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REVIEWS

Cryoballoon ablation of atrial fibrillation: a practical and effective approach

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Medical management of atrial fibrillation (AF), the most common arrhythmia in the general population, has had modest efficacy in controlling symptoms and restoring and maintaining sinus rhythm. Since the seminal observation in 1998 that pulmonary veins host the triggers of AF in the majority of cases, electrical isolation of all pulmonary veins constitutes the cornerstone of ablation in patients with symptomatic AF. However, due to the elaborate and tedious technique of the conventional point-by-point method with radiofrequency ablation guided by electroanatomical mapping, newer, more versatile single-shot techniques, such as cryoballoon ablation, have been sought and developed over recent years and are progressively prevailing. Cryoballoon ablation appears to be the most promising practical and effective approach, and we review it here by presenting all available relevant data from the literature as well as from our own experience in an attempt to apprise colleagues of the significant progress made over the last several years in this important field of electrophysiology.

KEYWORDS

atrial fibrillation, catheter ablation, radiofrequency, cryoballoon, cryoablation, pulmonary vein isolation

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, afflicting 1% to 2% of the general population, with an age-dependent incidence reaching ~10% in individuals age >80 years. In the United States, its prevalence was estimated to range from ~2.7 million to 6.1 million in 2010, predicted to rise to 12.1 million in 2030.[1] In the European Union, the prevalence of AF in adults age >55 years was estimated to be 8.8 million in 2010, projected to rise to 17.9 million in 2060.[2]

AF increases morbidity, mainly related to stroke and heart failure (HF), as well as overall mortality. It is therefore clear that it constitutes a growing major public-health burden, with considerable socioeconomic impact. As medical management has had modest efficacy in controlling this arrhythmia, over the last several years hope has been rekindled with the advent of more-effective ablation techniques. Since the seminal observation of pulmonary-vein triggers in AF,[3] there has been a significant increase in the number of AF patients submitted to pulmonary vein (PV) isolation (PVI), which constitutes the cornerstone of ablation in patients with symptomatic, drug-refractory AF.[4,5] However, due to the elaborate and tedious technique of the initial point-by-point method with radiofrequency (RF) ablation guided by electroanatomical mapping, penetration of this conventional approach was slow. Most recently, the advent of single-shot techniques, such as cryoballoon ablation, has ushered in a new era in the management of AF patients.[6,7]

2 | AF MECHANISMS

Despite the significant progress made in understanding the complex pathophysiology of AF, the precise mechanisms underlying its onset and persistence remain elusive. In brief, AF requires both a trigger and a susceptible substrate.[8] The trigger for initiation and maintenance of AF seems to be related to an enhanced electrical activity of foci, most commonly located within the PVs; non-PV sources may lead to more persistent AF. These rapidly discharging foci commence irregular electrical activity through the atria, leading to fibrillatory conduction. AF is subsequently maintained by a primary "driver" mechanism, which may be either ectopic focal sources or rapid local reentry with multiple reentry circuits varying in time and space in a vulnerable substrate.

Electrical and structural remodeling is considered the main mechanism for AF persistence, whereas inflammatory burden, oxidative stress injury, autonomic balance, and neurohormonal activation are singled out as important modifiers of AF susceptibility.

Electrical remodeling, which is mostly due to calcium-regulated ion-channel dysfunction and encompasses shortening of the atrial refractory period and slowing of conduction velocity, decreases circuit size and leads to stabilization and persistence of the arrhythmia.[9] Structural remodeling of the atria is a major reentry-promoting factor and comprises atrial fibrosis and changes in atrial size and cellular ultrastructure. Atrial fibrosis produces heterogeneous pathways of slow conduction, and atrial dilatation provides larger pathways that facilitate multiple reentrant circuits. Galectin-3, a β-galactoside–binding protein, a member of the lectin family highly expressed in fibrotic tissues, has been proposed as a mediator of sustained AF-induced atrial electrical and structural remodeling, contributing to AF perpetuation. Galectin-3 inhibition has been suggested as a potential new upstream therapy for the prevention of AF progression.[10] Both AF itself and the underlying heart disease are responsible for the development of the arrhythmogenic substrate.[11] A multitude of risk factors may promote AF and should be considered as targets for both AF prevention and management, in addition to specific antiarrhythmic therapies.[12]

3 | INDICATIONS AND PATIENT SELECTION FOR ABLATION

According to current guidelines,[13,14] catheter ablation is recommended for patients with symptomatic paroxysmal AF refractory to antiarrhythmic drugs (class I/level of evidence A), or it may even be considered as a first-line therapy, after weighing the risks of the ablation procedure (class IIa/B). Ablation has also been assigned a class IIa recommendation for symptomatic persistent AF refractory to antiarrhythmic medication (class IIa/C) or a class IIb recommendation as an initial strategy (class IIb/C) in this group. Less frequently, ablation may be considered for symptomatic long-standing (>1 year) persistent AF refractory to antiarrhythmic drug therapy (class IIb/B).

Key to all these recommendations is that the procedure should be performed by a proficient electrophysiologist in an experienced center.[5,13,14] Also, AF ablation should be considered in symptomatic patients with AF and heart failure with reduced ejection fraction to improve symptoms and cardiac function when tachycardiomyopathy is suspected (class IIa/C). Anticoagulation for stroke prevention should be continued indefinitely after apparently successful ablation of AF in patients at high risk of stroke (IIa/C). Finally, all experts agree that catheter ablation can be effectively performed by isolating all PVs by using RF ablation or cryothermy balloon catheters.[13–15]

4 | CURRENT ABLATION TECHNIQUES AND TOOLS

Catheter ablation of AF is a demanding and challenging electrophysiological procedure, at least to date with use of the conventional approach, which is principally designed to isolate the triggers (PVI).[4,5] PVI is the most effective approach for both paroxysmal and persistent AF. Additional substrate-modification techniques beyond PVI, such as linear ablation lesions connecting the PVs or extended to the mitral isthmus, and/or ablation of complex fractionated atrial electrograms, almost routinely employed in the past for persistent AF, do not seem to improve the efficacy of ablation.[16]

The conventional approach to PVI involves a strategy of creating a series of point-by-point RF lesions that encircle the 2 left and 2 right PVs. Irrigated RF ablation catheters are the most common type of ablation catheter used, and 3-dimensional electroanatomical mapping and navigating systems are employed to guide the technique, whereas PVI is routinely confirmed with use of a circular multipolar electrode catheter. However, this is a double-catheter technique, as the sheaths carrying the ablation catheter and the mapping catheter have to be introduced separately into the left atrium, requiring either a single-puncture double transseptal catheterization or a double-transseptal puncture technique, with their attendant risks and complications. Contact-force–sensing ablation catheters have recently been employed in an attempt to improve outcome.[7]

Over recent years, "single-shot" ablation techniques, including circular multi-electrode array RF catheters and cryothermic balloons, have been introduced, promising to facilitate and simplify a safe and effective PVI.[5,7] The initial version of the multi-electrode technique was associated with higher incidence of silent cerebral microemboli compared with RF and cryoballoon ablation. Cryoablation is an alternative energy source employing liquid nitrous oxide that is delivered under pressure within a balloon to freeze the surrounding tissue.[6,7] A separate circular mapping catheter placed through the balloon catheter is used to map and confirm PVI. This single-shot technique has recently spurred great interest as a simplified approach with the hope of improving outcomes in AF ablation.

Other sophisticated techniques for ablation of rotor and focal AF sources were suggested and produced some initial enthusiasm, but they were proven to be futile.[17,18] Robotic navigation and laser balloon techniques are other investigational tools.[7]

4.1 | Biophysics and biomechanics of cryoablation

The mechanism responsible for inducing freezing in cryoablation is based on the Joule-Thomson effect (the change in temperature of an expanding gas). Cryoablation is realized through the delivery of pressurized cryorefrigerant (currently liquefied nitrous oxide) to the distal aspect of the inner balloon via an ultrafine injection tube.[6,19] Nitrous oxide has a boiling temperature of −88.47°C, providing adequate cooling power and safety margins to be used in cardiac-tissue ablation.[20] As the refrigerant cools, ice forms at the tissue contact site, causing the balloon to adhere to the tissue, stabilizing it in place for the duration of freezing.

Progressive cooling to below −40°C results in the formation of intracellular ice crystals. However, cell and tissue damage occurs both during the freezing process and afterward, in sequential stages (freeze, thaw, hemorrhage and reactive inflammation, and replacement fibrosis).[6,20] The extent of scarring that yields electrically silent tissues depends on the acute damage phase (the freeze/thaw cycle),

which consists of several variables.[20] In comparison with RF ablation lesions, cryolesions result in preservation of tissue architecture with less damage to large vascular structures or to the endocardium. Histologically, cryothermy results in the creation of well-demarcated homogeneous lesions that are less arrhythmogenic and thrombogenic than the ragged, indistinct lesions associated with RF ablation.[21]

4.2 | First- and second-generation cryoballoons

The first generation of cryoballoon (CB1) was the Arctic Front system (Medtronic Inc., Minneapolis, Minnesota), which consisted of a steerable 10.5-Fr catheter with a distally mounted polyurethane and polyester balloon. An intake lumen (injection tube) permitted the injection of cryorefrigerant to the inner balloon, an exhaust lumen facilitated its removal, and a central lumen permitted either a guidewire for positioning/support or a small-diameter circular diagnostic catheter for monitoring of PV potentials or the injection of contrast (Figure 1). The Arctic Front was available in 23- and 28-mm sizes.

The second-generation cryoballoon (CB2), the Arctic Front Advance (Medtronic), was released in 2012. It was designed to achieve more uniform cooling across the entire distal hemisphere of the balloon, using 8 injection tubes vs the original 4-port design of the CB1 (Figure 1).

4.3 | Cryoablation procedure and technique

Access to the left atrium is usually achieved via the femoral vein using a standard transseptal sheath and a Brockenbrough needle. A low anterior transseptal puncture in juxtaposition to the limbus of the septum may allow more space for the balloon to be rotated posteriorly to the right inferior PV and improve balloon contact with the inferior aspects of the PVs. A long, stiff guidewire is then employed to exchange for the steerable 81-cm-long delivery sheath (FlexCath; Medtronic) with an outer size of 15 Fr, which accommodates the current cryoballoon (CB2).[22] Upon entering the left atrium, anticoagulation is promptly initiated with IV heparin targeting and maintaining an activated clotting time of 350 to 400 seconds.

A small-caliber (3.3-Fr) circular mapping catheter (Achieve; Medtronic) with an 8-electrode distal loop (15 or 20 mm in size) is advanced via the wire lumen of the delivery sheath and enters the

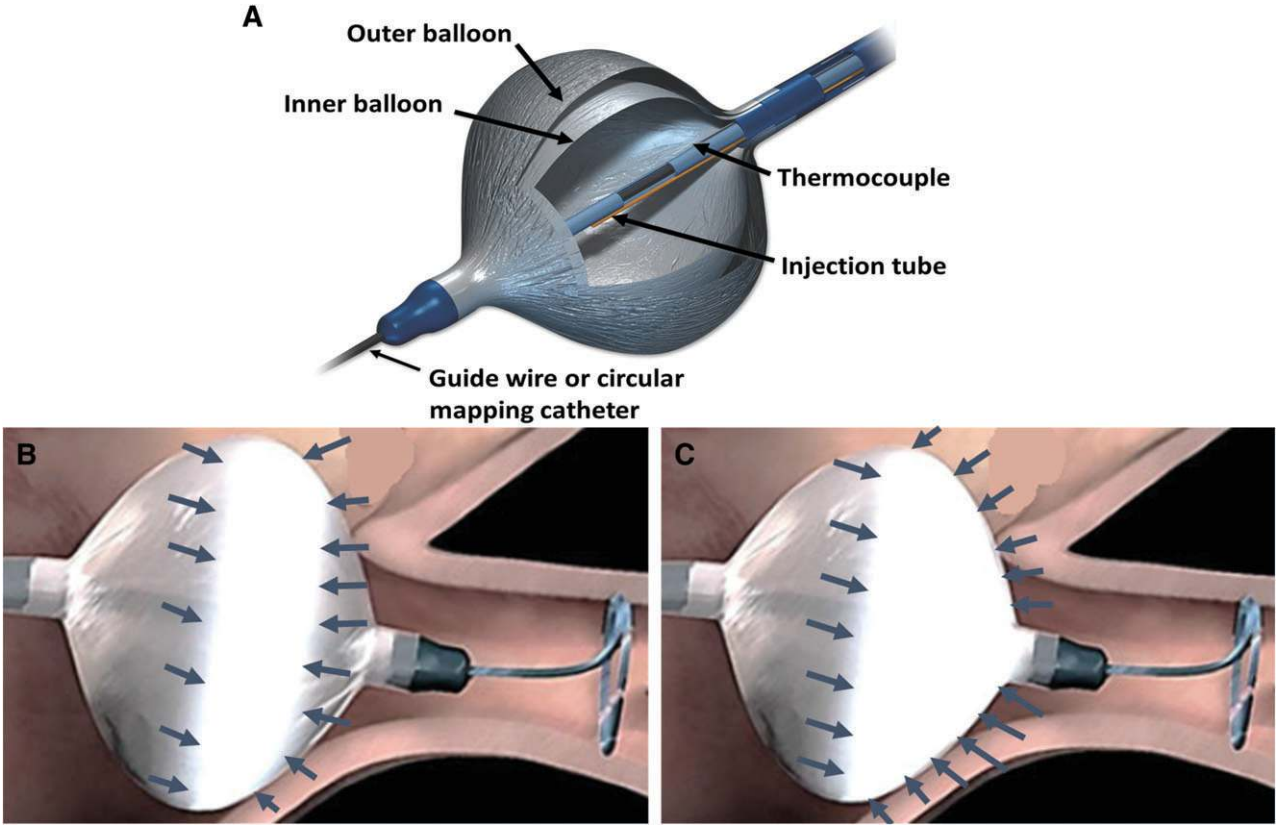

FIGURE 1 (A) The components of the balloon: the refrigerant (N_2O) is delivered into the inner balloon through the injection tube and vacuumed back into the console during the freezing/unfreezing process. The thermocouple monitors the temperature of the vaporized refrigerant. The outer balloon is maintained under vacuum and constitutes a safety feature to reinforce and protect the inner balloon in case of accidental compromise. The circular mapping catheter (not shown) is deployed through the cryoballoon guidewire lumen, may guide the balloon into the PV, and also provides recordings of real-time PV potentials before, during, and after cryoablation. The distal mapping section of the mapping catheter is a circular loop with 8 evenly spaced electrodes for mapping and cardiac stimulation. When the balloon is positioned at the PV antrum, contrast dye is injected through the guidewire lumen to assess vein occlusion via fluoroscopy. Comparing the design of (B) the CB1 and (C) CB2 cryoballoons, one notes the difference of the relatively narrow band-like cooling zone in CB1 (arrows) and the extended span of the cooling zone of CB2, which encompasses the entire distal half of its surface including the distal tip (arrows). This new design produces a larger cooling surface area and reduces additional maneuvering for better balloon positioning for optimal tissue contact. Abbreviations: CB, cryoballoon; N_2O, nitrous oxide; PV, pulmonary vein. (materials for the figure were used with the permission of Medtronic, Inc.© 2016)

PV to serve both as a supporting guidewire by atraumatically guiding the stiffer balloon catheter to the PV antrum and also provide recording of the PV potentials.[23]

The deflectable FlexCath sheath is aligned with the angle of the targeted PV and provides the primary support during PV occlusion by the inflated balloon (Figure 2). PV angiography may be performed via the delivery catheter to depict the anatomy of the PV (Figure 2A, arrow). After balloon positioning at the PV antrum, injection of radiopaque contrast provides venographic evidence of balloon occlusion or leak detection (Figure 2). With the best-fit occlusion, the mapping catheter is repositioned to obtain PV potential recordings; otherwise, it is withdrawn proximally after the end of the freezing application to assess for the disappearance of the potentials (Figure 2C–E).

Historically, freezing with the CB1 was applied for the duration of 4 minutes and additional ("bonus") lesions were commonly delivered, as based on the protocol followed in the Clinical Study of the Arctic Front Cryoablation Balloon for the Treatment of Paroxysmal Atrial Fibrillation (STOP AF) trial.[24] However, since the release of CB2, shorter (3-minute) application times have been found to be equally effective, without the need for a "bonus" strategy. The indicator of successful PVI is the disappearance of PV potentials as identified by the mapping catheter (Figure 2D,E).

5 | CLINICAL RESULTS

Since the release of CB1 in the United States in 2010, data from both single-center studies and multicenter registries have demonstrated acute PVI and freedom from AF at rates comparable with those of RF ablation.[24–26] In a systematic review of studies using CB1, 1-year freedom from recurrent paroxysmal AF was reported to be 72.8%, whereas freedom from persistent AF was only 45%.[26] Using the CB2, the time to achieve PVI has been shortened and acute PV reconnection is rare.[27] Several studies examined the long-term outcome of cryoablation using CB2 compared with CB1; in all of them, the overall success rate of cryoablation was significantly higher in the CB2 group compared with CB1.[28–30] This important step in improving efficacy using CB2 is verified in a recent meta-analysis of 15 studies involving 2363 AF patients.[31] The overall clinical success rate of PVI using CB2 was 82% for paroxysmal AF patients and 70% for persistent AF patients 1 year after the procedure. Recurrence during the first 3-month period after the procedure, which is termed the "blanking period," has been proven to be the most potent predictor of long-term AF recurrence following persistent AF ablation with the CB2.[32,33] Efficacy of CB2 is very high in young patients affected by drug-resistant lone paroxysmal AF, with freedom from AF at 13-month follow-up reaching 93%.[34]

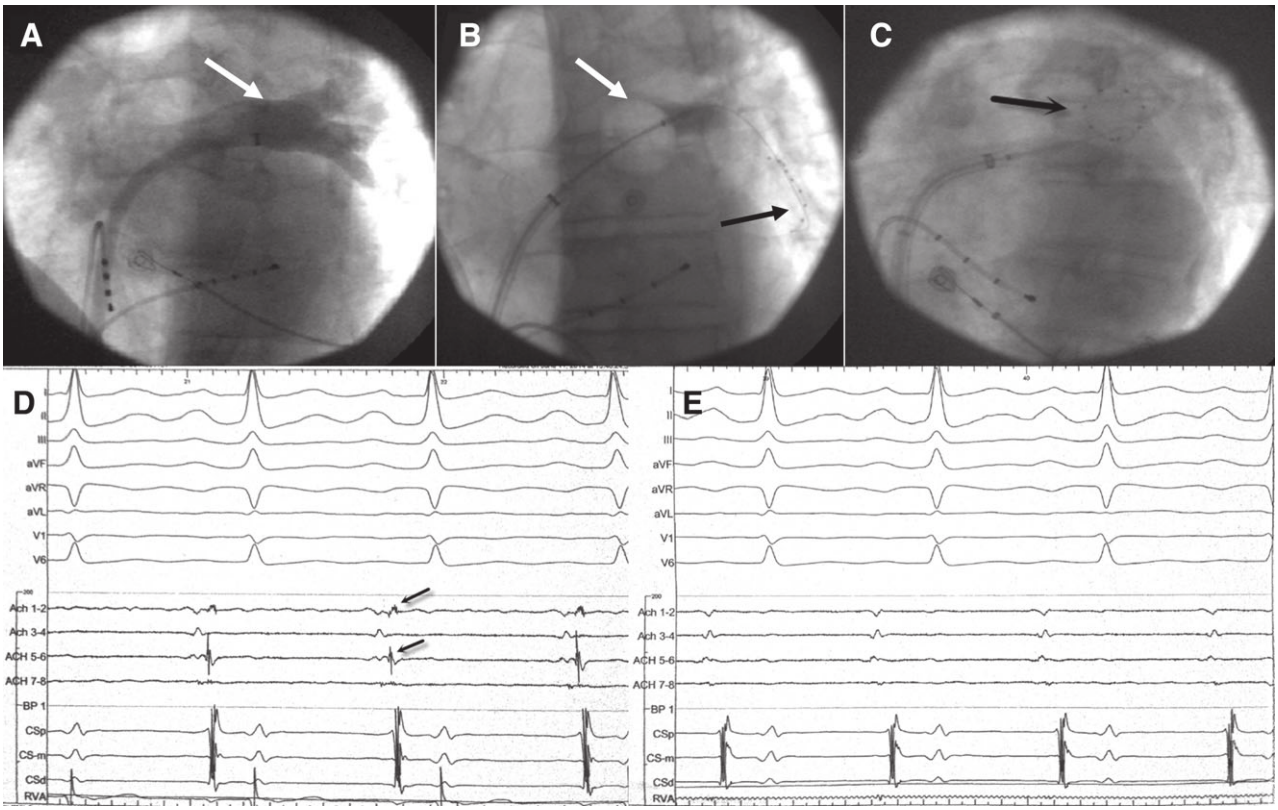

FIGURE 2 An actual case of a patient undergoing AF cryoablation. After accessing the left atrium via a transseptal approach, PV angiography performed via the delivery sheath allows for (A) imaging of the target PV, here the left PVs (arrow). Then the balloon catheter is advanced to (B) the PV antrum, with the circular mapping catheter inserted into the left inferior PV (black arrow), and the balloon is inflated and pushed against the antrum to occlude the PV (white arrow). Occlusion is assessed fluoroscopically by contrast injection into the PV, and when local dye stasis with no backflow is observed, the freezing process is commenced and the balloon ablates the tissue circumferentially. Upon completion of the freezing application, the balloon is deflated and the circular mapping catheter, if too distal, is (C) withdrawn proximally (arrow) to allow for PV potential recording. PV isolation is confirmed when (D) the PV potentials (arrows) are (E) eliminated. In many cases, current technology may allow real-time observation of PV potential elimination during cooling. Abbreviations: AF, atrial fibrillation; PV, pulmonary vein.

5.1 | Predictors of successful and durable PVI

Among the potential predictors of successful and durable PVI, a minimal temperature of < −51°C, time to PVI <60 seconds, and balloon warming time or interval thaw time at 0°C >10 seconds appear to reduce the possibility of PV reconnection.[35–37] Different sites of transseptal puncture have no influence in grades of PV occlusion, rates of isolation, mid-term outcome, and rates of complications during cryoablation.[38] Intracardiac echocardiography guiding exact balloon placement may predict acute ablation success and prevent acute narrowing of PV ostia.[22] Dosing of cryoenergy has not been shown to affect procedural success, with similar success rates obtained with 3- and 4-minute applications.[39] In summary, a single 3-minute freezing application with no need for a bonus strategy appears to suffice, providing shorter procedure and fluoroscopy time; very low nadir temperature and short time to PVI are good predictors of successful and durable PVI.[31,39]

Finally, longer observational time and adenosine challenge at the end of the procedure may be able to detect PV reconnections; however, the incidence of spontaneous and adenosine-induced PV reconnection following ablation with the CB2 is very low, occurring in 4% of initially isolated veins.[40] Thus, obtaining good PV occlusion with the balloon that will attain nadir temperature below < −51°C and rewarming time >10 to 28 seconds can identify absence of acute reconnections, thus obviating the need for extra waiting time and adenosine challenge that will prolong the procedure.

5.2 | Complications

Comparing the ablation techniques (RF and cryoenergy), fewer major complications appear to occur with the advent of the cryoballoon (Table 1).[5,41–46] Nevertheless, there are still vascular-access complications as well as phrenic nerve injury (PNI), pericardial effusion and tamponade, thromboembolism (including transient ischemic attack or stroke), and, very rarely, the catastrophic atrioesophageal fistula formation.[24,45–47] Fortunately, the worrisome high incidence of PNI relates to transient palsy, with the majority recovering fully over time.[5,15,47]

PNI, one of the most frequently encountered complications, is secondary to the anatomical course of the right phrenic nerve, which runs in the vicinity of the right PVs. Routinely, to avoid PNI during ablation of the right PVs, an electrode catheter is inserted in the superior vena cava, and diaphragmatic stimulation is achieved by pacing the ipsilateral phrenic nerve at 50 to 60 times per minute at an output of 10–20 mA, and the contractions of the diaphragm are continuously monitored by abdominal palpation.[22] Recording of diaphragmatic compound motor action potentials amplitude on a modified lead I of a 12-lead electrocardiograph is also a reliable and sensitive method for predicting PNI.[47] Intracardiac echocardiography may also enhance monitoring and diagnosing of PNI through continuous direct diaphragmatic visualization without the use of fluoroscopy.[22] Femoral venous pressure waveform analysis has also been described as an effective method to assess phrenic nerve function during cryoablation.

5.3 | Pericryoablation and postcryoablation monitoring

Pericryoablation monitoring is usually similar to other ablation procedures, comprising continuous blood pressure and oximetry monitoring.[5] Furthermore, monitoring anticoagulation and maintaining an activated clotting time >300 seconds is of great importance to avoid thromboembolic complications. The use of adenosine testing for assessment of dormant PV reconnection has been of limited value and use.[40] Postprocedural groin management is important, as for any ablation procedure. An increased rate of groin-access complication due to larger sheath size has not been reported.

The duration of postablation anticoagulation treatment is similar to RF ablation procedures, although some may consider shorter duration given the lesser endocardium injury with cryoablation.[22] Specifically, oral anticoagulation is recommended for all patients for ≥3 months, and indefinitely thereafter for those with stroke risk factors according to the CHA_2DS_2-VASc score (ie, CHA_2DS_2-VASc score of ≥1 for men and ≥2 for women).[14,46] The 3-month blanking period postablation is routinely observed for all patients, with recurrences noted during this period initially considered nonpredictive of long-term failure; however, recent studies indicate that early recurrences of atrial tachyarrhythmias during this period are associated with late recurrences.[48]

6 | COMPARING RF WITH CRYOABLATION

Results from randomized trials designed to compare CB1 with RF for PV isolation are sparse. The first was the Cryoenergy Or Radiofrequency (COR) for AF ablation trial, a prospective single-center randomized study designed to compare the efficacy of CB1 vs RF PVI.[49] The primary endpoint was freedom from AF recurrences at 12 months; this endpoint was met in 48% of CB1 patients and in

TABLE 1 Complications

Complications	RF Ablation[5,41–45]	Cryoablation[5,24,45–47]
Major complications (%)	3.6–6.0	1.6–2.2
Death (%)	0.05–0.1	0
Tamponade (%)	1.2–1.6	0.2–0.5
TE (%)	0.4–1.1	0.2
Vascular complications (%)	1.0–4.3	0.8–1.9
PV stenosis (%)	0.2–3.4	0
Endocarditis (%)	0.01–0.2	0
Atrioesophageal fistula (%)	0.08–0.2	0[1]
PNI (%)[2]	0.0–0.3	4.6–11.2
Transient (%)		5.4–9.7
Persistent (%)		0.2–1.9

Abbreviations: PNI, phrenic nerve injury; PV, pulmonary vein; RF, radiofrequency; TE, thromboembolism.

Data are presented as percentages.

[1] 0% reported in patient series, but 5 case reports have been reported separately.

[2] More frequently with the use of balloon ablation catheters in the right superior PV.

68% of RF patients (P = 0.05). Taking into account only patients with verified acute PVI, there was no difference between groups in the primary endpoint (67% vs 68%; P = 0.94). In a meta-analysis of 3 randomized controlled trials and 8 retrospective trials with a total of 1216 patients, pooled analysis demonstrated that, as compared with RF, CB1 was associated with a similar proportion of patients free from AF at a mean 16.5 months of follow-up (66.9% vs 65.1%; P = 0.87).[50] Similar were the results of the German ablation registry, with a total of 2306 patients with symptomatic paroxysmal AF, where AF recurrence rate at 1-year follow-up was similar in the RF and CB1 groups.[25]

However, the advanced version of CB2 exhibited significant improvements in procedural and clinical outcomes as compared with its predecessor. A number of randomized and nonrandomized trials have compared CB2 with non-force-sensing and contact-force-sensing RF catheters (Table 2). Initially, CB2 was compared with open-irrigated, non-force-sensing RF and the combined use of both CB2 and RF in the single-center randomized Cryo Versus RF Trial.[51] Success at 1 year was achieved in 47% in the RF group, 67% in the CB2 group, and 76% in the combined group (P < 0.001 for RF vs CB2). In a multicenter, retrospective, nonrandomized analysis of 1196 patients (76% with paroxysmal AF) undergoing PVI using CB2 (n = 773) and open-irrigated, non-force-sensing RF (n = 423), freedom from AF at 12 months was greater with CB2 vs RF (76.6% vs 60.4%; P < 0.001).[37] In the larger randomized FreezeAF Trial, CB2 was also compared with open-irrigated, non-force-sensing RF, and freedom from AF at 1 year was similar in both groups (73.6% vs 70.7%), including an analogous proportion of redo procedures (20%).[52] CB2 was compared with contact-force-guided RF in nonrandomized studies. One single-center study comprising 150 patients reported that AF recurrence at 12 months occurred in 14.7% in the CB2 group and in 12.0% in the RF group (P = 0.682).[53] In a larger multicenter study (n = 376), PVI using contact-force guided RF and CB2 led to comparable single-procedure arrhythmia-free survival (76% vs 73.3%, respectively) at up to 18 months, with a similar overall complication rate.[54]

FIRE AND ICE (Comparative Study of Two Ablation Procedures in Patients With Atrial Fibrillation) was a large randomized controlled trial that compared the efficacy and safety of the single-step cryoballoon ablation technique with the point-by-point RF ablation approach in 762 symptomatic patients with paroxysmal AF.[15] The trial confirmed its primary efficacy objective of the noninferiority of cryoballoon ablation at 1 year with an estimated event rate of 34.6% in the cryoballoon and 35.9% in the RF arm (P < 0.001 for noninferiority). Overall safety was also not significantly different (1 year Kaplan-Meier event rate estimates: 10.2% with cryoballoon and 12.8% with RF; P = 0.24). In a subsequent analysis, there were statistically significant differences in favor of cryoballoon ablation with respect to repeat ablations (11.8% cryoballoon vs 17.6% RF; P = 0.03), cardioversions (3.2% cryoballoon vs 6.4% RF; P = 0.04), all-cause rehospitalizations (32.6% cryoballoon vs 41.5% RF; P = 0.01), and cardiovascular rehospitalizations (23.8% cryoballoon vs 35.9% RF; P < 0.01).[55] There were no differences between groups in the quality-of-life surveys (both mental and physical).

Preliminary data of the FREEZE cohort study (NCT 01360008; 10.4236/ijcm.2014.519149), a prospective observational,

TABLE 2 Clinical trials comparing RF and cryoballoon ablation for AF

Study	No. of Patients (CB/RF)	AF Type	Contact-Force-Sensing	Primary Endpoints/Outcome	Safety/Complications
Aryana et al[37] [1]	1196 (773/423)	PAF (76%)	Non-CF	78.4% (CB) vs 60.8% (RF), P < 0.001 in PAF; 72% (CB) vs 59.2% (RF), P = 0.089 in persistent AF	PC: 1.6% (CB) vs 2.6% (RF), P = 0.207; transient PNP: 7.6% (CB) vs 0% (RF), P < 0.001; persistent PNP: 1.2% (CB) vs 0% (RF), P = 0.026
FreezeAF[52] [2]	315 (156/159)	PAF	Non-CF	73.6% (CB) vs 70.7% (RF), P < 0.001	PC: 12.2% (CB) vs 5.0% (RF), P = 0.022; PNP: 5.8% (CB) vs 0% (RF), P = 0.002
Jourda et al[53] [3]	150 (75/ 75)	PAF	CF	85.3% (CB) vs 88.0% (CF), P = 0.682	NS in PC
Squara et al[54] [4]	376 (178/198)	PAF	CF	73.3% (CB) vs 76% (CF), P = 0.63	NS in PC; PNP 5.6%; P = 0.001 vs CF; severe NLC: 2.5%; P = 0.03 vs CB
FIRE AND ICE[15,55] [5]	750 (374/376)	PAF	Non-CF/CF	66.4% (CB) vs 64.1% (RF), P < 0.001	Death, CVC, NLC: 10.2% (CB) vs 12.8% (RF), P = 0.24

Abbreviations: AF, atrial fibrillation; CB, cryoballoon (ablation); CF, contact-force (guided); CVC, cerebrovascular complications; NLC, nonlethal complications; NS, not significant; PAF, paroxysmal atrial fibrillation; PC, periprocedural complications; PNP, phrenic nerve palsies; RF, radiofrequency (ablation).

Definition of primary endpoint by study:

[1] Freedom from AF/atrial flutter/tachycardia.

[2] Freedom from atrial arrhythmia with absence of persistent complications (12 months).

[3] AF recurrence.

[4] Freedom from atrial arrhythmia (18 months).

[5] Recurrence of AF, occurrence of atrial flutter or atrial tachycardia, use of antiarrhythmic drugs, or repeat ablation.

multicenter, multinational study comparing safety and effectiveness of cryoballoon with RF ablation in patients with paroxysmal or persistent AF, indicate that in clinical practice, cryoablation is preferentially performed in patients with paroxysmal AF, whereas RF ablation is equally distributed between patients with persistent and paroxysmal AF. Furthermore, the procedure is faster with the cryoballoon, particularly with use of the CB2, but the radiation exposure may be higher. Also, there is a trend for fewer recurrences and complications in the cryoballoon group compared with the RF group (Table 1).[56]

6.1 | Combined techniques

Some investigators have combined the RF and cryoablation methods, either by adding RF lesions when the balloon did not completely isolate the PV or adding balloon applications to PVs isolated with RF.[51] However, although PVI with the cryoballoon was faster and had a higher single-procedure success rate than conventional point-by-point RF, the combined approach was not superior to cryoablation alone.

6.2 | Long-term results

Although a large number of studies have already reported on the feasibility of the cryoballoon for PVI for the treatment of paroxysmal and persistent AF, there are limited long-term data in the literature using cryoballoon ablation. In the largest series reported to date, Vogt et al investigated the efficacy of cryoablation in 551 AF patients. At a median follow-up of 30 months, 69.5% were free of AF recurrence after the 3-month blanking period.[57] In a study of 114 drug-refractory patients with paroxysmal AF undergoing cryoablation, freedom from AF was 42.9% for CB1 over 33.4 ± 14.9 months and 74.2% for CB2 over 27.2 ± 10.6 months of follow-up.[33] In another small study of 40 patients undergoing cryoablation with CB1, freedom from AF off antiarrhythmic drug treatment after a single procedure at a mean follow-up of 36.6 ± 4 months was 57.5%.[58]

6.3 | Perceived advantages of cryoablation

Cryoballoon ablation has emerged as a valid alternative to RF ablation, with the added advantage of combining mapping and PVI in a single-shot and shorter procedure.[22,31,34,37] The technical developments of CB2 and the emerging clinical trial data showing improvement in procedural and clinical outcomes compared with RF may establish cryoballoon ablation as the gold-standard approach to PVI. Furthermore, CB ablation appears to be a more practical method, as it is associated with more reproducible procedural times and is less influenced by operator skills, compared with the traditional point-by-point RF approach. This single-shot strategy and the fact that cryothermal ablation is associated with significantly less thrombus formation compared with RF may also lead to a significant decrease in the incidence of cerebrovascular events, one of the most worrisome complications of any AF ablation procedure.[6]

7 | CURRENT CRYOABLATION APPROACH

The steps of the current cryoablation technique are depicted in Figure 2. Presently, CB2 is routinely employed, mostly as a single 3-minute freeze applied to each PV when total occlusion is visualized fluoroscopically, and PVI is confirmed with elimination of PV potentials (Figure 2); otherwise, further attempts may be made in the respective PV. During ablation of the right PVs, continuous phrenic nerve pacing is performed via an electrode catheter positioned in the superior vena cava. The procedure may be performed under local anesthesia aided by light or deep sedation, especially during freezing applications and phrenic nerve stimulation. In some centers, intracardiac echocardiography is concurrently employed, but this adds extra cost to the procedure.

7.1 | Our approach and results

Over the last 3 years, 87 cryoballoon ablation procedures were performed in 81 AF patients in our center (Table 3; Figure 2). Data are

TABLE 3 Clinical characteristics and procedural results in 81 patients with AF undergoing cryoablation in our center[1]

No. of procedures	87
No. of patients	81
Age, y	55.4 ± 10.5
Male gender	58 (71.6)
AF type	
PAF	55 (67.9)
Persistent AF	21 (25.9)
Long-term persistent AF	5 (6.2)
Antiarrythmic drugs	
Class I	33 (40.7)
Class III	24 (29.6)
Class II	5 (6.2)
Combinations	19 (23.5)
Acute PVI, PVs	87 (100)
Fluoroscopy time, min	25 (16.5–30)
Duration of the first ablation, min	3 (2–5)
Duration of the procedure, min	100 (90–120)
CVTI at first ablation procedure, patients	11 (13.6)
Follow-up time from first ablation, mo	12 (4.2–24)
AF recurrences, patients	20 (24.7)
Atrial flutter after ablation, patients	8 (9.9)
Redos, patients	6 (7.4)
Complications, patients[2]	3 (3.5)
Clinical success (free of AF recurrence)	67 (82.7)

Abbreviations: AF, atrial fibrillation; CVTI, cavo-tricuspid isthmus (ablation for atrial flutter); IQR, interquartile range; PAF, paroxysmal atrial fibrillation; PV, pulmonary vein; PVI, pulmonary vein isolation; SD, standard deviation.

Data are presented as n (%), mean ± SD, or median (IQR).

[1] All procedures were performed with the second-generation cryoballoon except for 3 cases where the first-generation cryoballoon was used.

[2] Two patients with cardiac tamponade (1 required cardiothoracic surgery and 1 responded to pericardiocentesis) and 1 patient with phrenic nerve palsy.

reported with the use of descriptive statistics (mean ± SD or median and interquartile range for continuous variables, and absolute values and percentages for nominal variables). The first-generation cryoballoon was employed in the first 3 patients and the second-generation balloon was used in all other patients; only the 28-mm balloon was employed. Hence, no comparisons were possible between different generations of cryoballoon, and thus no inference statistics are provided. The study group comprised 58 men and 23 women, mean age 55.4 ± 10.5 years (range, 33–79 years), suffering from paroxysmal AF (n = 55), persistent AF (n = 21), or long-term persistent AF (n = 5). They all had failed therapy with ≥2 antiarrhythmic agents. Informed written consent was obtained for the procedure from each patient. All patients had undergone a routine standardized preprocedural workup. Patients with persistent AF also underwent transesophageal echocardiography prior to the procedure to assess for intracardiac thrombi. Anticoagulation was briefly interrupted 1 day prior to the procedure and restarted on the evening of the procedure.

Successful acute PVI was accomplished in all patients (100%) at a mean duration of the procedure of 1.7 hours and a fluoroscopy time of 25 minutes. Complications occurred in 3 (3.5%) patients (2 cardiac tamponade and 1 phrenic nerve palsy); tamponade responded to pericardiocentesis in 1 patient, and the other underwent successful surgical evacuation. There were no cases of periprocedural stroke or death. Patients underwent transthoracic echocardiography the next day to assess for pericardial effusion and/or other problems; all were negative. Patient follow-up was arranged with the referring physician and/or at the outpatient arrhythmia clinic initially at 3 months and then at regular 6-month intervals and with periodic ambulatory electrocardiography recordings during the first 2 years. During a mean follow-up of 12 months, arrhythmia recurrences were observed in 20 (24.7%) patients, with 6 of them submitted successfully to a second cryoablation procedure. Thus, the rate of clinical success with abolition of the arrhythmia was 75.3% after 1 procedure and reached 82.7% after the second procedure.

8 | CONCLUSION

Over recent years, the advent of cryoballoon ablation as a single-shot effective and safe ablation approach to patients with AF has spawned new interest and a great surge in the ablative procedures that may be able to control this most common cardiac arrhythmia by restoring lasting sinus rhythm. Growing clinical evidence and experience with this more practical method indicates that a previously demanding and challenging ablation procedure can be simplified while preserving and/or enhancing safety and clinical outcomes. Further technological advances may provide better means to guide the procedure and produce more durable lesions, but also apply the cryoballoon ablation to isolate extrapulmonary sources of AF triggers, like those emanating from the superior vena cava and other sites. Already a new version of the cryoballoon recently has been introduced, with a 40% shortened tip length compared with the previous devices, in an attempt to improve visualization of real-time recordings of PV potentials during the cryoablation procedure and thus more readily assess time-to-PVI, which is an important predictor of successful and durable PVI.[59,60] Further randomized controlled studies with longer follow-up, such as the ongoing Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial,[14] are needed to evaluate the long-term success of these ablative procedures in the large AF population. Importantly, cost-effectiveness studies should also be conducted to compare these various ablative approaches.

However, it is important to keep in mind that all interventional approaches to control AF have only managed so far to alleviate symptoms and improve quality of life in our patients, as hard data of influencing survival are still lacking. The technological progress, as delineated in this review, will need the assistance of studies further exploring and elucidating the still-elusive facets of the pathophysiological mechanisms of this most common arrhythmia, which may be vastly different in each individual patient, calling for a more individualized and shared decision-making approach.

Conflicts of interest

GG and ASM declare no potential conflict of interest; Dr. Tsiachris serves as a proctor for Medtronic for cryoablation procedures in Europe.

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