Interventional Cardiology

Ablation of paroxysmal atrial fibrillation in 2015: radiofrequency or cryoenergy?

Pulmonary vein isolation is the cornerstone of paroxysmal atrial fibrillation ablation. Radiofrequency (RF) ablation is currently the most widespread technique. Recently, cryoballoon ablation has emerged as an alternative to RF ablation for paroxysmal atrial fibrillation. Until now there are no data from randomized trial comparing these two techniques. The purpose of this report was to review the pulmonary vein isolation acute success, the efficiency at follow-up and the safety of these two ablation strategies. Additionally, some considerations are made concerning the contact-force sensing RF catheters and the second-generation cryoballoon.

Keywords: atrial fibrillation • cryoballoon ablation • paroxysmal • radiofrequency ablation

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Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia imposing substantial morbidity and mortality [1]. Since the pioneering work of Haïssaguere *et al.* [2], pulmonary vein isolation (PVI) has been demonstrated to be the cornerstone of AF ablation strategy [3,4], with radiofrequency (RF) currently being the most widespread energy source. However, the RF ablation is complex, time consuming and highly dependent on operator experience given the difficulties associated with creating contiguous curvilinear lesions with a single tip RF catheter [5].

Meanwhile, various techniques and different ablation strategies have been developed in an effort to simplify PVI, to allow a broader number of patients to access this therapy. Cryothermal energy is an alternative energy source that has been used for decades by cardiac surgeons for the treatment of cardiac arrhythmias [3]. Cryoballoon (CB) ablation potentially offers a simpler and faster means of achieving PVI, that theoretically is less reliant on operator dexterity [6].

However, few data are available comparing the clinical efficacy and safety of these two techniques. Currently, larger multicenter prospective evaluations are being conducted to compare the CB to focal RF catheters: FIRE AND ICE [7], FREEZE cohort [8] and FreezeAF [9] with regard to safety, efficacy and efficiency of both techniques.

Meanwhile, as the results of these studies are not available, the authors made a review on the data available on CB and RF for paroxysmal AF, focusing on the form and delivery of energy, the acute PVI and the procedural findings, the efficiency at follow-up and the safety. The authors also point out some considerations regarding the contact-force (CF) sensing RF catheters and the second-generation CB that probably will have an impact in the efficacy and safety of these ablation strategies.

Different energies, different modalities…

There are fundamental differences between the two technologies, both in the form of energy and on the delivery of energy.

RF energy achieves myocardial ablation by the conduction of alternating electrical current through myocardial tissue. The tissue resistivity results in dissipation of RF energy as heat, which is conducted passively to deeper tissue layers. A temperature of greater than or equal to 50°C for more than

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several seconds is necessary to promote tissue irreversible necrosis that will evolve into a nonconduction scar [3]. When continuity of the endothelium is interrupted, anticoagulation properties are lost and subendothelial components such as collagen, tissue factor, and von Willebrands's factor become exposed to circulating blood. Consequently, platelet adhesion and activation and thrombin production ensue [10]. Also, RF-induced tissue lesions are created by sequentially moving a pointed tip catheter along the desired ablation line. Therefore, a considerable operator expertise is necessary in order to create a continuous durable electrical barrier.

As a consequence of the great surface area of tissue ablated, with increased markers of myocardial injuring [11,12], the large cumulative energy delivered, the risk of systemic thromboembolism and the close location of structures susceptible to collateral injury, such as phrenic nerve, pulmonary veins (PV) and esophagus [3], RF ablation is associated with some complications, fortunately the serious complications are rare.

The introduction of a CB to isolate the PVs in paroxysmal AF patients was considered a breakthrough technology because it would theoretically allow PVI with a single application [13], reducing the procedure time and consequently some of the complications.

Cryoablation systems work by delivering liquid nitrous oxide under pressure through the catheter within the balloon, where it changes to gas, resulting in cooling of surrounding tissue. The mechanism of tissue injury results from tissue freezing with a creation of ice crystals within the cell that disrupts cell membranes and interrupts both cellular metabolism and any electrical activity in that cell. In addition, interruption of microvascular perfusion may interrupt blood flow, contributing to cell death [3]. This mechanism of injury, maintaining the endothelium intact, produces a homogeneous lesion with a low thrombogenic potential, and thus potentially minimizing the complication rate [10,14–18]. Since it does not disrupt tissue architecture, it could also reduce pulmonary venous stenosis and atrio-oesophageal injury [19].

In addition, operators may acquire this technique with a shorter learning curve [20], allowing more centers to perform AF ablation and consequently allow more patients to be treated.

Taking these aspects in consideration, CB appears to be simpler, less time-consuming and probably safer than RF ablation. Despite this immediate theoretical advantage, little is known about the chronic course of a CB lesion-induced, as opposed to RF lesion. Does the isolation persist over the years? This is a main factor determining clinical success, because previous studies have shown that recurrent PVs reconduction is pivotal in arrhythmia recurrence after catheter ablation of paroxysmal AF [21,22].

Procedural findings & acute pulmonary vein isolation

One of the probable theoretical advantages of CB ablation is the delivery of therapy in few applications (namely one or two), consequently less time-consuming and a smaller learning curve, maintaining a high isolation rate of PVs. The results of the comparison of CB (first generation balloon) versus conventional RF (without CF) for paroxysmal AF ablation are showed in Table 1.

The results of these trials demonstrated comparable acute efficacy rates of both RF and CB ablation [19,23–26]. The results of CB ablation for PVI are in line with previous reported data [6,27–29]. Nonetheless, this high acute isolation rate with the CB was achieved in some cases with the use of another catheter to perform focal ablation. This was already documented in others CB ablation trials, with the need of focal ablation in approximately 16–17% of patients [6,27–29]. As with RF ablation, good tissue contact is important for generation of effective lesions, which may be difficult to achieve in some particular anatomies. This problem is better solved with RF catheter ablation due to better catheter flexibility, and so adverse anatomic features can be managed easier [23,27].

Some trials [19,24] reported that CB ablation was less time-consuming then RF ablation, but in the largest registry published in 2014 [26], there were no significant differences between the two groups. The average procedure time reported in the major CB trials was between 170–206.3 min [6,27], a little higher than the results displayed in Table 1. In the STOP AF trial [29], the mean procedure time was even longer (371 min), mainly due to the learning curve and a 30 min protocol assessment period at the end of ablation.

Regarding fluoroscopy time, RF ablation appears to have some advantage, mostly due to the German Ablation Registry [26]. This result was obtained, even taking in account that in CB group, the mean fluoroscopy time was smaller than those reported by Neumann *et al.* [27] and Andrade *et al.* [6] (40 and 46 min, respectively) and also the 63 min documented in the STOP AF trial [29]. This finding probably is in relation with the utilization of 3D navigation system in RF ablation, which can allow a smaller utilization of the fluoroscopy.

In RF ablation, a wide range of procedural parameters has been reported: a meta-analysis of RF ablation trials revealed a mean total procedure time ranged from 81 ± 31 to 357.4 ± 47.6 min and a mean fluoroscopy of 64 ± 48 min [30].

A learning curve is also present with CB ablation, as reported in the STOP AF trial, where centers with

Table 1. Acute pulmonary vein isolation and procedural finding in studies comparing first generation cryoballoon versus radiofrequency (without contact-force) catheters in paroxysmal atrial fibrillation patients.

Patients (n); CB vs RF	Acute PVI (%); CB vs RF	Need of focal ablation in CB (patients)	Mean total procedure time (min); CB vs RF	Mean fluoroscopy time (min); CB vs RF	Ref.
20 vs 20	95 vs 100; p = NS	6	174 vs 200; p = NS	49 vs 55; p = NS	[23]
124 vs 53	83 vs 99	74	108 vs 208; p < 0.001	27 vs 62; p < 0.001	[19]†
136 vs 260	100 vs 100; p = NS	5	112 vs 192; p < 0.000001	36 vs 31; p = NS	[24]
71 vs 71	100 vs 100; p = NS	20	170 vs 171; p = NS	49 vs 41; p = 0.03	[25]
905 vs 2870	97.5 vs 97.6; p = NS	96	160 vs 165; p = NS	34 vs 24; p < 0.0001	[26]

†The data of mean procedure and fluoroscopy times refers only to the 90 paroxysmal AF patients.
AF: Atrial fibrillation; CB: Cryoballoon; NS: Not significant; PBI: Pulmonary vein isolation; RF: Radiofrequency.

extensive experience reported a progressive decrease in procedural time, fluoroscopy time, number of CB applications and need for additional focal ablation with increasing operator experience. Likewise, single procedural success rates increased progressively with increasing familiarity with the procedure (77.5% for the latest quartile of patients treated vs 39.5% for the earliest quartile of patients treated) [29].

So, it appears that the theoretical advantages of the CB ablation do not seem to reflect in the clinical practice, at least in the early trials. CB ablation also presents a learning curve (probably a faster one), does not appears to reduce significantly the time of the procedure and requires a higher fluoroscopy time. The overall acute success rate of first-generation CB ablation is equivalent to the RF ablation, but at the expense of the utilization of another catheter to perform focal ablation. Nevertheless, all these data have to be interpreted very cautiously as CB is a quite recent technique, mainly developed since 5–7 years, whereas RF is now well known and used in routine in most referent centers since more than 15 years.

Outcomes of both techniques

Unfortunately, during follow-up, the recurrence of left atrial arrhythmia is not uncommon.

There are not many trials comparing the outcome of the two techniques. The data available is represented in Table 2, but the number of patients included in these trials and the short follow-up time do not allow a clear answer to the question about the mid- or long-term efficacy of both the techniques.

The mean follow-up ranged from 6 to 28 months, and the percentage of patients free from recurrent AF was similar in the two groups [19,23–25].

Freedom from AF in the CB group ranged from 48 to 77%, in line with data from previous CB trials [6,27–29]. At 12 months of follow-up, Andrade *et al.* [6] reported that 72.83% were free from recurrent AF; Defaye *et al.* [28] reported a 69% freedom from tachyarrhythmia in the paroxysmal group; Neumann *et al.* [27] reported a 74% freedom from AF and Packer *et al.* [29] reported a 69.9% freedom from recurrent AF. The data from these studies appear to be more stable (around 70% at 12 months) comparing to data in Table 2, probably because of a longer follow-up presented in the latter.

In the studies presented at Table 2, freedom from recurrent AF in the RF group ranged from 45 to 72% [6,23–25]. Data from RF trials also present a wide range of success according to the expertise of the center, the strategy employed and the type of catheter utilized. As so, at 12 months of follow-up, 88% of paroxysmal AF patients can be free of arrhythmia recurrence at an experienced center [31]. Even at 10 years, in a high volume center, only 28% had a clinical recurrence [32].

However, in the real world, the efficiency of RF ablation is not so high. Ganesan *et al.* [33] reported a single procedure efficacy at 12 months of 66.6% for paroxysmal AF, and a 54.1% freedom from AF at more than 36 months of follow-up, which can rise to 79% with multiple procedures (average number of procedures 1.45). Calkins *et al.* [34] reported at follow-up, a single procedure success rate of 57%, reaching 77% after multiple procedures. In the updated worldwide survey [35], almost 75% of paroxysmal AF patients were free from AF without any antiarrhythmic drugs at 10 months of follow-up.

A recent meta-analysis comparing the CB versus irrigated RF ablation reported no statistical difference at 16.5 months (66.9 vs 65.1%, respectively) [36].

At mid-term follow-up, both techniques appear to have a similar efficiency. However, outcome data from long-term CB ablation is not yet available.

Safety

Overall major complications have been reported in approximately 2.9–6.3% of patients undergoing RF

Table 2. Freedom from recurrent atrial fibrillation in follow-up.

Patients (n); CB vs RF	Mean follow-up (months)	Blanking period (months)	Freedom from recurrent AF (%)			Ref.
			CB	RF	p-value	
20 vs 20	6	1	55	45	NS	[23]
90 vs 53	12	3	77	72	NS	[19]
136 vs 260	23	3	63.2	57.3	NS	[24]
71 vs 71	28	3	48	56	NS	[25]

AF: Atrial fibrillation; CB: Cryoballoon; NS: Not significant; RF: Radiofrequency.

ablation for AF [34–35,37–38]. The rate of acute procedural complications reported with CB ablation is relatively low (<3–5%) [5,29].

In recent prospective trials published in 2014, the rate of overall complications does not differ statistically between the two techniques. (Table 3) The only main difference was the higher rate of phrenic nerve palsy (PNP) observed with CB ablation [24,26].

Some complications deserved a more detailed discussion

The rate of PNP with RF ablation ranged between 0.4 and 4.9% [30,34,37]. With CB ablation, an initial rate of 3.99% was described [6]. However in the recent STOP AF trial, the reported PNP rate was 11.2%, with a resolution of the majority of cases (82%) in the first 12 months [29]. Fortunately, despite PNPs being a relatively common occurrence with CB ablation, the majority of cases are transient with smaller than 0.4% of PNPs persisting greater than 1 year [6]. Nonetheless, while persistent PNP is rare, the incidence appears to be approximately twice that reported with conventional RF ablation [35]. However, PNP is probably underestimated due to the absence of assessment in most RF trials.

Probably, the complication rate described in the CB ablation can drop with the use of the 28 mm CB size, once Andrade *et al.* [6] described that 64.7% of PNP occurred with the use of the smaller balloon and in the prospective study of Neumann *et al.* [27] 24 of the 26 PNPs described were caused with the utilization of the 23 mm catheter balloon. Nevertheless, the rate of both transient and persistent PNP still remains high with the second-generation CB [39–41].

Thromboembolic complication remains a major complication of the RF ablation. Cryoballoon ablation was presented as a safer alternative due to its mechanism [14–18]. Additionally, lower incidence of thrombus formation with cryoenergy versus RF catheter ablation had been previously described [10]. Meanwhile, in the review performed by Andrade *et al.* [6], the incidence of thromboembolic complications, including stroke or transient ischemic attack, was 0.32%, similar to the conventional RF ablation (0.3–0.94%) [34–35,42]. Also, in the MEDAFI-Trial [43], no significant microembolization was visualized with the two ablation techniques, suggesting other mechanisms beyond the destruction of the endothelium surface to explain thrombus formation, like the catheter insertion, the transseptal puncture, the placement of thrombogenic sheats, the extended catheter periods in the left-sided circulation and air embolism [44,45]. Finally, Siklódy *et al.* [46] also did not find any significant differences in their work in tissue damage, platelet activation or inflammatory processes after CB or irrigated-tip RF procedures.

While multiple CB studies employing the use of systematic screening reported no PV stenosis, the STOP-AF trial noted a 3.07% incidence of radiographic PV stenosis [29], due to a different criteria to define significant PV stenosis. Reassuringly, the rate of symptomatic PV stenosis or PV stenosis requiring intervention was low (0.17%) and comparable to that observed with RF (0.1–0.3%) [34–35,42]. In addition, it seems probable that the use of the bigger balloon (28 mm) will significantly decrease the risk of PV stenosis.

Finally, with CB, the reported rate of cardiac tamponade was 0.6%, of groin complications was 1.8% and the incidence of atrial-esophageal fistula was 0% [6]. In comparison, corresponding reported complication rates with RF ablation were 0.8–1.3% for cardiac tamponade, 1.2–1.5% for groin complications and 0.04–0.1% for atrium-esophageal fistula [34–35,37,42].

Once more, due to the great difference in both techniques, complication rates should also be interpreted with caution. However, the data available appear not to support the concept of an improved safety profile of CB compared with RF ablation, for paroxysmal AF.

Technology development: second-generation CB & CF sensing RF

Successful ablation depends on the ability to achieve lesions that are reliably transmural. With excellent contact, energy coupling to tissue is optimized and less energy is dissipated into the circulating blood pool. Thus, more predictable and reliable lesions can be created with excellent catheter contact to the endocardium. So it is hypothesized that monitoring electrode–tissue contact can improve procedure success and maybe also reduce the rate of complications, particularly cardiac tamponade [3]. The CF between catheter tip and target tissue has been shown to be a major influencing factor in providing effective tissue lesion [47–51] and recent studies reported a high overall success and a reduced procedural time and x-ray exposure using a CF-sensing catheter [52–54].

On the other end, second-generation CB has been developed to optimize lesions in various settings of PV anatomies allowing a better contact with the tissue [55–57] without the need of focal ablation to obtain PVI [31,58]. Second-generation CB have demonstrated a high rate of acute PVI, with a significantly shorter ablation time procedure and also with a reduction of radiation exposure compared with first-generation CB [39,40]. This high success rate of PVI can be also explained by a wider circumferential lesion, which can include some ganglionic plexi and/or some non-PV rotors [59]. More recently, Ciconte *et al.* [58] reported a 94.1% acute PVI with a single 3 minutes freeze, and an 82.3% freedom from atrial tachyarrhythmia recurrence at 1 year. If these results can be reproducible in large multicenter trials, it will decrease the procedural time, the radiation exposure and probably also the complication rate.

A prospective single-center study compared the outcomes at 1 year of these two ablation catheters [31]. Acute pulmonary isolation was achieved in all patients of the two groups. The procedure duration and the radiation exposure were significantly lower with the CF catheter. This despite the fact that the average procedure duration in the CB group was 134.5 min and the average fluoroscopy time was 25.3 min, numbers far below that were described in the literature [6,27,29]. No procedural complications differences were observed (2.7 vs 1.3% in the CF and CB groups, respectively). At 12 months, 85.3% of CB patients and 88% of CF RF patients were free of AF recurrence.

These data [31], even if not randomized, suggest that the CF real-time assessment with RF catheter and the second-generation CB display a very similar procedural efficacy, safety and outcomes. However, more data is needed to verify if these newer technologies will result in more permanent isolation and consequently in higher long-term freedom from AF after a single procedure.

Some considerations between the two techniques

Real-time assessment of PV disconnection

In CB ablation, PVs disconnection can be visualized at real-time in the vast majority of patients (97.7%) [60]. The benefit of the real-time disconnection visualization has been associated with shorter procedure and fluoroscopy times [58,61], a higher procedural success rate in cases of early PVs disconnection [62,63] and can probably lead to a lower incidence of complications due to fewer applications [60].

Need of another catheter

As noted above, need of additional catheter was described in the initial experiences with the first-generation CB [6,27–29]. Meanwhile, with second-generation CB and with the growth of experience, PVI is achieved without the need of focal ablation [31,58].

Even if CB can provide an efficient and durable PVI, an additional catheter is sometimes necessary in a minority of patients in which paroxysmal AF is not PV dependent [64].

Also, as we know, several patients present with atrial flutter associated to AF episodes. In the STOP-AF trial, almost 41% of patients were submitted to right atrial flutter ablation [26]. So with CB ablation, a considerable percentage of patients will need a different catheter to perform atrial flutter or a non-PV ablation, leading to a second procedure or increasing the procedure cost. Something that with RF catheter ablation is not needed!

Cryoablation for redo procedures?

In the vast majority of cases, the recurrence mechanism in paroxysmal AF is due to PVs reconnection. Due to its different form of induce lesion, it is conceivable that CB ablation may provide a more durable PVI in redo procedure after an initial RF ablation has failed. However, the work of Pokushalov *et al.* [65] demonstrated that RF may still be preferable to CB for a redo ablation strategy in patients with paroxysmal AF, after an initial RF ablation has failed.

Table 3. Complication rate with radiofrequency and cryoballoon ablation for paroxysmal atrial fibrillation.

Overall complications (%); CB vs RF	PNP (%); CB vs RF	Stroke/TIA (%); CB vs RF	Major bleeding (%); CB vs RF	Aneurysm/AV fistula (%); CB vs RF	Tamponade (%); CB vs RF	Ref.
19.1 vs 14.2; p = NS	8.1 vs 0; pc < 0.00001	–	1.5 vs 0; p = 0.05	0 vs 0.8; p = NS	0.7 vs 1.5; p = NS	[24]
4.6 vs 4.6; p = NS	2.1 vs 0; p < 0.001	0.3 vs 0.3; p = NS	0.6 vs 1.1; p = NS	0.8 vs 1.1; p = NS	0.8 vs 1.4; p = NS	[26]

AF: Atrial fibrillation; AV: Aartero-venous; CB: Cryoballoon; NS: Not significant; PNP: Phrenic nerve palsy; RF: Radiofrequency; TIA: Transient ischemic attack.

Limitations

The authors acknowledge several limitations in the data reported in this review article.

Most of the data come from retrospective or non-randomized prospective studies, and so the presence of bias cannot be excluded.

Different methodologies were applied in these studies, with different strategies of PVI, different RF catheters and also different CBs' size and generations.

Cryoablation is a relatively recent ablation technique with globally less experienced centers and operators, so more long-term data is needed to perform a fair comparison.

Conclusion

CB and RF ablation present a similar acute PVI, procedure time, efficiency at mid-term follow-up and an equivalent rate of major complications. RF requires less fluoroscopy time due to the utilization of 3D navigation systems. This suggests that no significant differences appear to exist between the two techniques, however, data from ongoing randomized trials are needed in order to perform a clear and fair comparison.

Future perspective

Technology catheters and systems navigations are growing at an exponential velocity.

The capability of monitoring electrode–tissue contact are having and will have a huge impact in RF ablation, improving procedure success and decreasing radiation and procedure time. At the same time, second-generation CBs are demonstrating similar outcomes, with recent data demonstrating an high-acute PVI and freedom of atrial tachyarrhythmia at 12 months with only a 3 min application. A third-generation CB will soon be launched and will need to be evaluated.

Probably, when data from multicenter prospective trials are published, new data will be needed to compare CF RF ablation to second- or third-generation CB.

Newer technologies as well as new sources will also certainly appear in the next years.

Financial & competing interests disclosure

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Executive summary

Procedural findings & acute pulmonary vein isolation

- Overall acute pulmonary vein isolation is equivalent with the two strategies for paroxysmal atrial fibrillation. Radiofrequency ablation requires less fluoroscopy time, with no significant difference in procedure duration.

Outcomes

- A similar efficiency was reported with the two techniques at mid-term follow-up. No long-term data is still available with cryoballoon ablation.

Safety

- Both strategies present a comparable overall rate of major complication, with cryoballoon ablation presenting a higher rate of phrenic nerve palsy.

Technology development

- Contact-force radiofrequency catheter and second-generation cryoballoon are safe techniques, presenting a higher acute success and efficiency at 1 year.
- Both techniques will have an impact on outcomes after an ablation for paroxysmal atrial fibrillation. However, data from randomized trials are still needed.

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