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A Review of the Use of Cryoballoon Ablation for the Treatment of Persistent Atrial Fibrillation

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Abstract

Purpose of Review Cryoballoon ablation is the standard-of-care treatment for patients with paroxysmal atrial fibrillation, but its efficacy in addressing persistent atrial fibrillation is unclear. Current research is underway to identify origins of persistent atrial fibrillation in locations outside of the pulmonary veins, which are likely high-yield targets for catheter ablation.

Recent Findings Randomized studies suggest that targeting non-pulmonary vein (PV) locations has not proven to significantly improve outcomes in patients with persistent atrial fibrillation. A growing body of evidence suggests that cryoballoon ablation achieves freedom from persistent atrial fibrillation with pulmonary vein isolation alone.

Summary Use of cryoballoon ablation for non-PV regions is ongoing but still novel. Application of the cryoballoon to non-PV regions may improve with further development of the cryoballoon catheter.

Keywords Persistent atrial fibrillation · PerAF · Catheter ablation · Cryoballoon

Introduction

Pulmonary vein isolation (PVI), achieved via catheter ablation, is considered standard-of-care treatment for patients with paroxysmal atrial fibrillation (AF) [1]; however, the role for catheter ablation in persistent AF is unclear. Patients with persistent AF tend to have larger left atrial size and increased arrhythmogenic substrate, both of which contribute to the difficulty of treatment with antiarrhythmic drugs (AADs) and conservative treatment. In a sub-study from ROCKET-AF, patients with persistent AF had increased morbidity and mortality compared to those with paroxysmal AF [2]. Current strategies do not address the urgency associated with restoring normal sinus rhythm for prevention of stroke and other complications. Catheter ablation, either with radiofrequency (RF) or cryoballoon catheters, is considered effective in treating paroxysmal AF with pulmonary vein isolation (PVI) [1]. However, persistent AF may arise from arrhythmogenic foci located outside the pulmonary veins. There is a lack of consensus on the best modality of treatment to address these extra-pulmonary vein targets in patients with persistent AF. Here, we review catheter ablation for treatment of persistent AF with emphasis on the use and effectiveness of cryoballoon ablation.

Catheter Ablation as Preferred Treatment for Atrial Fibrillation

Treatment options for paroxysmal AF include pharmaceutical therapy with antiarrhythmic drugs (AADs), catheter ablation, and surgical ablation [1]. These treatments are also options for patients with persistent AF, though often with decreased efficacy. AADs are often insufficient to suppress AF and can result in side effects intolerable to or hazardous to the patient. Studies have demonstrated that catheter ablation results in higher rates of freedom from AF compared to AADs in patients with paroxysmal AF. Wilber et al. showed 66% patients who underwent RF ablation were free from paroxysmal AF after 9 months, compared to 16% of patients treated with

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AADs [3]. Similar results have been observed with cryoablation. In the STOP AF trial, only 7.3% of patients on AADs were free from paroxysmal AF after 12 months, compared to 69.9% of patients who received cryoballoon PVI [4•]. Together, these studies have established that catheter ablation results in higher rates of freedom from paroxysmal AF compared to AADs.

Applications of these results to patients with persistent AF are unclear, as the mechanisms for progression from paroxysmal to persistent are not well understood. However, the use of AADs rather than re-ablation following recurrence is associated with a higher rate of AF progression [5]. Furthermore, AADs are less effective than catheter ablation in patients with persistent AF. Persistent AF patients report better symptomatic relief and exercise tolerance following catheter ablation [6].

Surgical ablation is another option for persistent AF, but more invasive than catheter ablation approaches. In the past, surgical ablation has provided greater freedom from recurrent AF than catheter ablation, but at the expense of safety [7]. A recent study by Adiyaman et al. [8] demonstrated that catheter ablation was non-inferior to surgical ablation in terms of freedom from recurrence, with additional benefit in safety. Surgical ablation often relies solely on anatomic ablation rather than the advanced electrical mapping systems, which is common in catheter ablation procedures. Initial catheter ablation techniques aimed to reproduce the surgical technique, but improvement in technology and mechanistic understanding allowed catheter ablation to evolve past this approach [9]. An anatomic approach is a stepwise procedure, moving from one location to another without concern for which areas are electrically relevant. Although some operators [10] report success with this technique in catheter ablation, success often depends on repeat procedures [11]. Targeting electrical activity with mapping systems allows for targeted ablation without creating unnecessary substrate.

As patients with persistent AF usually have enlarged and electrically remodeled atrium, some have suggested catheter ablation would not be the best choice in addressing persistent AF. However, the duration of AF is not a predictor of substrate. Recent evidence has shown that the structural remodeling of the left atrium is independent of both AF type and comorbidities [12]. However, catheter ablation cannot be ruled out as an effective treatment solely on the basis of AF duration. In addition, catheter ablation with either RF or cryoballoon has demonstrated safety in treatment of patients with persistent AF. The question remains as to which technology is more effective and which techniques can improve procedural outcomes.

Radiofrequency Versus Cryoballoon Ablation

The two most commonly utilized catheter ablation modalities are RF and cryoenergy. Regardless of ablation source, approach to first-time ablation for the treatment of AF begins with PVI. Success with RF ablation was established first and remains the most common technique for PVI. Cryoballoon is a recent technology but is increasingly used to treat atrial arrhythmias. The FIRE AND ICE trial [13••] was the largest, randomized controlled trial comparing RF versus cryoballoon PVI for the treatment of paroxysmal AF. In this trial, 762 patients were randomly assigned to either RF or cryoballoon ablation to isolate the pulmonary veins. The trial demonstrated non-inferiority of the cryoballoon to RF ablation, with the overall safety rate not significantly different. However, the question of which ablation modality to address patients with persistent AF remains unclear.

Advantages and Disadvantages of Radiofrequency Catheter Ablation

Radiofrequency ablation is an effective, well-established treatment for patients with AF. The adaptability of RF catheters allows for creation of a variety of lesions, which allows for targeting arrhythmias in the pulmonary veins and other areas. The flexibility to create a variety of lesions with RF catheters also renders the tool highly operator-dependent [14]. Achieving lesions of appropriate depth, size, and interlesion distance without utilizing high power, contact force, or long ablation time is technically difficult [15••]. Poor technique can result in serious complications, including cardiac tamponade from perforation, steam pop, or thrombus [16]. In addition, point-by-point technique to create circumferential lesions for PVI, if performed incorrectly, can result in reconnection of electrical circuits, and ultimately, recurrence of AF [17].

Performing this complex procedure can result in prolonged duration of procedures. Careful imaging to prevent perforation and other complications also results in increased use of fluoroscopy. Although fluoroscopy duration was higher in the cryoballoon cohort compared to the RF treatment group in the FIRE AND ICE [13••], European operators did not utilize intracardiac ultrasound or 3D mapping technology at that time. These tools, when used during RF ablation, result in decreased procedural times and decreased patient exposure to fluoroscopy [18].

Advantages and Disadvantages to Cryoballoon Catheter Ablation

The primary advantage of the cryoballoon tool is the shape of the balloon. The shape of the balloon allows for circumferential, wide antral ablation of the pulmonary veins, which is associated with good outcomes in both patients with paroxysmal and persistent AF [19]. The cryoballoon creates a uniform lesion through the application of equal thermal energy throughout the surface of the balloon. Proper contact, for appropriate lesion depth, is ensured by the cryoballoon's adhesion to the tissue. This "one-shot" technique means the cryoballoon is less dependent on operator skill. Unfortunately, the shape is also the balloon's primary disadvantage. The balloon is difficult to maneuver to address small areas and the shape is unwieldy for creating linear lesions, such as those achieved with RF catheters.

Complication rates for both RF and cryoballoon ablation are similar, as demonstrated in the FIRE and ICE trial [13••]. RF complications such perforation, cardiac tamponade, and thrombus are well known. However, cryoballoon is associated with pulmonary vein stenosis, phrenic nerve palsy, and perforation due to long dosing and/or friable tissue [20]. While concerning, these complications can be avoided with appropriate dosing and intraoperative monitoring. Intraprocedural detection of ablated collateral tissue can be reversed by stopping ablation, allowing rewarming of tissue with return of function; this is the unique advantage of cryoablation [21].

In the context of persistent AF, an additional advantage of the cryoballoon is the absence of irrigation, compared to RF catheters. As previously mentioned, persistent AF is associated with significant comorbidities, such as tachycardia-induced cardiomyopathy [22]. Catheter ablation in patients with non-ischemic cardiomyopathy has shown to reduced heart failure exacerbations and mortality [23]. Irrigation during RF ablation can exacerbate heart failure, while cryoablation has the benefit avoiding fluid overloading patients [24].

Regardless of their advantages and disadvantages, both RF and cryoablation are prevalent and effective for the treatment of AF. Both RF contact-sensing catheters and cryoballoon tools are undergoing further improvements for better outcomes in patients with persistent AF.

PVI with Cryoballoon Ablation for Persistent AF

The primary ablation target for both paroxysmal and persistent AF is antral modification to isolate the pulmonary veins. These high-yield areas have long been considered a primary target for ablation for the elimination of AF [25]. The cryoballoon is an excellent tool for achieving PVI. With proper contact, the energy source and shape of the cryoballoon tool creates circumferential, homogeneous lesions, ensuring consistency in terminating irregular electrical circuits [26]. Results are reproducible and consistent across operators and centers, likely due to the similarity between the wide circumferential area of the balloon and the area of PV antral modification [27••]. Multiple studies have demonstrated durability of PVI, as well as consistent success rates in achieving freedom from persistent AF [19, 28, 29].

Numerous studies have examined the effects of PVI alone in patients with persistent AF. Guhl et al. [30] demonstrated a success rate of 59% following cryoballoon PVI. Another study by Koektuerk et al. [31] showed that 67% of patients maintained normal sinus rhythm at 12 months post ablation, which was similar to previous studies with fewer complications [32]. Most recently, the CRYO4PERSISTENT AF trial [33••] was a prospective, multicenter, single-arm trial in patients with persistent AF undergoing single cryoballoon ablation of PVI without additional empirical lesions. At 12 months, freedom from AF was 60.7%, with significant improvement in symptoms and quality of life. Success rates after 1 year, however, have been shown to decrease. A study by Tondo et al. [34] reported freedom from atrial arrhythmias 63.9% at 12 months, but this decreased to 51.5% at 18 months. In addition, Tscholl et al. [35] followed their patients for 2 years, demonstrating 73% recurrence in patients with persistent AF. This data is summarized in Table 1.

Non-pulmonary Vein Lesions

While electrical isolation of the pulmonary vein has remained the cornerstone for AF ablation, success rates continue to be modest. Targeting of non-pulmonary lesions to address underlying substrate in patients with persistent AF has been an emerging strategy for AF ablation. MRI data of patients undergoing atrial fibrillation demonstrates that atrial fibrosis and scarring by delayed enhancement MRI is an independent trigger for atrial fibrillation [36]. These locations include common trigger sites, such as the mitral annulus and left posterior wall [37]. Complex fractionated atrial electrograms (CFAE) represent another target for substrate of AF maintenance. CFAEs are very rapid and continuous electrograms that may represent "pivot points," where substrate creates opportunity for reentry for AF [38, 39]. Early studies showed that ablation of these targets can eliminate AF [40]. In addition, identification and ablation of rotational drivers with novel mapping system dramatically increase freedom for atrial arrhythmias, as in the CONFIRM study [41]. Thus, extra-PV targets have become of increasing interest to improve outcomes in patiens with persistent AF.

Several randomized trials have investigated the targeting of non PVI trigger sites using RF ablation. The STAR AF II [42] trial was a prospective, randomized trial comparing three strategies: PVI alone, PVI and triggers sites, and PVI and CFAE. A total of 589 patients were recruited, all with persistent AF. Results showed no significant differences between who received PVI only versus additional lesions, with PVI only showing shorter procedural duration and lower rate of complications. The RASTA [43] trial, which compared PVI only versus PVI plus additional lesions, showed no significant difference in outcomes between the two groups. The CHASE AF [44] trial did not show significant difference between PVI only versus a stepwise approach in ablating extra-PV lesions. Another study comparing traditional PVI versus PVI plus substrate modification, including CFAE and linear ablation, showed no significant differences in freedom from atrial arrhythmias at 12 months [45]. The SELECT-AF [46] trial investigated

Table 1 PVI only strategy for persistent AF

Study name	Author	Patients enrolled (#)	Success at 12 months (%)	Success at > 12 months (%)
	Koektuerk et al.	100	67%	N/A
	Tondo et al.	486	63.90%	51.50%
	Guhl et al.	69	59%	N/A
	Tscholl et al.	22	N/A	73%
	Yalin et al.	133	67%	
Cryo4persistent	Boveda et al.	101	61%	N/A

whether a strategy of selective versus generalized CFAE ablation, followed by PVI, would in similar outcomes. Results showed similar incidence of acute AF termination, with decreased incidence of repeat procedures and long-term recurrence of atrial arrhythmias in the generalized CFAE approach.

The use of the cryoballoon to address extra-PV targets has also been investigated. In a meta-analysis [47], no difference was seen between PVI only versus PVI plus bonus lesions with the cryoballoon. Patients with persistent AF had success rate of 73% and 63% at 1 year, for PVI only and PVI plus bonus lesions, respectively. In another study, persistent AF patients had an overall success rate of 69%; however, patients were divided into groups, 11 receiving PVI only and the other 38 receiving bonus lesions [48]. In either group, the additional lesions did not provide any statistically significantly greater success in achieving freedom from AF. These results are listed in Table 2.

Creating additional lesions also requires longer procedure times. Using the cryoballoon in multiple locations, especially without proper time allotted for thawing, could also result in greater complication rates. He et al. [47] demonstrated a higher rate of phrenic nerve palsy in patients undergoing bonus lesions when compared to PVI only. PVI only has a shorter procedure time and smaller complication rate, and avoids the risk of creating additional, unnecessary arrhythmogenic substrate.

The search for AF drivers and non-PV targets is being investigated to improve outcomes in patients with persistent AF. Concerns have been raised about the ability of the cryoballoon to successfully ablate these regions. While RF is the standard therapy for extra-PV targets, the second-generation cryoballoon is an effective tool to address these locations. Su et al. [49•] demonstrate that the second-generation cryoballoon could effectively ablate 11 anatomic cardiac locations, including the coumadin ridge, left atrial roof line, and mitral annulus. In a study of 225 patients, patients underwent ablation of both PVI and non PVI targets, showing 88%, 71%, and 55% freedom from atrial arrhythmias at 1 year in patients with paroxysmal, persistent, and long-standing persistent AF, respectively.

Improvement to cryoballoon technology and catheter design will increase success in achieving freedom from atrial arrhythmias. PVI is already a successful and established technique with the second-generation cryoballoon. Adoption of the cryoballoon for non-PV lesions is less accepted by the electrophysiology community due to catheter flexibility as well as inconsistent results of improving outcomes in persistent AF with targeting of extra-PV lesions [42, 43]. However, cryoablation offers advantages over RF. A recent case report demonstrated that, on autopsy after 6 months after PVI cryoablation in the atrium, there were transmural lesions with width size of 6 mm, which is much wider and deeper than conventional RF [50]. New designs to the third generation may provide better flexibility and maneuverability, such as 40% reduction of catheter tip length [51].

Ablation of the Atrial Ganglion Plexi

Recent evidence has demonstrated the role of the autonomic nervous system in both promoting AF and atrial remodeling [52, 53]. Stimulation of ganglionic plexi (GP) results in increased sarcoplasmic reticulum calcium release in the pulmonary veins and shortening of action potential duration, causing early after depolarization and triggering AF [54]. There are four endocardial GP located in close association with each of the pulmonary veins and the surrounding myocardium. Small, randomized trials in which GP ablation with either pulmonary vein isolation (PVI) or alone showed promise in reducing AF burden and demonstrated a role of GP in AF pathophysiology [55–57]. The largest trial to determine the efficacy of pulmonary vein isolation with adjunctive GP ablation in paroxysmal atrial fibrillation showed improvement in combined PVI and GP ablation versus (1) PVI only and (2) GP only ablation [58]. At 2 year follow up, 74% of patients with PVI and GP ablation remained in sinus rhythm, compared to 56% and 48% of the PVI and GP only group. While there is a lack of consensus on approaching these lesions, cryoballoon remains a viable option. The second-generation cryoballoon was designed to create transmural contiguous lesions. The shape of the balloon allows for collateral ablation of the GP during PVI ablation. Using the 28-mm cryoballoon, the four major atrial GP were ablated during PVI given the wide, antral modification [59••]. Ablation of GP causes injury to the autonomic nervous

Table 2 Additional strategy for persistent AF

Study name	Study author(s)	Patients enrolled (#)	PVI-only patients (#)	PVI-only success (%)	Additional strategy (#)	Additional strategy success rate (%)
STOP AF II	Verma et al.	589	67	59%		
					PVI + CFAE	
					263	49%
					PVI + linear	
					259	46%
Alster-Lost-AF	Fink et al.	118	61	54%		
					+ Stepwise	
					57	57%
SELECT-AF	Verma et al.	84				
					+ generalized CFAE	
					42	50%
					+ specific CFAE	
					42	28%
CHASE-AF	Vogler et al.	142	61	63.90%		
					+ Stepwise	
					71	57.70%
RASTA	Dixit et al.	156	N/A	N/A		
					+ Simulation	
					55	49%
					+ Triggers	
					50	58%
					+ CFAE	
					51	29%
CONFIRM	Narayan et al.	92	N/A	N/A		
					Conventional	
					71	44.90%
					Rotors	
					36	82.40%
CONFIRM2						
					Conventional	
					65	77.80%
					Rotors	
					27	38.50%
	He et al.			73%		
					"Bonus"	
						63%
	Lemes et al.	49	38			
					"Bonus"	
					11	55%

system, such as vagal reactions causing bradycardia [60]. Cryoballoon has the advantage of a window where additional injury is reversible. Restoring tissue temperature at the onset of these vagal reactions may reverse tissue injury within a certain time period. More research will be needed to optimize GP ablation strategy before it is considered standard technique.

Cryoballoon Ablation Technique

Proper handling and intraoperative monitoring during use of the cryoballoon should not be ignored due to a perceived less risk in comparison to radiofrequency ablation. While cryoablation is theoretically safer than RF energy, cryoablation procedures can still result in serious complications, such as phrenic nerve palsy and atrio-esophageal fistula [20]. While there are no defined parameters on proper dosing during cryoablation, evidence suggests that that time to effect dosing may be lower than previously suggested [61]. Common practices rely on "freeze-thaw-freeze" method, which does not allow for appropriate tissue warming prior to re-ablation. The risk of collateral tissue injury or damage increases with longer freezing periods and increases in the total amount of lesions produced [62]. In addition, proper PV occlusion by the balloon should be confirmed by echocardiography (transesophageal or intracardiac) and/or 3D electroanatomic mapping. Without proper occlusion, isolation of the pulmonary veins is not attainable, with greater risk of reconnection. Ablations should not be performed for > 180 s, as opposed to previously recommended 240 s. Longer time-to-effect may indicate poor balloon-to-tissue contact. Tissue must thaw prior to consecutive ablations, avoiding temperatures < − 55 C to prevent collateral tissue injury [62].

Given increased risk of complications and unnecessary, prolonged ablation, we recommend against an anatomical, stepwise approach when utilizing the cryoballoon. The stepwise approach relies on a series of high-yield substrate and drivers associated with AF. Serial ablation of these locations is intended to eliminate drivers and reentry resulting in AF. Starting with the interface between the left atrium and coronary sinus, then the base of the left atrial appendage, operators then make linear lesions on the left atrial roof and mitral isthmus. This is followed by right atrial and SVC triggers [63]. Per recent publications, ablation of persistent AF with the stepwise approach only yielded freedom from AF in 35.3% after 1 year with diminishing results after a longer passage of time [64]. The CHASE-AF trial demonstrated that the stepwise approach did not provide any additional benefit for persistent AF. In fact, the stepwise approach lengthened procedure time, RF application time, and fluoroscopic exposure [44, 64]. The seemingly needless ablation of multiple locations does more harm than good, creating extra substrate, lengthening procedural times with a greater risk of complications. We recommend current practice as detailed by the practice guidelines endorsed by cardiac electrophysiological societies [1].

Conclusion

Cryoballoon ablation is a safe, efficient, and effective procedure proven to achieve PVI in patients with paroxysmal AF. Recent evidence continues to indicate that cryoballoon ablation is safe in patients with persistent AF. Although use of the cryoballoon to apply extra-PV lesions is under investigation, a PVI-only approach has been demonstrated to have high rates of freedom from AF in patients with persistent AF while avoiding prolonged procedural times and creation of unnecessary substrate.

Compliance with Ethical Standards

Conflict of Interest All the authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards.

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