Pulmonary Vein Isolation with the Cryoballoon: Simpler, Faster...But Equally Effective?

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ABSTRACT

Atrial Fibrillation (AF) is the most frequently encountered arrhythmia in clinical practice that represents an enormous burden for our current health care systems. Since the demonstration of pulmonary vein (PV) ectopic activity as the main trigger of paroxysmal AF, radiofrequency ablation (RF) of this arrhythmia has become an increasingly popular procedure in many electrophysiology laboratories. Nowadays creation of circumferential lesions around the PVs is certainly the most widespread technique to achieve PV isolation. Recently, novel balloon shaped ablation catheters have proven very effective in producing PV isolation with the added potential ability of achieving complete circular lesions with a single application. However, the cryoballoons currently available do not always adapt themselves well to the anatomical variants and do not systematically isolate the PVs in one application. Ideally, a more compliant balloon which would fit into most PVs might lead to a more effective procedure. Future technological improvements might lead a larger number of electrophysiologists to adopt such a technique.

KEYWORDS
Ablation, atrial fibrillation, catheter, cryoballoon, isolation, pulmonary vein
Introduction

Atrial Fibrillation (AF) is the most frequently encountered arrhythmia in clinical practice that represents an enormous burden for our current health care systems. Since the demonstration of pulmonary vein (PV) ectopic activity as the main trigger of paroxysmal AF (1,2), radiofrequency ablation (RF) of this arrhythmia has become an increasingly popular procedure in many electrophysiology laboratories. Nowadays creation of circumferential lesions around the PVs is certainly the most widespread technique to achieve PV isolation. In most centers, this procedure is achieved by performing a “point by point” lesion that renders the creation of continuous lines difficult and permits the formation of electrical gaps which may lead to arrhythmic recurrence (3). Additionally even in experienced hands this approach is still too cumbersome (4). Furthermore, AF ablation using RF is associated with a certain number of serious complications such as PV stenosis, thrombo-embolism, pericardial tamponade, and atrio-oesophageal fistula (4).

Recently, novel balloon shaped ablation catheters have proven very effective in producing PV isolation with the added potential ability of achieving complete circular lesions with a single application (5). Among the latter, the Cryo-
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The Cryothermal Balloon Device

This tool (Fig 1) represents a very appealing system to perform PV isolation being able to produce electrical isolation with virtually one single application. Mainly designed to approach drug resistant paroxysmal AF, the cryoballoon therapy apparatus include the Arctic Front® doubled-walled cryoballoon catheter, which inflates and fills with coolant (\(N_2O\)) to ablate between the pulmonary veins and the left atrium; the FlexCath® Steerable Sheath, which helps deliver and position the cryocatheter in the left atrium (LA) and the CryoConsole®, which houses the coolant, electrical and mechanical components that run the catheter during a cryothermal procedure. The refrigerant \(N_2O\) is delivered into the balloon where it undergoes a liquid-to-gas phase change, resulting in cooling temperature of approximately -80°C. As other cryothermal tools the endocardial lesion created by the cryoballoon occurs in three main phases. The first phase is characterized by the immediate effect of freezing on the cardiac tissue by the formation of ice crystals in both the extracellular and intracellular space. When reaching temperatures lower than -20/-25°C ice cristal formation occurs in the extracellular space. Further ablation reaching temperatures lower than -40°C leads to cellular damage by the means of intracellular ice cristal formation. This phenomenon provokes destruction of cytoplasmic organelles and architectural subversion of the cell membrane. Irreversible cellular death will occur when temperatures reach values lower than -70°C. When cryothermal energy is stopped, a rapid vasodilatation and a state of augmented vascular permeability lead to hemorrhage and edema with further tissue injury. During this hyperemic response endothelial damage results in platelet aggregation and microthrombus formation with microcirculation stagnation for roughly 30 to 45 min. The third phase is characterized by scar formation. During the latter, tissue repairment occurs by collagen deposits, fatty infiltrations and neovascularisation. The fibrotic scar will first develop from the peripheric areas of the lesion eventually reaching the centre (9,10).

The cryoballoon catheter has a central lumen, which can be used for different scopes such as the insertion of the guide wire, the injection of contrast medium (diluted 1:1 ratio...
with 0.9% saline) for PV angiograms and eventually the insertion of a circular mapping catheter to evaluate PV isolation during cryothermal energy application (8). Navigation of the balloon inside the LA is simplified using the ‘over-the-wire’ technique in addition to the steerable sheath (12 F, FlexCath, Medtronic Cryocath™, USA). In addition, the cryoballoon itself is steerable thanks to a pull wire mechanism integrated in the handle of the catheter itself.

The Procedure

Usually a single transseptal puncture is then performed using the right femoral venous approach. In some centers, a double transseptal puncture is achieved in order to have simultaneous electrical information during the freezing phase. After gaining the LA access, a 70 IU/Kg heparin iv bolus is given and afterwards repeated to maintain the activated clotting time over 300 s. Selective PV angiograms are then performed. Immediately after, a steerable 15 F over-the-wire sheath (FlexCath, Cryocath, Medtronic, USA) is positioned in the LA. Through the latter, a 23 or 28 mm double walled cryoballoon (Arctic Front, Medtronic, USA) is up to the LA. An inner lumen circular mapping catheter (Achieve, Medtronic, USA) is positioned in the PV ostium to gather real time recordings (Fig 2). The balloon is then inflated and advanced over the circular mapping catheter in the PV ostium of each vein. Optimal vessel occlusion is considered to have been achieved when selective contrast injection shows total contrast retention with no flow to the atrium. If occlusion is not possible using the circular mapping catheter, the latter can be exchanged with a guide wire that might offer better stability. For each vein, cryoablation usually consists of a minimum of 2 applications lasting 5 minutes each. Whenever possible, the operator tries to engage with the guide-wire 2 different branches of the same vein and to orient the balloon differently, in the attempt of covering a wider ostial surface. However, if successful occlusion could only be obtained in one branch, both applications are delivered by leaving the guide-wire in the same branch. Usually, the left superior PV (LSPV) (Fig 3) is
treated first, followed by the left inferior PV (LIPV), right superior PV (RSPV) and right inferior PV (RIPV). During ablation, the circular mapping catheter offers real time information of the electrical activity in the vein. Usually, PV isolation can be observed “real-time” during energy delivery. In order to avoid phrenic nerve palsy, a complication observed during cryoballoon ablation in the RSPV and RIPV, a bipolar catheter is inserted in the superior vena cava in order to pace phrenic nerve with a 1000 ms cycle and a 20 mA pulse output. Diaphragmatic contraction during pacing will indicate correct phrenic capture. If this contraction suddenly stops or weakens, the cryoablation should be immediately interrupted. The reason of pacing at such a slow rate is to prevent catheter displacement in the early phases of application due to diaphragmatic contraction. In case of persistence of PV potentials extra cryoballoon applications were performed until complete PV isolation. In case of failure of the cryoballoon, a focal RF or cryothermal energy catheter is used to complete PV isolation.

In clinical practice isolating the inferior PVs can be particularly challenging in comparison to the superior ones (11). Specifically, occluding and isolating the RIPV is often quite tricky due to the proximity of this vein to the site of transatrial access and its posterior orientation, especially in patients with relatively small LA (LA diameter < 35 mm). Various ablation techniques aiming at overcoming these anatomical obstacles have been reported: the “hockey stick” technique, the “pull-down” technique. The “hockey stick” technique is applied in patients with an early branching inferior PV and consists of a maximal bending of the sheath towards the superior-posterior LA, allowing the cryoballoon to be pushed and to adhere to inferior part of the PV ostium. The RIPV can be addressed using the “pull-down” technique. This procedure consists in starting the freeze at the ostium of the PV, regardless of the incomplete occlusion and when the latter adheres to the interpulmonary carina (typically at -20°C) to pull down all the cryoballoon apparatus, in order to close the inferior gap.

**Pulmonary Vein Isolation: Acute Results**

According to recent publications about PV isolation can be demonstrated in more than 90% of veins following cryoballoon ablation. Successful PV isolation with the cryoballoon is highly dependent on a perfect contact to the atrial wall at the level of the PV ostia. Indeed, lack of blood back-flow allows the cryoballoon to obtain lower temperatures with the result of achieving more deeper lesions (12). Anatomical difficulties seem to represent the main obstacle to complete PV isolation when using the cryoballoon; Van Belle et al. reported that oval shaped PV ostia or veins inserting into the LA with a sharp angulation are the most difficult to occlude (12). However like in all other techniques, the learning curve and the level of the operator’s experience will condition the efficacy of cryoballoon ablation. Our group analyzed the degree of adenosine induced LA-PV isolation following cryoballoon ablation (13). Adenosine is known to induce transient reconduction in isolated PVs, due to incomplete lesions after RF ablation (14,15). In our series of patients, transient PV-LA reconnection occurred only in 4.6% PVs compared to a mean 30% of veins following PV isolation with RF. A possible explanation of this discrepancy is that a balloon strategy might lead to more continuous lesions than point by point circumferential PV isolation.
Pulmonary Vein Isolation: Chronic Results

Fürnkranz and colleagues (16) analyzed the sites of PV reconnection in 26 patients undergoing repeat ablation for recurrent symptomatic AF or atrial tachycardia after initial cryoballoon ablation for paroxysmal AF. They found a high rate of PV reconnection (around 50%) at a median follow-up of about 6 months. Reconnection mostly occurred in the inferior segments of the inferior PVs and on the LA appendix -LSPV ridge. They postulated, in accordance to the previous findings described by others (12) that a straighter alignment of the balloon with the superior PVs as compared with the inferior ones provides more contact force on the LA wall and lower temperatures. Accordingly to these findings, Ahmed and coworkers evidenced at 8-12 weeks months follow up that 88% of PVs previously ablated with the cryoablation therapy were still isolated and that reconnections occurred mainly in the LIPV and in the inferior aspects of each vein (17). Both groups of authors underlined the importance of full PV occlusion during cryoablation.

Follow-Up

Unfortunately, data on follow-up of patients having undergone AF ablation is extremely heterogeneous and varies immensely from center to center. The success rates following AF ablation on the long-term should thus be interpreted with extreme caution. However, data available in the literature reports promising results. Klein et al (18) first reported the success rate of cryoballoon ablation at 6 months. In their study up to 86% of patients were AF free on a short term follow-up. Neumann et al, rounding up the biggest series up to now, obtained at 1 year a success rate of 74% (5). Kühne et al.(19) reported a success rate of 71% at 1 year follow up too. Linhart and colleagues, which compared cryoballoon ablation to RF in a small series of patients (20), found a deceiving success rate of about 50% at 1 year of follow-up. However as the authors explained this finding with the fact that the blanking period in their study was of only 4 weeks. Additionally, many AF recurrences following the cryoballoon ablation occurred immediately after the procedure and decreasingly lowered in the following observational period.

Adverse Events

Phrenic Nerve Palsy (PNP)

Cryoablation is historically known as a safe ablative energy source. However, it is also the procedure known to be mostly associated with PNP among all the PV isolation techniques. Although mostly associated with the 23 mm balloon, PNP has been demonstrated during ablation with the bigger balloon as well. Luckily, it is in nearly all cases a transient phenomenon that reverts spontaneously. According to the recently presented STOP AF data at the American College of Cardiology 2010, this complication occurred in 11% of the 228 patients studied (21). Fortunately in 98.2% of patients the complication spontaneously resolved. A recent publication, (20) comparing cryoballoon technology with RF ablation in a group of patients affected by paroxysmal AF, right PNP occurred in about 11% of patients undergoing cryoballoon ablation and all these cases resolved spontaneously. Interestingly, all of them were associated with the use of a 23 mm cryoballoon. This could be explained by the fact that the smaller cryoballoon might achieve a more distal lesion occurring closer to the phrenic nerve’s anatomical course.


**PV Stenosis**

Only the data presented on the STOP AF (21) reported PV stenosis as a possible collateral effect of cryoballoon ablation. In fact, the rate of PV stenosis was 3.1% versus a complete absence of this complication in the already published reports. This difference might be explained by the fact that in the STOP AF trial the PV stenosis was intensively investigated during the follow-up and that the definition of PV stenosis was quite strict.

**Esophageal Lesions**

More interestingly, atrio-esophageal fistula has never been described among procedural complications of cryoballoon ablation. Esophageal lesions following cryoballoon ablation is another matter of debate. In fact, whereas Fürnkranz et al.(22) demonstrated that PV isolation with the cryoballoon was not associated with thermal esophageal lesions in any of 38 studied patients, Ahmed et al.(23) on the contrary showed appearance of transient esophageal ulcerations in 17% of the patients following this procedure. Interestingly, a correlation with temperature changes inside the esophageal lumen was found by the authors.

**Pericardial Effusion**

Pericardial effusion is another potentially life threatening complication observed associated to AF ablation. Our group (24) compared the incidence and clinical outcome of pericardial effusion following cryoballoon ablation and RF ablation. A total of 133 consecutive patients with paroxysmal AF were included in this study. Pericardial effusion was detected in 14.2% of the 133 patients. Sixteen patients presented mild effusion, one moderate effusion, and 2 pericardial tamponades (related to transseptal puncture). Interestingly, there was no significant difference in the incidence of pericardial effusion between the cryoballoon and the RF group (11 vs. 16%). Fortunately, pericardial effusion was mostly mild and asymptomatic, with benign clinical outcome not requiring additional hospitalization days.

**Cerebral Embolisation**

Cryoballoon ablation is known to be associated to less thrombus formation. However the recent MEDAFI study (25), not only reported a 14% of new cerebral lesions following ablation but, more importantly showed no significant difference in this event between patients undergoing ablation with RF or Cryoballoon. Luckily, all these neurological lesions proved to be asymptomatic. However, it does prove that the anticoagulation strategy when working in the LA with any tool is of utmost importance.

**Conclusion**

Cryoballoon ablation is a very promising technique to treat AF. However, the cryoballoons currently available do not always adapt themselves well to the anatomical variants and do not systematically isolate the PVs in one application. Ideally, a more compliant balloon which would fit into most PVs might lead to a more effective procedure. Future technological improvements will certainly overcome some of the abovementioned issues and might lead a larger number of electrophysiologists to adopt such a technique. The future randomized trials such as the ongoing Freeze AF trial (26) will certainly provide valuable answers to the most important issue: can cryoballoon reach the goal of becoming the “gold standard” for PV isolation? For the moment, this role is still played by “point by point” RF circumferential PV isolati-
on in most Electrophysiology Laboratories.

Conflicts of interests: Dr GB Chierchia has received compensation as a proctor for AF Solutions Medtronic.