0±6.0	0.124
Average 30-s temperature, °C	-33.6±4.0	-33.7±4.4	0.935
Total freeze duration, s	301±148	404±117	0.001
No. of lesions	1.9±0.7	2.3±0.6	0.006

PNI indicates phrenic nerve injury.

Table 6. Previous Literature for Complications and PNI

Total Population	Major Complications	Total PNI	Persistent PNI	Predictors of Complications	Predictors of PNI	Year	Reference
450	2.2%	10.8%	1.1%	None	Age, 23-mm balloon use	2016	Present study
345	5.9%	N/A	3.2%	None	None	2016	Knight et al ²³
500	2.0%	7.2%	2.2%	None	None	2015	Mugnai et al ⁵
316	N/A	10.0%	4.5%	N/A	None	2015	Saitoh et al ⁶
115	N/A	3.5%	2.6%	N/A	None	2014	Metzner et al ⁹
158	5.1%	6.9%	3.8%	Persistent AF, lower body height	23-mm balloon	2014	Boho et al ²⁰
65	N/A	6.0%	0.0%	N/A	Short distance between RSPV and SVC, lower 30-s temperature	2013	Kuhne et al ²⁴
163	6.1%	11.2%		None	23-mm balloon	2013	Packer et al ²⁵
130	N/A	16.9%	0.0%	N/A	23-mm balloon	2013	Ghosh et al ¹⁵
346	2.9%	7.5%	6.9%	None	23-mm balloon	2008	Neumann et al ¹⁶
57	7.0%	7.0%	3.5%	None	23-mm balloon	2007	Van Belle et al ²⁶

AF indicates atrial fibrillation; N/A, not available; PNI, phrenic nerve injury; RSPV, right superior pulmonary vein; SVC, superior vena cava.

only a single center and, thus, its generalizability may be limited. It is important to note that this is one of the larger studies to date looking at complications in cryoballoon PVI. Given the small percentage of major complications, some potential predictors may not have been identified. All patients had at least 1 month of follow-up, and given that the overwhelming majority of PNI occurs acutely because of its pathophysiology, it is likely that most of the PNIs were detected by using our surveillance methods. However, it is possible that any delayed PNI may have gone undetected. Additionally, it is possible that operator experience affected the complication and PNI rates; however, when comparing the first one-third of cryoballoon procedures with the second two-thirds of procedures performed at our institution, we did not see a significant difference in PNI rates. Finally, we did not include the procedural characteristics in the multivariate analysis because the differences in these characteristics were likely a result of acute PNI (ie, shorter freeze time and number of lesions); however, in doing this, we may have missed some predictors of PNI.

Conclusions

In a prospective observational cohort of 450 consecutive cases, the major complication rate of cryoballoon PVI was 2.2% with no identified predictors of major complications. The most frequent complication was PNI, which resolved in all cases. We identified use of 23-mm balloon and increased age as predictors for PNI. We also observed delayed PNI in 2 patients not detected during the procedure. Cryoballoon PVI

can be safely performed with a low incidence of major complications.

Disclosures

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