The Use of Cryoballoon Technology in Catheter Ablation of Atrial Fibrillation: State of the Art

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ABSTRACT. Pulmonary vein (PV) isolation using radiofrequency (RF) energy has been recognized as the cornerstone of catheter ablation for atrial fibrillation (AF). However, potentially life-threatening complications can occur during RF ablation of AF. Cryoballoon PV isolation has been recently introduced as an alternative to RF ablation. This treatment modality has been shown to be effective in the treatment of paroxysmal AF, but its usefulness in the management of persistent AF still needs further investigation. Phrenic nerve paralysis is the most frequent complication observed with the use of this technology, but it is fortunately reversible in the majority of cases.

KEYWORDS. catheter ablation of atrial fibrillation, cryoablation, cryoballoon, cryoenergy, cryothermal energy, cryothermia.

Introduction

Catheter ablation has become one of the primary treatments of symptomatic drug-refractory atrial fibrillation (AF). Although ablation techniques vary among centers, it is generally accepted that pulmonary vein isolation (PVI) represents the cornerstone of catheter ablation of AF. Achieving PVI with focal radiofrequency (RF) catheters is a time-consuming and technically challenging process which requires a high level of expertise. Moreover, this treatment modality is associated with a complication rate of 2–5% according to some studies. As a result, novel tools and techniques, including various balloon ablation catheters using different energy sources, have been introduced into clinical practice with the aim of providing a safer, faster, more standardized, and more effective PVI procedure. So far the greatest clinical experience with balloon ablation technologies has been with the cryoballoon.

Principles of cryothermal energy

RF tissue heating results in tissue destruction, an intense inflammatory response, and the risk of thrombus formation requiring anticoagulation during and after the procedure to prevent stroke. Moreover, delivery of RF lesions within venous structures such as the coronary sinus or pulmonary veins (PVs) is associated with a risk of venous stenosis, endoluminal thrombosis, and perforation, possibly leading to tamponade or damage to adjacent arterial structures. Cryothermal energy is an alternative energy source that has been developed to overcome some of the disadvantages of RF ablation such as tissue disruption by excessive heating and generation of inhomogeneous lesions. The immediate cause of injury is the deleterious effect of freezing and rewarming cycles on the cells. The delayed effects consist of progressive failure of the microcirculation and ultimately vascular stasis. Previous studies imply that cryosurgery also triggers apoptosis. Cryolesions are sharply demarcated and the margins are infiltrated by fibrin, collagen stranding, and capillary growth. The final phase in the evolution of a stable cryolesion is seen within 2–4 weeks. All this results in preservation of tissue architecture and endocardial contours and minimal thrombus formation, thus making cryogenic lesions homogeneous, sharply defined, and with a low arrhythmogenic potential.

Pulmonary vein isolation using cryoballoon technology

Features of the cryoballoon strategy

Cryoablation has some potential advantages for AF ablation. This ablation energy has a lower thrombogenicity...
and has never been associated with atrioesophageal fistula (AEF), even though this complication is theoretically possible since esophageal lesions have been detected in animal studies using cryoablation.22,23 Catheter point-by-point cryoablation is an effective method to create electrical PVI with clinically satisfactory results and no risk of pulmonary vein (PV) stenosis.24 However, procedure times are long, due to the longer individual ablation applications required to produce equivalent lesions, considering that one single ablation point takes about 4 min, making focal cryoablation for AF impractical.

As a result a cryoballoon device (Arctic Front, Medtronic, Cryocath, Quebec, Canada) has been developed which allows circumferential PVI.19,20,25–27 In contrast to sequential point-by-point ablation using a cryo or an RF focal catheter, the cryoballoon technique allows simultaneous energy delivery at the left atrium (LA)–PV junction circumferentially, often resulting in isolation of the PV with a single cryothermal energy application.27,28

Cryoballoon technology

The CryoConsole (Medtronic) houses the coolant as well as electrical and mechanical. The refrigerant nitrous oxide is delivered into the inner balloon where it undergoes a liquid-to-gas phase change, resulting in an inner balloon cooling temperature of approximately −80°C. A central lumen is used for the insertion of the guidewire and injection of contrast medium for PV angiograms. Using the “over-the-wire” technique in conjunction with the 12-F steerable sheath (FlexCath, Medtronic), the balloon can be navigated to each PV ostium.28

The catheter is available in 23 mm and 28 mm diameter sizes, as appropriate for the diameter of each PV. Preprocedural (computed tomography/magnetic resonance imaging) or intraprocedural (angiography, intracardiac ultrasound) imaging can be helpful to correctly size the balloon to the PV ostia. Many operators however advocate using the 28-mm balloon for most pulmonary veins. After transseptal puncture, the catheter is deployed to the LA. A stiff guidewire is placed deep into a branch of the PV to achieve stability, and the balloon is then positioned in front of the PV ostium. In case of multiple freezes, it is possible to select different branches with the guidewire at every freeze to achieve a better contact of the balloon with the entire contour of the antrum. In order to avoid any mechanical damage, special care must be taken to inflate the balloon outside the PV. After inflation, the catheter is applied to the vein and the optimum position in the PV ostium is usually confirmed by PV angiography. It is important for isolation success to achieve complete occlusion of the vein. It is believed that blood flow alongside the balloon (peri-balloon leaks) and incomplete vein occlusion account for higher temperatures which have been deemed responsible for reversible lesions.27

Occlusion-monitoring strategies

The minimal temperature achieved during cryoballoon ablation and the slope of rewarming, acquired using a temperature sensor located in the back of the balloon together with the CryoConsole software, are correlated with depth of the lesions, but no precise cut-off value has been correlated with effective PVI.20,26 Transesophageal echocardiography (TEE) allows monitoring of balloon positioning and PV occlusion via color Doppler. After inflation, the balloon is advanced, aiming for PV flow disappearance as documented by color Doppler. TEE-guided assessment of PV occlusion during cryoballoon ablation has been proven feasible, effective and able to predict effective PV electrical isolation with a positive predictive value of 98%.29 However, performing TEE-guided cryoballoon PVI requires additional well-trained personnel and the use of general anesthesia. Siklody and colleagues showed that occlusion and electrical isolation of the PVs during cryoballoon ablation can be predicted by a PV wedge pressure curve recorded at the tip of the catheter,30 one limitation of this technique is that no pressure curve can be registered beneath 0°C, so that exclusive pressure monitoring would fail to detect late balloon dislocations occurring during cryoablation. Intracardiac echography (ICE) can be very helpful for adequate balloon sizing and might confirm occlusion of the PV not only before the initial freeze, but also while performing maneuvers and techniques of repositioning during the freezing period to help optimize contact.31

Ablation techniques with the cryoballoon

After confirmation of PV occlusion, a cryoablation is applied for 240–300 s for each vein. With optimal positioning, it has been demonstrated that electrical isolation can be obtained acutely with the delivery of a single, 240-s lesion,32 but bonus lesions are often performed to ensure a better PVI rate. Conduction recovery after cryoballoon PVI has been observed to occur with a higher incidence at inferior poles of the veins.33 As a result, every effort should be done to obtain good inferior contact. When occlusion is not as desired, the wire can be changed to a different side branch. Flexion of the sheath can also be attempted to ensure better occlusion. Special ablation techniques have been developed for different veins in order to optimize PV occlusion and isolation28 and these are detailed below:

- the “hockey stick” technique and the “pull-down” technique allow balloon to tissue contact at the inferior PV circumference of the inferior PVs by changing its position before or during the freezing period;
- the “big loop” technique helps to obtain right inferior PV occlusion if a large inferior gap is present (figure 1).

When PVI is not achievable with a single cryoballoon, a double-balloon strategy (with two different sizes) or a
point-to-point cryotip catheter has been used to complete lesions.

**Clinical use and results – success rate of the cryoballoon catheter**

The acute PVI rate is relatively high with the cryoballoon, often exceeding 95%. The main reason for the inability to achieve complete isolation is anatomic features such as oval PV ostia or inferior veins inserting onto the LA with a sharp angulation.

At the present time, cryoballoon ablation of paroxysmal AF has the promise to be an effective approach and appears to have similar success rates as RF ablation after 6 months, with midterm success rates ranging from 55% to 86% with respect to AF-free survival. RF and cryoballoon strategies appeared to be equivalent in terms of practicability in a case–control study conducted by Linhart and colleagues, but AF recurrence and AF episode burden were lower after cryoablation (55% versus 45% of freedom from AF during a 6-month follow-up). The success rate was higher for a combination approach (cryoballoon plus point-to-point cryoablation) than for balloon-only ablation. The differences in success rates did not reach statistical significance. In the first published series of 57 patients treated with cryoballoon PVI, freedom from AF after 3 months was reached in 60%. Neumann et al achieved maintenance of sinus rhythm in 74% of patients with paroxysmal AF and 42% with persistent AF without antiarrhythmic drug therapy after cryoballoon ablation of 346 patients with a mean follow-up of 12 months. In a selected population of patients with paroxysmal AF and normally sized left atria, the 6-month success rate of the cryoballoon AF ablation approach reached 86%. The difference in the success rate among different groups might be explained by different follow-up strategies; if intensive follow-up is performed, the overall success rate of the first PV ablation appears to be quite low.

Cryoballoon PVI is relatively easy to perform and presents a steep learning curve. Klein et al observed that fluoroscopy times significantly decreased after only five or six procedures to a mean of about 36 min.

The cryoballoon system has been approved for clinical use in Europe and the United States and has been investigated in two randomized, multicenter trials comparing its safety and efficacy with that of antiarrhythmic drugs and RF ablation, respectively. In the STOP-AF trial, investigators enrolled 245 patients with paroxysmal AF at 26 centers with the purpose of comparing the cryoballoon ablation technique with antiarrhythmic drug therapy. During a 12-month follow-up, 69.9% of patients treated with cryoablation were free from AF compared with 7.3% of patients treated with antiarrhythmic drugs. Among the successfully ablated patients, 58% were free from AF at 1 year without the use of antiarrhythmic drug therapy, and 60% were free from AF after a single ablation procedure. The FreezeAF trial is underway and aims to compare the safety and efficacy of cryoballoon with RF ablation.

Future studies will have to show whether this new device is also cost-effective as first-line treatment of paroxysmal AF without any prior antiarrhythmic medication and whether cryoballoon ablation is also able to achieve a similar substrate modification compared with RF energy in patients with persistent AF. Table 1 summarizes the results of the most important clinical trials investigating cryoballoon ablation of AF.

**Complications associated to cryoballoon ablation of atrial fibrillation**

Cryothermal energy is known to be safer than other energy sources. The most widely known complication of cryoballoon ablation is phrenic nerve palsy (PNP). The occurrence of PNP when using cryoballoon ranges from 2% to 11%. It has been seen more frequently with ablation in the right superior PV. High-output phrenic nerve pacing during ablation of the right superior PV can considerably reduce this risk, through early detection of phrenic nerve injury and promptly discontinuing ablation. This kind of complication is usually not life-threatening; moreover, when the palsy had occurred, it predominantly regressed during follow-up. The small balloon/PV ostium ratio has been observed to favor phrenic nerve injury. It is believed that the smaller balloon can reach relatively deep into the PV and achieve closer proximity to the phrenic nerve. However, a PNP rate of 11% has been described in a study that investigated PV ablation with a single 28-mm cryoballoon approach. These findings indicate that a balloon position deep in the vein in close proximity to the phrenic nerve is responsible for the damage, and that...
<table>
<thead>
<tr>
<th>Study</th>
<th>No of patients</th>
<th>Age (years)</th>
<th>Follow-up (months)</th>
<th>Study design</th>
<th>Objectives</th>
<th>Results</th>
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<tr>
<td>Van Belle et al.</td>
<td>57</td>
<td>55 ± 9</td>
<td>3</td>
<td>Consecutive patients with paroxysmal AF treated with a 23 or 28 mm cryoballoon</td>
<td>Safety, feasibility and short-term outcome of cryoballoon ablation</td>
<td>84% acute PVI rate 60% free from AF after a single procedure Four phrenic nerve palsies (one persisted at 6 months)</td>
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<td>Linhart et al.</td>
<td>40</td>
<td>59.9 (38–77)</td>
<td>6</td>
<td>Cryoballoon: 59.9 (38–77) RF: 58.5 (40–73)</td>
<td>AF-free survival rate</td>
<td>AF-free survival comparable with both cryoballoon (55%) and RF (45%) strategies</td>
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<td>Chun et al.</td>
<td>346</td>
<td>Paroxysmal: 293; Persistent: 93</td>
<td>12 (7–16)</td>
<td>Consecutive patients with symptomatic, drug refractory paroxysmal or persistent AF treated with the cryoballoon with or without the aid of a cryotip catheter</td>
<td>Acute isolation rate of targeted PV; first ECG-documented recurrence of AF; complication rate</td>
<td>PVI rate: 97% maintenance of sinus rhythm in 74% of patients with paroxysmal AF and 42% of patients with persistent AF 26 phrenic nerve palsies, all reversible; no atrioesophageal fistulas</td>
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<tr>
<td>Klein et al.</td>
<td>21</td>
<td>56 ± 6</td>
<td>6</td>
<td>Consecutive patients with highly symptomatic paroxysmal AF, normal LA size, and frequent episodes of AF were treated with cryoballoon ablation</td>
<td>To test the 6-month efficacy of cryoballoon ablation of paroxysmal AF</td>
<td>95% of PVs completely isolated with a single balloon strategy. AF free survival 86% after a single procedure</td>
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<td>Freeze AF</td>
<td>244</td>
<td>–</td>
<td>–</td>
<td>244 patients with paroxysmal AF will be randomized for either RF or cryoballoon</td>
<td>To compare the efficacy and safety of PVI with either the cryoballoon or the open irrigated tip RF catheter</td>
<td>Underway</td>
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<tr>
<td>STOP-AF</td>
<td>245</td>
<td>–</td>
<td>12</td>
<td>245 patients with paroxysmal AF will be randomized at 26 centers to either antiarrhythmic drugs or cryoballoon</td>
<td>To compare cryoballoon vs antiarrhythmic drugs in paroxysmal AF</td>
<td>69.9% free of AF in the cryoballoon group vs 7.3% in the antiarrhythmic drugs group</td>
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the actual balloon size might only be a subordinated factor. Modification of balloon anatomy would be of some help to avoid inadvertent shift of the balloon into a more distal position.

Despite minor esophageal injuries that have been observed with balloon cryoablation, no AEF has occurred to date. In contrast, the incidence of AEF after RF ablation for AF is 0.04%.41 However, the total number of patients who underwent PVI so far using cryoballoon catheter is too small to conclude whether serious esophageal lesions can be excluded from the list of complications following cryoballoon ablation.

Even though PV stenosis had not been observed in earlier studies, the STOP-AF trial showed an incidence of PV stenosis as high as 3.1.36 This risk might be reduced by utilizing a 28-mm balloon, which is more likely to allow antral extra-ostial ablation.

**Further improvements to the cryoballoon technique**

**Combined cryoballoon–RF approach**

Clinical success of cryoballoon PVI for treatment of paroxysmal AF has not been achieved in patients with persistent AF. In fact, the clinical success rate in one study was only 39% among patients with persistent AF, likely because of the need for additional atrial substrate modification in this subgroup. Extensive substrate modification using focal cryoblation catheters is limited by a prolonged application time and the inability to drag the catheter during ablation due to cryocatheter adherence to tissue. In order to overcome this limitation, a combined approach has been described using a cryoballoon for PVI and a focal RF catheter for LA substrate modification. It was found that this approach is feasible, improves intraprocedural termination of AF compared with cryoballoon PVI alone, and is associated with favorable short- and mid-term maintenance of sinus rhythm (86% arrhythmia-free survival at 6 months) compared with that of cryoballoon PVI alone for persistent AF.42

**Real-time recording of electrograms during cryoballoon ablation**

Cryoballoon technique requires either two transseptal punctures to accommodate both an ablation catheter and a PV mapping catheter or a single transseptal puncture with the operator interchanging the cryoballoon catheter and mapping catheter. The use of a cryoballoon catheter equipped with a 6-pole micromapping spiral catheter (Promap, ProRhythm Inc., Ronkonkoma, NY), inserted through its central lumen for the purpose of mapping and ablation during PVI procedures, has been proven to be both feasible and effective.32,43 The mapping catheter introduced into the central lumen can be used as a guidewire as well as a recording device, thus allowing the real-time recording of PV electrograms and making possible to monitor the isolation of the vein during the freeze. One limitation of this novel device is that sometimes the mapping catheter has to be positioned deep inside the target vein during ablation to achieve complete occlusion of the vein and has to be withdrawn immediately after each ablation attempt to test the PV potential. With this approach, the operator does not either need to interchange the two catheters (cryoballoon and circular mapping catheter) nor to perform double transseptal punctures.

**Conclusion**

Cryoballoon ablation of paroxysmal AF is a novel promising technique. Clinical trials are needed to study its efficacy in patients with persistent AF. The most frequent complication of this approach is phrenic nerve paralysis, which has been shown to be reversible in most cases. New developments like modifications of the...
balloon anatomy or over-the-wire techniques to enable circular PV potential recordings during cryoablation will contribute to a further simplification of the ablation procedure and an optimization of its safety profile.

References


