Lessons From Radiofrequency Redo-Procedure After Cryoballoon Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation

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Background: To gain further insights into mechanisms leading to atrial fibrillation (AF) recurrence after a first ablation procedure using cryoballoon technique, the data collected during redo procedure were analyzed.

Methods and Results: From a total of 112 patients who underwent cryoballoon pulmonary vein isolation (PVI) for paroxysmal AF, 44 had a second ablation procedure using radiofrequency catheter, because of recurrent atrial arrhythmia. PV reconnection was observed in 109 of the 171 initially isolated veins (64%). Conduction recovery was found, respectively, at the left inferior PV, right inferior PV, right superior PV and left superior PV in 35 patients (80%), 26 patients (67%), 23 patients (52%) and 17 patients (39%). The mean number of reconnected PVs per patient was significantly lower with the 23-mm cryoballoon as compared to the 28-mm. Conduction gaps were focal and located at inferior parts of inferior veins and at the ridge between left atrial appendage and left veins. Mean procedure and fluoroscopy time were 109 ± 32 min and 14.7 ± 8.3 min, respectively. A 3-D mapping system was used in only 8 patients (18%).

Conclusions: Atrial arrhythmia recurrences following cryoballoon PVI were associated with focal PV reconnections, occurring at preferential anatomical sites. These gaps were readily ablated with focal radiofrequency delivery, explaining the lack of need of 3-D mapping system and short procedure time. These results do not support the use of cryoballoon to perform redo procedures. (*Circ J* 2013; **77**: 2009–2013)

Key Words: Atrial fibrillation; Cryoballoon ablation; Pulmonary vein isolation; Redo procedure

Atrial fibrillation (AF) is the most common atrial arrhythmia and is associated with reduced functional status, cardiac performance and survival.¹ Drug-refractory paroxysmal AF is now frequently treated by catheter ablation, in order to obtain complete and sustained pulmonary vein isolation (PVI).^{2,3} Using a single-shot approach, the cryoballoon technique has been proven to be as effective and safe as point-by-point radiofrequency (RF) ablation to perform PVI.⁴ Even though the technical approach is different, the AF recurrence rate seems similar whether RF catheter or cryoballoon is used during the initial procedure. Following RF PVI, AF recurrence is strongly associated with PV reconnection, which can occur at several PVs and at multiple sites around each PV. To gain further insights into the mechanisms leading to AF recurrence in patients who underwent their first AF ablation procedure using the cryoballoon technique, we sought to analyze the electrophysiological data collected during the redo procedures.

Methods

First Cryoballoon AF Ablation Procedure

One hundred and twelve patients, referred for medically refractory, paroxysmal AF, underwent cryoballoon PVI from October 2008 to December 2011 in Rouen University Hospital, France. The group consisted of 69 men (62%) and 43 women (38%), with a mean age of 57 ± 11 years. Eighty-eight patients (79%) had normal cardiac function.

Up to November 2010 ($n=81$ patients), 2 long transseptal sheaths had been introduced into the left atrium: a 12-F steerable sheath (FlexCath®, Medtronic, Minneapolis, MN, USA) was used to manipulate the cryoballoon and a standard 8-F sheath allowed the use of a 20-pole deflectable circular PV mapping catheter (Afocus®, St. Jude Medical, St. Paul, MN, USA) with a diameter of 20 mm. The cryoballoon was applied onto the PV antrum over an extra-support guidewire positioned into the PV. From November 2010 to December 2011 ($n=31$ patients), 1 single transseptal puncture was performed, cryoballoon positioning and PV mapping being obtained using

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an 8-pole circular catheter (Achieve®, Medtronic) introduced through the central lumen of the cryoballoon catheter. A 28-mm diameter balloon was used in 85 patients (76%) and a 23-mm balloon in 23 patients. The choice of balloon size was based on pre-procedural imaging. Cryoenergy applications of 300s were performed until PVI was confirmed, and then an extra freeze of 300s was systematically performed. PVI could not be achieved with the cryoballoon in 32 patients (28%). An 8-mm-tip cryocatheter (FREEZOR MAX, Medtronic) was used to complete PV isolation in 16 of them. Conduction gaps were ablated at the right inferior PV in 11 patients, at the right superior PV in 3 patients and at the left inferior PV in 3 patients (1 patient had remaining gaps in both inferiors veins). During our early experience of the cryoballoon technology, we wanted to evaluate it as the sole technique to treat AF. Therefore, we did not use other ablation techniques in these 16 patients at the time of the first procedure.

RF Redo Ablation Procedure

Among the 112 consecutive patients who underwent a cryoballoon ablation procedure for refractory AF, 62 patients (55%) experienced atrial arrhythmia recurrences over a mean follow-up period of 35±13 months. Forty-four of them (71%) had a redo ablation procedure because of symptomatic recurrence of AF in 34 patients, and left atrial macro-reentry in 10 (7 roof dependent, 2 septal, 1 perimitral). The study group consisted of 26 men and 18 women with a mean age of 57±12 years. Two patients suffered from ischemic cardiomyopathy, 1 from dilated cardiomyopathy, 1 from hypertrophic cardiomyopathy and 1 from valvular cardiomyopathy. Other patients (n=39) had normal cardiac function. The procedure was performed under conscious sedation (n=34) or under general anesthesia (n=10). A quadripolar catheter (Inquiry®, St Jude Medical) was positioned in the coronary sinus. After atrial transseptal punctures, a 20-pole circular mapping catheter (Afocus®, St Jude Medical) and a 4-mm irrigated-tip ablation catheter (Coolpath duo®, St Jude Medical) were introduced into the left atrium.

The circular mapping catheter and ablation catheter were successively moved into each PV to identify location of conduction gaps between left atrium and PVs. Each PV antrum was divided into quarters: antero-superior, antero-inferior, postero-superior and postero-inferior. The following parameters were collected: (1) number of reconnected veins per patient; (2) rate of conduction recovery at each PV; (3) location of conduction

gaps within each PV; and (4) size of the conduction gap. Location and extension of conduction gaps were identified using the 4-mm-tip ablation catheter and the circular mapping catheter.⁵ Their size was defined as limited to a quarter or extended to 2, 3 or 4 quarters of the circumference of each PV. These data were analyzed according to the cryoballoon size (23 or 28 mm) and the type of balloon support (Achieve® catheter or guide-wire) used during the first procedure.

Follow-up

All patients underwent a 24-h Holter at 2 months after the redo RF ablation procedure and were seen in at the outpatient clinic at 4 months and every 6 months thereafter.

Statistical Analysis

Continuous variables are expressed as mean±SD or number and percentage, as appropriate. Comparison of continuous variables was performed using the Student's t-test. Chi-square test was used to compare proportions. If sample sizes were <5, Fisher test was used. P<0.05 was considered significant.

Results

Electrophysiological Study

The redo ablation procedure was performed 7.7±9 months after the initial cryoballoon ablation in 44 patients.

No. Reconnected Veins per Patient Among the 171 isolated veins after cryoballoon ablation, conduction gaps were identified in 109 veins (64%), with a mean of 2.5±1.2 veins per patient (Figure 1). Four patients (9%), referred for left atrial flutter after cryoballoon ablation, still had complete PVI. Conduction recovery was observed at only 1 PV in 4 patients (9%), at 2 PVs in 15 patients (34%), at 3 PVs in 9 patients (20%) and at all 4 PVs in 12 patients (27%).

Conduction Recovery Rate at Each PV Among initially isolated PVs, reconnection was observed in 17/44 (39%) at the left superior PV (LSPV), in 35/44 (80%) at the left inferior PV (LIPV), in 23/44 (52%) at the right superior PV (RSPV) and in 26/39 (67%) at the right inferior PV (RIPV; Figure 2).

Location of Conduction Gaps Within Each PV In the LSPV and LIPV, conduction gaps were predominantly identified at the antero-inferior quarter (12 patients, 71%; and 27 patients, 77%, respectively; Figure 3). In the RSPV, the sites of reconnection were homogeneously distributed around the vein. In

Figure 3. Location of conduction gap within each pulmonary vein (PV) after first cryoballoon PV isolation. LI, left inferior; LS, left superior; RI, right inferior; RS, right superior.

Table. Impact of Initial Cryoballoon Ablation Parameters on Redo Procedure

	Cryoballoon size			Cryoballoon support			Immediate electrical isolation after cryoballoon		
	23 mm	28 mm	P-value	Guidewire	Intra-luminal catheter	P-value	Complete PVI†	Incomplete PVI	P-value
No. patients	27	85		81	31		96	16	
Rate of redo procedure	33 (9)	41 (35)	NS	37 (30)	45 (14)	NS	40 (39)	31 (5)	NS
Redo procedural time (min)	106±23	110±35	NS	111±30	104±39	NS	106±32	132±34	NS
Redo fluoroscopy time (min)	14±4	15±9	NS	15±8	15±9	NS	14±8	20±10	NS

Data given as mean±SD or % (n). †PVI was obtained with the use of an 8-mm cryocatheter in 16/96 patients (17%). PVI, pulmonary vein isolation.

the RIPV, reconnection was observed at the inferior part of the vein in the vast majority of cases.

Conduction Recovery Size The mean number of quarters with conduction gaps was 0.8 ± 1.1 in the LSPV, 1.4 ± 1.0 in the LIPV, 0.8 ± 1.1 in the RSPV, and 1.3 ± 1.4 in the RIPV.

Procedure-Related Parameters

Mean duration of the RF redo ablation procedure (including trans-esophageal echocardiography and a 30-min waiting period) and fluoroscopy was 109 ± 33 min and 14.7 ± 8.3 min, respectively. The use of a 3-D mapping system was at the discretion of the physician, and performed in only 8 patients (18%).

The AF ablation procedure consisted of PV re-isolation only in 28 patients (64%). Cavo-tricuspid isthmus ablation was additionally performed in 9 patients (20%), left atrial ablation lines in 4 patients (9%), complex atrial fragmented electrogram ablation in 1 patient (2%) and superior vena cava isolation in 2 patients (5%).

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Impact of Initial Cryoballoon Ablation Parameters on Redo Procedure

The cryoballoon size did not influence the rate of redo procedure, the redo procedure or fluoroscopy time. The mean number of reconnected PVs, however, was significantly lower when using the 23-mm cryoballoon as compared to the 28-mm cryoballoon (0.9 ± 0.9 and 2.7 ± 0.9 , respectively; $P < 0.001$; Table). In association, the rate of PV reconnection was also significantly lower at the LIPV and RSPV in the group of patients in whom the 23-mm balloon was used (Figure 4).

The use of a guidewire or the Achieve® catheter for cryoballoon positioning did not affect the procedure-related parameters or the electrophysiologic data of the redo procedure. Interestingly, the rate of redo procedure was similar in patients with complete and incomplete PVI at the end of the initial procedure.

Figure 4. Rate of pulmonary vein (PV) reconnection according to cryoballoon size. LI, left inferior; LS, left superior; RI, right inferior; RS, right superior.

Follow-up

After 12 months of follow-up, 10 patients (23%) experienced palpitations related to recurrent AF occurring 2.3 ± 0.7 months after the second procedure. Seven patients underwent a third ablation procedure 5.7 ± 0.8 months after the second. During the third ablation procedure PV reconnection was found in 6 patients only, predominantly located at inferior PVs. Four patients experienced reconnections at 2 separate PVs, and 2 patients at 3 PVs. Conduction gaps were observed at RIPV in 5 patients, at LIPV in 4 patients, RSPV in 3 patients and at LSPV in 2 patients. All these gaps were successfully ablated using RF energy. Five months after this third ablation procedure, 2 patients had AF recurrence leading to a fourth ablation procedure. One patient underwent a biventricular defibrillator implantation with atrioventricular node junction ablation because of dilated cardiomyopathy. The remaining 4 patients were free of arrhythmia.

Discussion

Because of the pathogenesis of AF and the fact that AF recurrence after an initial ablation procedure is strongly associated with PV reconnection, complete electrical PV isolation is the well-established cornerstone of RF paroxysmal AF ablation. Similarly to what has been observed following RF catheter ablation, the present study has shown that atrial arrhythmia recurrence is associated with PV reconnection after cryoballoon ablation. In a given patient, these PV reconnections most often occurred at several PVs. Interestingly, these PV reconnection were focal and occurred almost always at specific anatomical sites.

After RF PVI, acute and chronic PV reconnections have been frequently observed at the ridge between the LSPV and the left atrial appendage and intervenous ridge.⁶ Histopathology has shown variable atrial thickness around the PV ostia. In particular, important atrial muscle thickness has been observed at the ridge between the LSPV and left atrial append-

age.⁷ This would potentially imply more energy delivery at those anatomical sites compared to others to create a transmural lesion. Conversely to RF catheter ablation, however, energy titration is not possible using cryoballoon ablation, and assuming an appropriate PV/balloon contact, the same amount of energy is delivered all around the PV ostia. Similarly to what has been recently described by Fumkranz et al using the single big cryoballoon technique,⁸ we found that PV reconnections predominantly occurred at the ridge between the LSPV and the left atrial appendage. Difficulties in creating a transmural lesion with the cryoballoon would pave the way for conduction recovery at this particular anatomical site. In this setting, it is interesting to note that the mean number of reconnected PVs per patient as well as the rate of reconnection at the LIPV and RSPV were significantly lower when using the 23-mm cryoballoon as compared to the 28-mm cryoballoon (Figure 4). The refrigerant flow rate is the same in the 23- and 28-mm balloon (6.2 L/min) but, because the surface area of the 23-mm balloon is smaller than that of the 28-mm, there is likely more effective heat removal from the tissue in contact with the balloon, which could explain the present results. Another explanation would be related to the positioning of the balloon in the PV during the freezing phase. As compared to the 28-mm balloon, the smaller 23-mm balloon was probably located more distally in the vein where the muscle fibers are likely thinner, therefore more prone to transmural lesion.

Variability in ostial geometry may lead to incomplete PV occlusion and lack of circumferential tissue contact during cryoablation, which would prevent creation of an efficient tissue lesion. This is particularly true for the LIPV, for which the ostium usually presents an oval shape and the diameter is smaller than the superior veins, when using the 28-mm balloon (Figure 4).⁹ Because of the lack of congruence between a round non-deformable balloon and an oval LIPV ostium, good tissue contact may be difficult to obtain at the inferior part of the vein. This mechanism likely explained the high rate of PV reconnection observed at this site of the LIPV (overall

85%; 94% after cryoablation with a 28-mm balloon) in the present study.

Both anatomical factors and technical limitations may contribute to the high rate of both incomplete isolation and reconnection at the RIPV (77%). Because of the respective spatial orientation of the transeptal sheath in relation to the inferior PV ostia, full PV occlusion during cryoapplication may be particularly difficult to achieve. Given that the rate of RIPV reconnection was equally high in the groups of patients who underwent ablation with the 23- and the 28-mm balloon, these factors likely prevailed on cryoballoon powerfulness. Optimization of tissue contact may require utilization of technical maneuvers, such as the “hockey stick” or “pull down” techniques.¹⁰ Technological improvement of the deflectable sheath or towards a more deformable balloon may reduce this high rate of reconnection.

Contrary to what has been demonstrated with RF current, pressure against tissue is not a major parameter influencing the size of cryoenergy-related lesion. If a layer of blood between the balloon surface and the tissue exists, however, it will act as a thermal resistance, causing the temperature to be warmer at the tissue. This is why pushing on the balloon helps with energy delivery, because it allows the layer of blood to be displaced in favor of direct balloon contact with the tissue. This parameter is likely involved in the PV reconnection process, especially at PV with difficult geometries.

The use of the Achieve® catheter has been shown to significantly decrease fluoroscopy time and allow PV conduction monitoring during cryoapplication.¹¹ It has also been suggested that it could improve balloon support and positioning and subsequently improve PVI efficacy. Its use, however, did not result in a higher rate of acute PVI as compared to the use of a standard guidewire, in the present series. Similarly, we did not observe differences in long-term PV reconnection rate according to whether the Achieve® catheter was used or not.

In the present series, redo procedure using RF catheter was quickly performed with a mean duration of 111 min (<2 h, including trans-esophageal echography and 30-min waiting period). The main reasons for this relatively short procedure time were as follows: (1) because the conduction gaps were preferentially located at specific sites, mapping of these was readily achieved, explaining why we did not use 3-D mapping systems in most cases (improving in the meantime the cost-effectiveness of the procedure); and (2) because the conduction gaps between the PV and the left atrium were very limited in size, only few focal RF applications were needed to obtain PVI. In a recently reported series in which redo procedures were performed with the cryoballoon, the procedure time as well as the X-ray exposure time appeared longer as compared to the present results.¹² In that study, AF recurrence was still observed in 40% of patients, whereas in the present study only 23% of the patients suffered from AF recurrence at 1-year follow-up.

Conclusion

After a first cryoballoon ablation for paroxysmal AF, redo RF

ablation was readily performed with short procedure duration, reduced fluoroscopic exposure and mostly without 3-D mapping platform. These results do not support the use of the cryoballoon for redo-procedure.

Looking at the location of PV reconnections, and taking into account the impact of cryoballoon size on PV reconnection distribution, it is likely that the mechanisms leading to conduction recovery differ according to PVs: difficulty in correct positioning of the cryoballoon seems to be the predominant cause of PV reconnection at the RIPV; and geometrical mismatch between the cryoballoon and the PV ostium is likely involved in LIPV reconnection; Technological refinements of both the deflectable sheath and the cryoballoon catheter may improve energy delivery and the maintenance of PVI over time.

References

1. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke and medical costs. *Arch Intern Med* 1998; **158**: 229–234.
2. Kumagai K. Catheter ablation of atrial fibrillation: State of the art. *Circ J* 2011; **75**: 2305–2311.
3. Noro M, Kujime S, Ito N, Enomoto Y, Nakamura K, Sakai T, et al. Cost effectiveness of radiofrequency catheter ablation vs. medical treatment for atrial fibrillation in Japan: Cost performance for atrial fibrillation. *Circ J* 2011; **75**: 1860–1866.
4. Andrade JG, Khairy P, Guerra PG, Deyell MW, Rivard L, Macle L, et al. Efficacy and safety of cryoballoon ablation for atrial fibrillation: A systematic review of published studies. *Heart Rhythm* 2011; **8**: 1444–1451.
5. Miyamoto K, Tsuchiya T, Yamaguchi T, Nagamoto Y, Ando S, Sadamatsu K, et al. A new method of a pulmonary vein map to identify a conduction gap on the pulmonary vein antrum ablation line. *Circ J* 2011; **75**: 2363–2371.
6. Rajappan K, Kistler PM, Earley MJ, Thomas G, Izquierdo M, Sporton SC, et al. Acute and chronic pulmonary vein reconnection after atrial fibrillation ablation: A prospective characterization of anatomical sites. *Pacing Clin Electrophysiol* 2008; **31**: 1598–1605.
7. Cabrera JA, Ho SY, Climent V, Fuertes B, Murillo M, Sanchez-Quintana D. Morphological evidence of muscular connections between contiguous pulmonary venous orifices: Relevance of the interpulmonary isthmus for catheter ablation in atrial fibrillation. *Heart Rhythm* 2009; **6**: 1192–1198.
8. Fumkranz A, Chun J, Nuyens D, Metzner A, Koster I, Schmidt B, et al. Characterization of conduction recovery after pulmonary vein isolation using the “single big cryoballoon” technique. *Heart Rhythm* 2010; **7**: 184–190.
9. Schmidt M, Dorwarth U, Straube F, Daccarett M, Rieber J, Wanklerl M, et al. Cryoballoon in AF ablation: Impact of PV ovality in AF recurrence. *Int J Cardiol* 2011 December 27, doi:10.1016/j.ijcard.2011.12.017 [Epub ahead of print].
10. Andrade JG, Dubuc M, Guerra PG, Macle L, Rivard L, Roy D, et al. Cryoballoon ablation for atrial fibrillation. *Indian Pacing Electrophysiol J* 2012; **12**: 39–53.
11. Chierchia GB, Namdar M, Sarkozy A, Sorgente A, de Asmundis C, Casado-Arroyo R, et al. Verification of pulmonary vein isolation during single transeptal cryoballoon ablation: A comparison between the classical circular mapping catheter and the inner lumen mapping catheter. *Europace* 2012; **14**: 1708–1714.
12. Schade A, Langbein A, Spehl S, Barth S, Deneke T, Groschup G, et al. Recurrence of paroxysmal atrial fibrillation after cryoisolation of the pulmonary veins: Is a “redo” procedure using the cryoballoon useful? *J Interv Card Electrophysiol* 2013; **36**: 287–295.