ATRIAL FIBRILLATION

INNOVATIVE TECHNIQUES

Cryoballoon Ablation for Pulmonary Vein Isolation of Atrial Fibrillation: A Better Way to Complete the Circle?

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ABSTRACT. Cryoballoon ablation has emerged as a novel tool to perform pulmonary vein isolation in patients with atrial fibrillation. This balloon-based technology has the potential to simplify the procedure by creating continuous circumferential lesion sets with a limited number of energy applications. At the same time, electrophysiologists will encounter new challenges and pitfalls when performing cryoballoon ablation. The aim of this paper is to review the advantages and drawbacks of this technology and discuss some important technical issues.

KEYWORDS. atrial fibrillation, cryoballoon ablation, pulmonary vein isolation.

Background

Pulmonary vein (PV) isolation (PVI) is regarded as the cornerstone of interventional treatment of atrial fibrillation (AF). Therefore, since the inception of PVI more than 10 years ago, most endocardial and epicardial ablation strategies with the aim of eliminating AF still involve the PVs as their main target. Radiofrequency (RF) ablation catheters were once developed with the goal of creating focal lesions. However, in most current AF ablation strategies, these tools are used to create continuous circumferential or linear lesions. Achieving this using a point-by-point ablation technique is technically challenging and highly dependent on operator dexterity. Balloon-based ablation systems such as the cryoballoon (Arctic Front, Medtronic, Minneapolis, MN) have the theoretical advantage that they eliminate the need for point-by-point ablation by creating a single circumferential lesion around the PV with one or two applications of cryoenergy. One of the drawbacks of any balloon-based ablation system is that it is not a flexible system and can almost exclusively be used for PVI.

The aim of this article is to highlight the advantages and disadvantages of cryoballoon ablation and to discuss some important technical details and pitfalls. This is important because the device has just recently received Food and Drug Administration (FDA) approval for the treatment of paroxysmal AF in the United States based on the STOP AF trial.

Basics of cryoballoon ablation

Lesion formation with cryothermal energy is complex, and the freezing cycle involves both the freezing and the thawing process. Lesion formation is much slower than radiofrequency ablation, resulting in recommended freezing cycles with a duration of 5 min (per application) with the cryoballoon. Because of its biological effects, application of cryoenergy has been described to result in less endothelial disruption and less thrombus formation. Whether this translates into a lower thromboembolic risk is debatable. A recent study observing cerebral microembolic signals (MES) showed fewer MES with cryoballoon ablation than conventional (non-irrigated) RF ablation and no significant difference compared with ablation with irrigated-tip catheters. Furthermore, Neumann et al. showed that acute cerebral lesions (without neurological symptoms) are detected to a
similar extent both after cryoballoon and after RF ablation of AF.

The cryoballoon catheter is available in two different sizes (28 mm and 23 mm diameter). The catheter consists of a non-compliant outer balloon and a second inner balloon (Figure 1). The refrigerant nitrous oxide (N₂O) is injected into the inner balloon through injection tubes, thereby cooling the inner balloon to a temperature of −80°C. The temperature is measured by a thermocouple at the proximal end of the balloon. Therefore, temperature measurements are influenced by remaining blood flow from the targeted PV (in case of incomplete occlusion) or by atrial blood from another PV. Although no thermocouple is available measuring the temperature at the interface between balloon and tissue, Fürnkranz et al.⁹ have shown that the temperature measured using the currently available device predicts successful isolation of the PV.

**Advantages of cryoballoon ablation**

A “single (or dual) shot” technique for isolation of a PV is probably appealing to any electrophysiologist performing AF ablation procedures. Although more than the standard of two applications of cryoenergy per PV is required in a substantial percentage of veins, the available non-randomized comparisons between cryoballoon and RF ablation of AF consistently report shorter procedure times with the cryoballoon ablation system. The impact on fluoroscopy times, however, differs between the available studies.¹⁰⁻¹² If a switch to a focal ablation catheter is necessary after cryoballoon ablation in order to complete PVI, procedure times become significantly longer.¹³,¹⁴ A limiting factor to a further decrease in procedure time is probably the defined duration of the freezing cycle with a standard duration of 5 min.

Performing cryoballoon ablation is generally considered to depend less on operator dexterity. However, this general statement may certainly be challenged. Most electrophysiologists currently performing cryoballoon ablation have ample experience with left atrial ablations and therefore may have a steep learning curve. The problem of creating a continuous lesion with focal RF ablation catheters may be overcome by using the cryoballoon: the device creates a circumferential lesion with a single application with a very stable catheter position because the balloon is “frozen” to the tissue. On the other hand, the cryoballoon catheter is a relatively stiff device (requiring a 15 Fr outer diameter deflectable sheath) and operator skills in addition to advanced knowledge of left atrial anatomy are certainly needed to safely maneuver the balloon in the left atrium.

Atrio-esophageal fistula is a catastrophic complication of RF ablation of AF that has not been observed with cryoballoon ablation. However, esophageal lesions have been described, and given the fact that only approximately 1500 patients have been treated with the cryoballoon so far in published trials or case series, it may be too early to state that cryoballoon ablation does not result in atrio-esophageal fistula.¹⁵

Cryoballoon ablation is considered to result in a very low rate of PV stenosis when using a significant change in PV diameter as a standard definition. The STOP AF trial reported a PV stenosis rate of 3% when defining PV stenosis as a reduction in cross-sectional area (as opposed to diameter) of more than 75%.³

Probably the single most important question apart from safety is how cryoballoon ablation compares to RF ablation with regards to efficacy. No randomized trials are available to date, but non-randomized comparisons have shown similar efficacy.¹⁰⁻¹² However, randomized head-to-head comparisons are needed and are under way.

With regards to left atrial tachycardia or flutter occurring after PVI, the rate of these arrhythmias appears to be low after cryoballoon ablation of AF.¹⁶ This may be because ablation is performed somewhat closer to the PV ostia with the cryoballoon, although data from electro-anatomical mapping suggest that most PVs still undergo antral ablation with the cryoballoon unless there is a mismatch between the vein and the balloon.¹²

**Drawbacks of cryoballoon ablation**

One of the main drawbacks of cryoballoon catheters is a disadvantage that is inherent to any balloon-based ablation system: its limited flexibility. In a cost-sensitive system, patients undergoing AF ablation who have additional arrhythmias, such as typical isthmus-dependent atrial flutter or other supraventricular tachycardias, choosing the cryoballoon would not be advisable because a switch to a focal catheter is required. This obviously also holds true for patients with persistent AF who require additional linear or focal lesions in the left atrium. Of note, in the United States, the cryoballoon is only approved for ablation of paroxysmal AF. The necessity to switch to a

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**Figure 1:** Cross-sectional view of an inflated Arctic Front cryoballoon ablation catheter. Note the site of the injection tube and the proximal position of the thermocouple. Used with permission of Medtronic International Trading Sàrl. © 2006 Medtronic International Trading Sàrl.
focal catheter varies widely between different case series (range 2–60%) and probably depends on the number of applications with the cryoballoon catheter before a switch to a focal catheter is made (or if a switch is allowed at all).11,14,18,19

One of the most common procedural complications of cryoballoon ablation is the occurrence of phrenic nerve palsy. Owing to the close proximity of the right-sided PVs to the right phrenic nerve, phrenic nerve palsy during or after ablation has been reported in approximately 4–14% of patients.3,16,20 The majority of phrenic nerve palsies occur with the use of the small (23 mm diameter) balloon during ablation at the right superior PV. Therefore, only the 28 mm diameter balloon is used at our institution. Luckily, only a minority (<10%) of phrenic nerve palsies persist beyond 12 months. Franceschi et al.21 have recently described a potential novel preventive tool by recording diaphragmatic compound motor action potentials in mongrel dogs using an esophageal catheter.

Another drawback of cryoballoon ablation is that the demonstration of good circumferential tissue contact is usually achieved by contrast injection into the PV before starting the energy application. This may result in the use of a considerable amount of contrast medium (e.g. 174 ± 50 ml in one reported case series), making the technique problematic in patients with impaired renal function.18 Assessment of the pressure curve obtained at the tip of the catheter or using color Doppler during transesophageal echocardiography to document PV occlusion may overcome the problem of contrast administration during cryoballoon ablation, but these techniques have not been widely adopted.22,23 At our institution, no periprocedural imaging (intracardiac or transesophageal echocardiography) is used.

Finally, certain anatomical variants (e.g. presence of a left common trunk) are not suitable for cryoballoon ablation, and anatomical information using pre-procedural imaging (computed tomography or magnetic resonance imaging) is frequently obtained before choosing the ablation modality. This is helpful despite the fact that the cryoballoon ablation system is not compatible with electroanatomical mapping systems.

Technical aspects

Vascular access is an important part of any AF ablation procedure because the majority of complications, even though usually not life-threatening, occur at this point of the intervention with a rate of approximately 2%.24 Proper technique with vascular access is probably even more important with cryoballoon ablation because of the large caliber steerable sheath required for the cryoballoon (FlexCath, Medtronic, 15 Fr). We usually use the right femoral vein for vascular access and a three-catheter approach with a coronary sinus catheter (used as a reference and for pacing), a circumferential mapping catheter, and the cryoballoon. We used to place an additional catheter in the superior vena cava for phrenic nerve stimulation during ablation at the right-sided PVs, but now use the coronary sinus catheter for this purpose.

This may even have the advantage of achieving better stability in the superior vena cava for consistent phrenic nerve capture because a deflectable catheter is used.

Access to the left atrium is gained by performing trans-septal puncture, unless a patent foramen ovale is present. Because of concerns of persistence of iatrogenic atrial septal defects, especially with single puncture and passage of two catheters through one puncture, we usually perform two separate trans-septal punctures for the cryoballoon and the circumferential mapping catheter.25 This may be especially important when using a large caliber trans-septal sheath such as the 15 Fr deflectable sheath required for the cryoballoon catheter (FlexCath, Medtronic). The advent of a novel spiral catheter designed specifically for insertion through the cryoballoon allowing real-time recordings of PV signals during cryoballoon ablation may obviate the need for the separate circumferential mapping catheter and thus the second trans-septal puncture. The use of the spiral catheter is further discussed below. Once access to the left atrium has been obtained, intravenous Heparin is administered with a target activated clotting time (ACT) of 300–350 seconds.

Once the cryoballoon catheter is in the left atrium, care should be taken when maneuvering the device in the left atrium because the tip of the catheter is certainly stiffer than conventional RF ablation catheters. It is advisable to advance the guidewire out of the catheter (with the tip of the catheter well clear of the atrial wall to avoid perforation) into the targeted PV before advancing the

Figure 2: Left anterior oblique view (45 degrees) during contrast injection into the left superior pulmonary vein (PV) showing complete occlusion as a sign of good circumferential tissue contact. This PV was isolated after two freezing cycles of 5 min. Please note the appropriate central alignment of the sheath, the balloon catheter (arrow) and the PV. The circumferential mapping catheter in the left atrium and the coronary sinus catheter can also be seen.
catheter. After inflation, the balloon is advanced and contrast injection into the PV is performed through the lumen of the catheter. In an ideal case, complete occlusion of the targeted PV as a sign of good circumferential tissue contact is demonstrated (Figure 2). After saline injection through the balloon catheter, the freezing cycle with a standard duration of 5 min may be initiated. An average of two applications per PV is necessary for most PVs. We commonly perform two applications per PV before inserting the circumferential mapping catheter into the vein. We switch to a conventional focal ablation catheter if a PV cannot be isolated using up to six applications (30 min of cryoenergy). However, this varies between published studies.10-18

Based on the observation that especially the left-sided PVs may share common fascicles, performing applications of cryoenergy at the inferior PVs is advisable even if the superior PVs are not completely isolated after two freezing cycles. This holds true especially when remaining PV potentials are visible at the inferior circumference of the superior PV. Cryoballoon ablation at the inferior PV may result in isolation of the superior PV (or vice versa), a phenomenon that has been termed cross-talk (Figure 3).13,18

Good tissue contact to obtain permanent lesions is more difficult at the inferior circumference, especially with cryoballoon ablation at the inferior PVs, and this is also supported by the fact that more inferior PV reconnections are detected during repeat left atrial procedures in patients after cryoballoon ablation than during RF ablation.10 This has to do not only with the anatomy of the left atrium and the PVs, but also the general orientation of the trans-septal sheath. Correcting the central alignment of the sheath may suffice to achieve good circumferential tissue contact. This may be achieved by deflecting the sheath and the catheter (in opposite directions if needed) and by placing the guidewire in different branches of the PV. A gentle pull-down maneuver after the freezing cycle has been initiated and the balloon is frozen to the tissue at the superior circumference of the PV may help to further improve the alignment and the tissue contact in order to achieve permanent lesions (Figure 4).26

No study has shown that the problem of phrenic nerve palsy can be eliminated completely with the use of

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**Figure 3:** Left anterior oblique view (49 degrees) with the cryoballoon (arrow) at the antrum of the left inferior pulmonary vein (PV). After two freezing cycles at the left superior PV, the vein was not isolated. Cryoballoon ablation at the left inferior PV resulted in isolation of the left superior PV, a phenomenon known as cross-talk. The left inferior PV was not isolated after this freezing cycle (see Figure 4).

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**Figure 4:** Left anterior oblique view (49 degrees, same patient as in Figure 3) with the cryoballoon (arrow) at the antrum of the left inferior pulmonary vein (PV). (a) No complete occlusion of the left inferior PV can be achieved due to the lack of central alignment of the catheter. There is no sufficient tissue contact at the inferior circumference of the PV. (b) By improving the alignment of the catheter, an improved but still incomplete occlusion can be seen. (c) A gentle pull-down maneuver during the freezing cycle results in better central alignment of the sheath and better tissue contact at the inferior circumference of the left inferior PV and successful isolation of the vein.
Although the vast majority of phrenic nerve palsies occur with ablation at the right superior pulmonary vein (PV), phrenic nerve stimulation is performed with an output of 12 V/2.9 ms at a cycle length of 1000 ms during cryoballoon ablation of both right-sided PVs at our institution. Capture of the right phrenic nerve is confirmed by fluoroscopy and manual confirmation before the freezing cycle is initiated. During the freezing cycle, one member of the electrophysiology laboratory personnel is standing next to the refrigeration console (CryoConsole, Medtronic) and the freezing cycle is immediately terminated in case of loss of phrenic nerve capture or decrease in diaphragmatic contraction. One pitfall that is avoided easily is that right phrenic nerve damage may be missed if stimulation is performed distal to the potential site of damage (Figure 5). On the other hand, assuring a stable catheter position in the superior vena cava, if needed with the use of a deflectable catheter, and demonstration of consistent phrenic nerve capture before initiating the freezing cycle may help to avoid over-diagnosing phrenic nerve palsy. If the procedure is performed in conscious sedation (midazolam, propofol) as in our institution, adapting the level of sedation may help to improve the tolerability of phrenic nerve pacing.

**Future perspective**

One of the current limitations of cryoballoon ablation is that no real-time recordings from the PVs are available during the freezing cycle. This problem can be overcome...
by using a circumferential mapping catheter inserted through the lumen of the cryoballoon catheter. For this purpose, Chun et al.27 have used a spiral catheter (Promap, ProRhythm Inc., Ronkonkoma, NY) commonly used with the HIFU (high-intensity focused ultrasound) balloon and not designed for the cryoballoon ablation catheter. In their study, only 54% of all PVs were successfully isolated using the spiral catheter, suggesting that improvements in catheter design are necessary to increase the percentage of PVs that can be isolated using the spiral catheter. The second finding of the study was that time to effect (= time to PV conduction block) predicted sustained isolation of the PVs making real-time recordings of PV signals during the freezing cycle an attractive tool during cryoballoon ablation. If improved, the device has the potential to further streamline the procedure because unsuccessful freezes could be aborted early. Furthermore, if signal quality and maneuverability prove adequate, the use of the spiral catheter may eliminate the need to perform a second transseptal puncture and the use of a standard circumferential mapping catheter. A novel “through-the-balloon” circumferential mapping catheter (Achieve, Medtronic) has been developed and may be used in Europe, but has not yet received FDA approval (Figure 6). Although the new catheter is available with a 15 or 20 mm diameter, obtaining good signal quality and an adequate position not too deep in the PV and with circumferential tissue contact can still be challenging (Figure 7). Further studies are needed to determine whether most PVs can be isolated using this catheter alone and how reliable it is in confirming complete isolation of all PVs. Given the limited experience with the device, confirming complete PVI using a conventional circumferential mapping catheter is recommended.

Another limitation of cryoballoon ablation is the fact that isolation of a PV depends on good occlusion as a marker of adequate tissue contact. Individual anatomical variants that may at least in part be detected with pre-procedural imaging can make cryoballoon ablation especially challenging in some patients.28 New developments with more compliant balloons may overcome this limitation in the future.

Conclusion

Cryoballoon ablation has emerged as a novel tool to perform PVI in patients with strictly paroxysmal AF requiring complete isolation of the PVs, but no additional lesions. Although several advantages of this new technology have further simplified the procedure, important limitations exist and profound knowledge of left atrial anatomy is still required to perform PVI safely and successfully with the cryoballoon catheter.

References


