




Review Article



Current Status of Atrial Fibrillation Ablation with Balloon Strategy

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Conflict of Interest

Dr. Bordignon received speaking and
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ABSTRACT

Catheter ablation of atrial fibrillation (AF) has been established worldwide and is recommended for symptomatic paroxysmal AF patients according to international guidelines. Importantly, the cornerstone of any AF ablation represents pulmonary vein isolation (PVI). Traditional radiofrequency (RF) point by point ablation within a 3D electroanatomic left atrial (LA) map requires profound understanding of LA anatomy and electrophysiology. This ablation strategy can be highly efficient and safe if performed in experienced hands and centers. However, procedural complexity causes a long learning curve and has limited its wide spread utilization. In contrast, balloon based PVI ablation strategies are based on an anatomic principle. Currently, two balloon types (cryoballoon and laserballoon) have been adopted to clinical routine. Both balloons are positioned at the target PV and circumferential energy ablation is enabled. This simplified anatomic approach facilitates reaching the procedural endpoint of PVI and demonstrated less operator dependency. Therefore, balloon PVI appears to be associated with improved procedural reproducibility and safety. Importantly, large scale randomized trials proved non-inferiority of balloon guided AF ablation (cryothermal and laser energy) vs. experienced operators using traditional “gold standard” RF ablation in paroxysmal and persistent AF. Ongoing technological refinements of both balloons as well as the introduction of novel energy dosing strategies and ablation targets may potentially impact the current way of ablating AF in future. This review will summarize current clinical experience of contemporary balloon devices and will look into future developments.

Keywords: Atrial fibrillation; Ablation balloon technology

INTRODUCTION

Worldwide prevalence of atrial fibrillation (AF) is increasing and AF represents the most common arrhythmia affecting approximately 2 million patients in Germany.¹⁾ AF causes considerable morbidity and mortality and is associated with reduced quality of life as well as increased rates of clinical endpoints such as stroke and heart failure.²⁾ Identification of electrical triggers arising from the pulmonary veins (PVs) initiating AF led to the treatment concept of PV isolation (PVI) by focal radiofrequency (RF) ablation.³⁾ However, this approach

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Author Contributions

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was characterized by only moderate success but severe complications such as PV stenosis. Therefore, antral wide area circumferential RF lesions encircling the PVs guided by a three-dimensional (3D) electroanatomic mapping system emerged as the standard of care with the endpoint of conduction block between the PVs and left atrium (LA).⁴⁾ Recently, point by point irrigated tip RF energy ablation was optimized introducing the ability to measure local catheter tip to tissue contact.⁵⁾⁶⁾ According to current international guidelines AF ablation should be performed (class IA recommendation) in symptomatic paroxysmal AF patients after failure of one antiarrhythmic drug.²⁾ In line with the recently published CABANA trial, AF ablation remains superior compared to medical therapy in rhythm control providing improved quality of life and reduced AF burden.⁷⁾⁸⁾ Importantly, in the randomized CASTLE AF trial, catheter ablation of AF demonstrated a mortality benefit in selected heart failure patients.⁹⁾ However, procedural complexity striving for contiguous transmural lesions in the LA without inducing complications and/or long-term non-durability of RF lesions limits this ablation approach. In contrast, balloon based ablation strategies are attractive due to their greater simplicity. Balloons need less catheter manipulation at the target PVs resulting in safe and potentially more reproducible AF ablation along with a short learning curve¹⁰⁾¹¹⁾ (**Figure 1**). This review will focus on contemporary balloon devices (cryo, laser energy) discuss state of the art balloon ablation strategies and future developments.

CRYOBALLOON

Cryoablation has been recognized for several years as an alternative to conventional RF ablation. The current version of the doubled layer cryoballoon (CB) catheter (Arctic Front Advance; Medtronic, Minneapolis, MN, USA) is available in 2 different diameters (23 and 28 mm) containing central lumina for a spiral mapping catheter (Achieve; Medtronic) and contrast medium injection (**Figure 2, Supplementary Video 1**). The CB is navigated with a steerable sheath (12F ID, Flexcath; Medtronic). The refrigerant N₂O is delivered into the balloon where it undergoes a liquid-to-gas phase change, resulting in temperatures of approximately -80°C creating thermal lesions at sites of balloon to tissue contact. Use of

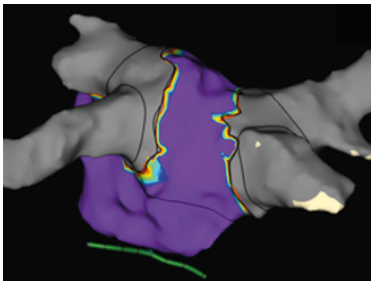
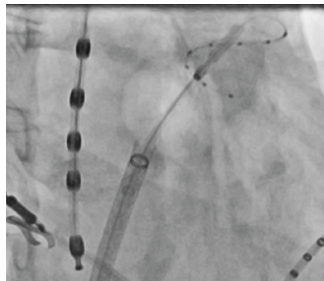
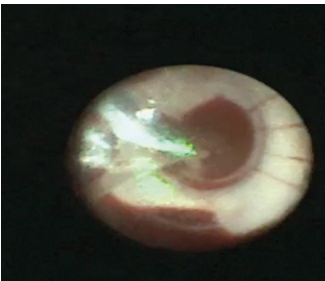
	RFC	Cryoballoon	Laserballon
			
Transseptal puncture	Double (8, 5F)	Single (12F)	Single (12F)
Left atrium navigation	3D mapping	Over the wire	Soft tip
Ablation type	Point by point	Single shot	Point by point
Energy titration	20-50 W	Freeze duration	5.5-12 W
Special features	Contact force ablation index	Single shot time to PVI	Camera automatic motor unit

Figure 1. Summary of technological specifics of contemporary balloon devices and RF ablation. RF = radiofrequency; PVI = pulmonary vein isolation; RFC = radiofrequency current; 3D = three-dimensional.

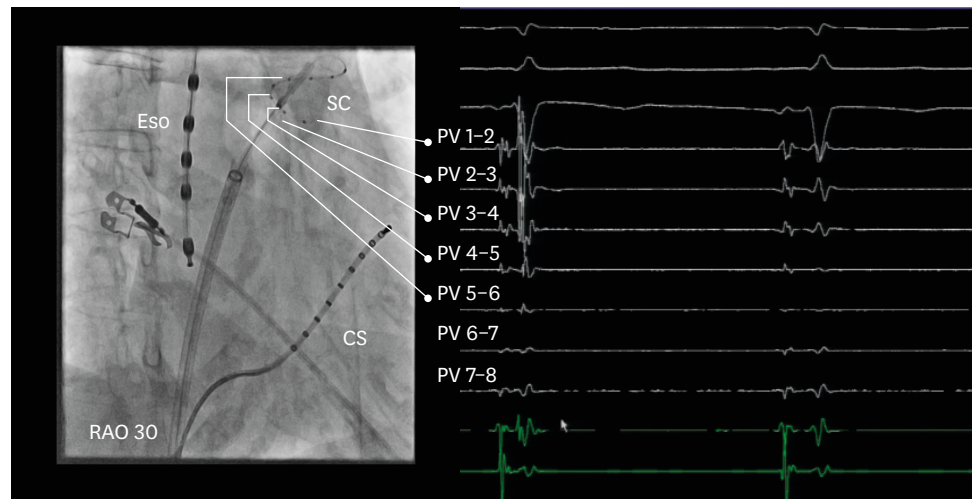


Figure 2. LSPV occlusion with 28 mm cryoballoon and real time visualization of electrical PV isolation. CS = coronary sinus; Eso = esophagus; LSPV = left superior pulmonary vein; PV = pulmonary vein; RAO = right anterior oblique; SC = spiral catheter.

the CB bears the theoretical advantage of homogenous circumferential energy deployment and single shot PVI. However, to achieve continuous lesions, an occlusive position of the balloon at the PV ostium is necessary to limit convective heating by leaking blood flow. Adequate balloon occlusion can be tested by contrast medium injection via the distal port of the balloon catheter, obviating the need for expensive additional tools. A number of CB maneuvers have been proposed to achieve occlusion. The so-called “single big balloon” strategy was introduced in 2009 which suggested the exclusive use of the 28 mm CB to deploy more proximal lesions, increase efficacy and minimize procedural complications.¹²⁾ The major step in the adoption of CB PVI to clinical routine was linked to the introduction of the second generation CB technology which carries 8 injections ports (CB2: Arctic Front Advance; Medtronic) leading to homogenous cooling of the distal hemisphere. Recently, a balloon update carrying a short tip (CB3) and a novel Achieve catheter (3 loop sizes: 15 mm, 20 mm, 25 mm) have been launched following the idea to increase the rate of real time PV recordings.

LASERBALLOON

The endoscopic ablation system (EAS; HeartLight™; CardioFocus, Inc., Marlborough, MA, USA) constitutes yet another approach to balloon PV isolation. It offers online information on balloon-tissue contact via a 2F integral fiberoptic endoscope. Once contact is achieved, the ablation region is directly visualized whilst the heart beats and laser energy can be delivered onto the desired segment of underlying myocardium. The current system consists of a non-steerable catheter with a sizeable compliant balloon at its tip (**Figure 3**). The catheter is navigated within the LA through a steerable transseptal sheath (ID 15F). The catheter was recently redesigned for single-operator utilization, with the possibility to maneuver the laser generator with a controller integrated in the catheter handle and greater balloon compliance (generation 2: Excalibur).¹³⁾ In contrast to the CB, the compliant laserballoon (LB) can be inflated to different sizes ranging from 9–35 mm according to the target PV. As a downside, the catheter offers no real time PV signal visualization. Therefore, guidance of ablation is purely anatomical and successful PVI has to be confirmed with a multipolar catheter thereafter. So far, direct lesion visualization is not reliable in all patients. Therefore,

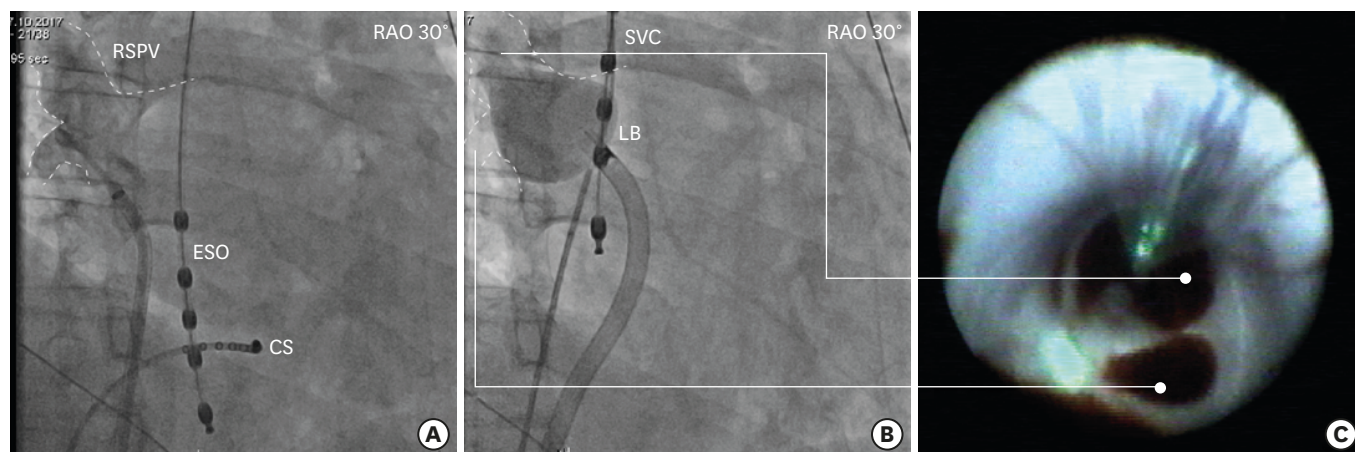


Figure 3. (A) Baseline PV angiogram of RSPV before laser PVI showing 2 RSPV branches and catheter settings. (B) LB occlusion of RSPV avoiding a distal position. (C) Endoscopic view of both RSPV branches. CS = coronary sinus; Eso = esophagus; LB = laserballoon; RAO = right anterior oblique; PV = pulmonary vein; PVI = pulmonary vein isolation; RSPV = right superior pulmonary vein; SVC = superior caval vein.

a tracking software was developed to facilitate contiguous lesions delivery. Ablation is performed with a 980-nm diode laser, housed in the central lumen. This may emit laser energy perpendicular to the catheter shaft covering an arc of a 30° angle. In contrast to single shot CB, LB delivers point-by-point circular ablation around each individual PVs. At this wavelength laser penetrates the tissue beyond the endothelial strata where it is absorbed by water molecules causing heating and coagulation necrosis. Deeper tissue layers are heated by conductive heating and the maximal depth reached in animal models was 12 mm. Energy delivery can be titrated by modulating power (5.5–12 W) in a set of predefined levels, each associated to different application duration (20 or 30 seconds). The latest LB update (generation 3: X3) combines improved balloon compliance with a motor control unit and recently obtained Conformite Europeenne mark in Europe. The novel integrated motor control unit allows for circumferential continuous laser arc movement with a speed of 2° per second (ideal scenario: 3 minutes ablation time per PV) allowing for uninterrupted ablation (**Supplementary Video 2**) controlled by the physician. In the initial clinical multicenter experience (n=60 patients) these technological refinements did result in faster PVI procedures without compromising safety.

CLINICAL DATA

Paroxysmal atrial fibrillation

The endpoint of AF ablation in paroxysmal AF has been defined to PVI. Therefore, use of balloons appear to be an appealing option for this indication. In an interesting work from France, CB AF ablation proved to be less dependent on the operator skills resulting in predictable outcome irrespective of the ablation center.¹⁰⁾ The randomized Fire and Ice trial (n=762 patients) was performed in experienced AF centers comparing wide area circumferential RF PVI (including contact force catheters) vs. CB (first and second generation, CB1, CB2) in paroxysmal AF. Importantly, the CB arm proved to meet the predefined primary endpoint of non-inferiority showing equal efficacy but was linked to shorter procedure times.¹⁴⁾ Importantly, surrogates of AF burden such as repeat ablation and cardioversion and re-hospitalization were significantly reduced in the CB group indicating an improved quality of life.¹⁵⁾ Of note, the advent of the second

generation CB (CB2) creating homogenous cooling of the distal hemisphere marked a turning point in the story of CB ablation. In our center, we performed the first human CB2 PVI case and it soon became obvious that all procedural parameters improved and translated into favorable long term outcome.¹⁶⁾ Subsequently, multiple studies consistently reproduced the high rate of acute procedural success¹⁷⁾ and favorable long-term outcome data (>80% success after 12 months in paroxysmal AF).¹⁸⁻²¹⁾ Maybe even more important, repeat electrophysiology (EP) studies assessing durability PVI after CB2 ablation proved unequivocally high rates of durable PVI after a single CB2 PVI procedure.²²⁾²³⁾ Analysis of repeat procedures from the Fire and Ice trial showed that PV reconnection was significantly less common in the CB as compared to RF ablation.

The LB has already demonstrated feasibility of PVI in paroxysmal AF. The initial strategy of creating one large lesion encircling both ipsilateral PVs has been shifted towards encircling each PV individually taking advantage of real time anatomy visualization, resulting in improved procedural data.²⁴⁾ In line with the CB experience, visually guided LB ablation can be associated with a high rates of durable PVI (>89%) after 3 months, irrespective of symptoms.²⁵⁾ The prospective randomized US trial comparing LB vs. RF ablation despite of participation of non-experienced LB operators demonstrated non-inferiority with regards to procedural safety and efficacy resulting in Food and Drug Administration approval.²⁶⁾ Currently, clinical success rates range between 70–80% after a single LB ablation procedure. Based on previous retrospective comparative analysis (CB1 vs. LB ablation) similar rates of sinus rhythm may be expected but longer procedure time and fluoroscopy exposure was observed in the LB group.²⁷⁾ To overcome the lack of comparative prospective randomized data for these two contemporary balloon devices, we accomplished inclusion (200 patients) in the randomized LB vs. CB2 trial data awaiting follow up data soon.

Persistent atrial fibrillation

Persistent AF represents an ill-defined clinical scenario of continuous AF lasting >7 days and <12 months duration. Different catheter ablation strategies have been proposed to treat this progressed AF stage. However, the prospective randomized STAR AF 2 trial²⁸⁾ recently failed to demonstrated a difference in rhythm outcome when PVI vs. PVI plus CFAE vs. PVI plus linear lesions was compared. Therefore, PVI only remains the cornerstone in persistent AF ablation. In this context, both CB and LB ablation may offer an interesting alternative to RF ablation due to reproducibility and single procedure high rates of PVI durability. Interestingly, initial single center data in persistent AF demonstrated 67% sinus rhythm 11 months after CB2 PVI and 73% after 12 months for the LB, respectively supporting the role of a balloon approach in this clinical setting.²⁹⁾ The prospective European multicenter Cryo4persistent AF trial confirmed this success rate (61% sinus rhythm after 12 months) along with favorable safety outcome following a CB2 PVI only approach in 102 patients.³⁰⁾ Early retrospective clinical study showed similar efficacy of using LB based PVI compared with RF PVI in persistent AF.³¹⁾ In the only prospective randomized European multicenter trial comparing LB vs. RF PVI in 150 patients, no difference was observed for acute procedural and outcome after 12 months.³²⁾ Recently, the so-called Fire and Ice 2 pilot trial (n=60 patients) has been started. The study randomizes persistent AF patients to either CB or RF ablation PVI. All patients obtain pre-ablation loop recorder implantation to determine AF burden before and after PVI. In addition, non-invasive electrocardiogram mapping (Cardioinsight; Medtronic) is performed in all patients to investigate persistent AF mechanisms.

Recently, the CB has been utilized to deploy additional lesions beyond the PVs. In non-controlled studies posterior wall as well as roof line ablation performed in the index

procedure demonstrated incremental efficacy after PVI.³³⁾³⁴⁾ Interestingly, the left atrial appendage (LAA) has been termed as the “5th” PV and may play a key role in persistent AF.³⁵⁾³⁶⁾ Single shot CB isolation of LAA is technically feasible.³⁷⁾ However, energy dosing and optimal treatment of a non-contracting isolated LAA remains a matter of debate.³⁸⁾³⁹⁾ Based on our retrospective experience, left atrial appendage closure (LAAC) should be recommended. The upcoming ASTRO AF study will randomize CB LAA isolation followed by LAAC vs. substrate based RF ablation in the setting of chronic PVI. In future, more data from randomized trials will shed further light on the effect of ablation beyond the PVs. It may be expected that balloons will find their role in persistent AF ablation.

Energy dosing

As mentioned before, the LB offers the unique option to individualize energy spot delivery at different sites. Typically, ablation along the anterior section of left sided PVs benefits from higher energy compared to the posterior LA wall. However, energy levels in the initial feasibility studies were not standardized and influenced by parameters such as balloon-to-tissue contact, target site along the PV or by the proximity of extra-cardiac structures such as the esophagus or the phrenic nerve (PN). Consequently, our group investigated the impact of high dose (≥ 8.5 W) vs. low dose ablation (< 8.5 W) in 60 patients on acute procedural efficacy and rhythm outcome. Interestingly, the use of high power was associated with superior procedural data and improved success rate of 83% vs. 60% sinus rhythm without compromising safety. Subsequently, Metzner et al.⁴⁰⁾ confirmed this finding in a series of 30 patients. Therefore, we attempt high power ablation if balloon contact allows adequate tissue visualization.

Individualizing energy dosing utilizing the CB2 is more complex. In the Fire and Ice trial the ablation protocol recommended a freeze duration of 240 seconds followed by an empirical bonus freeze.¹⁴⁾ In contrast to the LB the CB technology allows for real time visualization of PV potentials and thus determination of the time to isolation (TTI). Based on previous studies it was evident that a short TTI predicts an effective freeze.⁴¹⁾⁴²⁾ Multiple non randomized dosing strategies have been suggested based on freeze duration or TTI.⁴³⁾⁴⁴⁾ We further investigated the clinical value of the TTI concept in the first prospective randomized ICE T pilot study. Two groups were defined: control group 240 seconds + empiric bonus freeze vs. single freeze in case of short TTI (< 75 seconds). The TTI based single freeze group demonstrated similar efficacy ($> 80\%$ sinus rhythm during 12 months) along with a reduced complication rate. Recently, a freeze duration of 180 seconds was suggested which resulted in shorter procedure times along with similar clinical outcome.⁴³⁾ In our recently published ICE-RE study we could demonstrate a greater risk for PV re-conduction if a total freeze duration of 180 seconds instead of 240 seconds was performed.⁴⁵⁾ Therefore, in our experience TTI based single freeze duration of 240 seconds appears to be preferable if no signs of PN or esophageal damage emerge.

Safety

Catheter ablation of AF can be linked to many potentially life-threatening complications.⁴⁶⁾ Balloons share some of the typical RF complications but carry their own specific complication profile.

In general, cardiac tamponade is linked to different mechanisms (transeptal puncture, mapping, ablation, steam pop) and may occur in 1–2% of RF ablation cases. Un-controlled tamponade represents the major reason for procedure related death. Interestingly, the rate of

tamponade was lower in the Fire and Ice trial (5 in the RF group vs. 1 in the CB group). Larger data sets confirmed a significant lower risk for cardiac tamponade in balloon vs. RF PVI.⁴⁷⁾⁴⁸⁾

Atrio-esophageal (AE) fistula is a very rare but often lethal complication and is estimated to occur in 0.01–0.05% of patients following AF ablation. AE fistulas have been reported after CB PVI whereas to best of our knowledge no case occurred after LB PVI. This is probably in part explained by the lower number of treated patients. Interestingly, a luminal esophageal temperature (LET) cut-off of 15° was able to reduce the risk for post-ablation CB2 thermal esophageal lesions⁴⁹⁾ and should thus be adopted in CB2 ablation. For LB PVI, LET monitoring is recommended adopting a cut-off value of 39°C. However, no clear correlation between temperature and esophageal lesions has been established.

PN injury represents the typical balloon complication during AF ablation accounting for >10% cases in non-experienced centers.⁵⁰⁾ If the ablation balloon is pushed hard to occlude right sided PVs, the distance to the PN may be reduced or the CB may reach an inside distal PV position. Therefore, only the big 28 mm CB and larger LB diameters should be utilized. Continuous PN pacing and palpation of diaphragmatic excursions from the junction of the superior caval vein and subclavian vein as well as CMAP monitoring may contribute to early detection of PN dysfunction. All signs should lead to immediate termination of ablation.⁵¹⁾⁵²⁾ Still, we discourage to use the 28 mm CB in right-sided PVs at diameters of ≥ 26 mm. Implementing these measures of the rate of persistent PN lesion can be reduced to <3%. Importantly, PN function typically recovers within 12 months. In addition, if distal PV ablation is avoided, severe PV stenosis appears to be absent.⁵³⁾

PERSPECTIVE

Following the initial promising clinical experience using balloons as a vector in AF ablation different RF energy strategies have been developed and are currently under investigation. Balloon guided ablation beyond PVI may impact future ablation targets.

CONCLUSION

Both, LB and CB have been well established in paroxysmal and persistent AF ablation. Current designs of balloon-based devices for PV isolation offer predictable acute and long-term success rates along with a favorable safety profile. Further technological refinements of both balloons as well as the introduction of novel energy dosing strategies and ablation targets may potentially impact the way of future AF ablation.

SUPPLEMENTARY MATERIALS

Supplementary Video 1

Real time visualization of LIPV isolation using a “hockey stick” maneuver.

[Click here to view](#)

Supplementary Video 2

LSPV ablation with the latest X3 version. The novel integrated novel motor unit allows for automatic continuous laser arc movement with a speed of 2° per second (ideal scenario: 3 minutes ablation time per PV) allowing for faster ablation.

[Click here to view](#)

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