

Cryoballoon Versus Laserballoon: Insights from the First Prospective Randomized Balloon Trial in Catheter Ablation of Atrial Fibrillation

Running title: *Chun et al.; Cryo- vs. Laserballoon PVI in Atrial Fibrillation*

Julian KR Chun, MD^{1,2}; Stefano Bordignon, MD¹; Jana Last, MD¹; Lukas Mayer, MD¹;
Shota Tohoku, MD¹; Simone Zanchi, MD¹; Lorenzo Bianchini, MD¹; Fabrizio Bologna, MD¹;
Takahiko Nagase, MD¹; Lukas Urbanek, MD¹; Shaojie Chen, MD¹; Boris Schmidt, MD¹



¹Cardioangiologisches Centrum Bethanien (CCB), Medizinische Klinik III, Kardiologie, Agaplesion Markuskrankenhaus, Frankfurt am Main; ²Medizinische Klinik II, Kardiologie/Angiologie/Intensivmedizin, Universitätsklinikum Schleswig-Holstein, Universität zu Lübeck, Germany

Correspondence

Priv.-Doz. Dr. KR Julian Chun
Cardioangiologisches Centrum Bethanien – CCB
Med. Klinik III, Markuskrankenhaus
Wilhelm-Epstein-Str. 4
60431 Frankfurt
Tel: +49 69-945028-110
E-mail: j.chun@ccb.de

Journal Subject Terms: Atrial Fibrillation; Catheter Ablation and Implantable Cardioverter-Defibrillator

Abstract:

Background - Pulmonary vein isolation (PVI) represents the cornerstone in atrial fibrillation ablation. Cryoballoon (CB) and laser balloon (LB) catheters have emerged as promising devices but lack randomized comparisons. Therefore, we sought to compare efficacy and safety comparing both balloons in patients with persistent and paroxysmal AF.

Methods - Symptomatic AF patients (n=200) were prospectively randomized (1:1) to receive either CB or LB PVI (CB: n=100: 50 PAF + 50 persistent AF vs. LB: n=100: 50 PAF + 50 persistent AF). All antiarrhythmic drugs (AAD) were stopped after ablation. Follow-up included 3-day Holter-ECG recordings and office visits at 3, 6 and 12 months. Primary efficacy endpoint was defined as freedom from atrial tachyarrhythmia (ATa) between 90 and 365 days after a single ablation. Secondary endpoints included procedural parameters and peri-procedural complications.

Results - Patient baseline parameters were not different between both groups. In all (n=200) complete PVI was obtained and the entire follow-up accomplished. Balloon only PVI was obtained in 98% (CB) vs. 95% (LB) requiring focal touch up in 2 and 5 patients, respectively. Procedure but not fluoroscopy time was significantly shorter in the CB group (50.9±21.0min vs. 96.0±20.4 min; p<0.0001 and 7.4±4.4 min vs. 8.4±3.2min, p=0.083). Overall, the primary endpoint of no ATa recurrence was met in 79% (CB: 80.0% vs LB: 78.0%, p=ns). No death, atrio-esophageal fistula, tamponade or vascular laceration requiring surgery occurred. In the CB group, 8 transient but no persistent phrenic nerve palsy (PNP) were noted compared to 2 persistent PNP and 1 TIA in the LB group.

Conclusions - Both balloon technologies represent highly effective and safe tools for PVI resulting in similar favorable rhythm outcome after 12 months. Use of the cryoballoon is associated with significantly shorter procedure but not fluoroscopy time.

Key words: catheter ablation; atrial fibrillation; atrial fibrillation arrhythmia; pulmonary vein isolation; cryoballoon; laserballoon

Nonstandard Abbreviations and Acronyms

AAD-antiarrhythmic drug

AF-atrial fibrillation

AFL-atrial flutter

ATa-atrial tachyarrhythmia

CB-cryoballoon

LA-left atrium

LET-luminal esophageal temperature

LB-laserballoon

PN-phrenic nerve

PVI-pulmonary vein isolation

RF-radiofrequency



Circulation: Arrhythmia and Electrophysiology

Introduction

Recently, balloon guided catheter ablation of atrial fibrillation (AF) has gained increased attraction. At present, two balloon strategies (cryoballoon, CB and laserballoon, LB) have been adopted to clinical routine in Europe and the United States^{1 2}. Balloon based pulmonary vein isolation (PVI) is typically characterized by a short learning curve, decreased operator dependency but increased procedural reproducibility compared to 3D mapping guided radiofrequency (RF) ablation³. Recently, randomized trials have demonstrated for the first time non-inferiority of CB and LB guided AF ablation if compared to the traditional “gold standard” RF ablation in paroxysmal and persistent AF^{4 5}. However, a prospective randomized “head to head” comparison of both aforementioned contemporary balloon devices is lacking.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patients were randomized in a 1:1 fashion to receive either CB ablation (ICE T protocol) or LB PVI (high dose protocol) as previously described in detail. Figure 1 illustrates the patient randomization process including predefined subgrouping into paroxysmal and persistent AF based on the recent ESC 2016 guidelines. Both CB and LB group consisted of n=100 patients (paroxysmal AF: n=50 + persistent AF:n=50), respectively. The study complies with the declaration of Helsinki. The protocol has been reviewed and approved by the local ethics committee and registered at the German Clinical Trials Register (DRKS00012423).



Patients

All patients gave written informed consent before study enrollment. Patients with symptomatic paroxysmal (<7 days) or persistent (>7 days and <1 year) AF refractory to the treatment of at least 1 antiarrhythmic drug (AAD), including β blockers (class I–III) were eligible to enter the study. Patients had to be 18 to 80 years old. Mild-to-moderate LA enlargement <45 mm was allowed, as well as a mildly reduced left ventricular ejection fraction (>45%). Patients were excluded if they had undergone previous PVI attempts or were ineligible for treatment with oral anticoagulation. Moreover, presence of an intracardiac thrombus and moderate or severe mitral valve disease led to exclusion from the study. No preprocedural imaging such as MRI or CT scans was performed.

Study Endpoints

The primary endpoint was defined as freedom from AF or any atrial tachyarrhythmia >30 seconds between days 90 and 365 after the index procedure off AAD.

The secondary endpoints included procedural parameters and peri-procedural safety events such as major bleeding requiring intervention, phrenic nerve palsy, pericardial tamponade, thromboembolic events, atrio-esophageal fistula, or death.

Ablation Procedure

In this study, three experienced EP physicians served as first operators for both groups (KRJC, BS, and SB). All procedures were performed under deep sedation using boluses of midazolam and fentanyl and a continuous infusion of propofol. In all patients, an esophageal temperature probe (Circa Probe, Circa Scientific, Englewood, CO; SensiTherm, St. Jude Medical, Inc., St. Paul, MN) was inserted to monitor luminal esophageal temperature (LET). If LET reached the predefined safety cut-off temperature (CB: 15° and LB: 39°C) ablation was prematurely terminated. In case of CB ablation time to PVI was noted and no empiric bonus application delivered based on previously published ICE T criteria. In case of LET rise >39°C, cooling down was required and different beam position using low power 5.5W was utilized to close the gap. The right phrenic nerve (PN) was continuously paced from the superior cava vein during freezing at the septal PVs. In case of loss of PN capture or cessation or weakening of right hemidiaphragm contractions, freezing was immediately terminated as described. Definition of transient PN injury was met if PN function resumed before hospital discharge. Definition of persistent PN injury was met if PN function did not resume until hospital discharge ⁶. In case of a balloon defect and/or non-successful PV isolation, focal RF ablation was allowed according to the operator's discretion. Acute procedural endpoint was defined as PV entrance block.

Cryoballoon Ablation

The principle of single transseptal 28-mm CB PVI has been described in detail before ⁷. In all patients the second generation CB was inserted into the left atrium (LA) guided by a spiral

catheter (SC, Achieve, 20mm, Medtronic, Minneapolis, MN) ⁸. The SC was positioned as proximal as possible to provide PV potential recording. In some cases, skewed/flipped back SC position enabled enhanced PV potential recordings. Local PV occlusion was assessed using distal contrast injection. A variety of established CB maneuvers were utilized. The pull-down maneuver was defined by accepting an inferior leak of contrast medium followed by pulling down sheath and balloon to achieve sequential PV occlusion and isolation. CB energy dosing followed the ICE T concept ⁹. In brief, single shot PVI along with short TTI (<75s, defined as the time from freeze initiation to the last recorded PV potential) was attempted. In case of short TTI (<75s) no bonus application was delivered. Only the initial freeze at each PV qualified for TTI analysis. If no TTI information could be obtained, the SC was pulled back after the freeze to the angiographically defined PV ostium and PVI was re-assessed. In this scenario, after proof of PVI a bonus application was delivered. Procedure time was defined from skin puncture to removal of CB/ablation catheter. No waiting time was applied.

Laserballoon Ablation

The transseptal sheath was exchanged for a 12F steerable sheath (CardioFocus) via a guidewire in the left superior PV. The LB (first n=32 and second generation n=68) was navigated to each individual PV using the steerable sheath and inflated to obtain optimal PV occlusion. Laser energy was deployed in a point-by-point fashion thereby covering 30° of a circle with each ablation lesion. As previously reported the principle of the previously published high dose LB protocol was followed ¹⁰. According to the degree of tissue exposure 12-5.5W overlapping beams along with corresponding 20s to 30s duration was attempted. After complete visually guided circular ablation, the PVs were remapped using the circular mapping catheter. In case of residual PV conduction, additional LB ablation was performed according to the activation

sequence in the circular mapping catheter. Electrical PVI was defined as entrance block.

Procedure time was defined from skin puncture to removal of LB/ablation catheter. No waiting time was applied.

Post Procedural Care and Follow-Up

All patients underwent post-procedural transthoracic echocardiography after the procedure and the next day to rule out pericardial effusion. After the procedure, direct oral anticoagulation was resumed after 4-8 hours. Patients on therapeutic vitamin K antagonist continued anticoagulation (International Normalized Ratio 2–3). In all patients, membrane-active AADs were discontinued after the procedure. Telemetric electrocardiographic (ECG) monitoring was obtained in all patients until hospital discharge.



In case of early ATa recurrence use of AAD was confined to the 90 days blanking period.

During the blanking period repeat ablation was strongly discouraged and AAD treatment re-administered. After hospital discharge a blanking period of 90 days was applied, patients were scheduled at 3, 6, and 12 months for follow-up visits, during which baseline ECG and 72-hour Holter ECG recordings were obtained. Furthermore, in symptomatic patients event recording was initiated and telephone calls were performed throughout the follow-up period.

Statistical Analysis

Based on the historical first generation CB vs LB data >680 patients would have been required to show a difference between both devices and thus deemed non-realistic. So far, there is no prospective data comparing both contemporary CB vs. the LB systems. We therefore proposed that a descriptive comparison of 200 patients using latest balloon technologies should generate clinically relevant information. Mean \pm standard deviation (SD) was used to describe continuous variables with normal distribution. Median and interquartile range were used when appropriate.

The student t test was performed to calculate differences between groups of continuous variable with normal distribution. The χ^2 test or the Fisher exact test was used to perform between group comparisons of categorical variables. The Rank-sum-Test was used for comparing non-normal variables when appropriate. The difference in freedom from AF/AT recurrence was compared by means of Kaplan-Meier analysis with log-rank test. A two-sided P value of less than 0.05 was considered to indicate statistical significance. The statistical analyses were performed by using the SPSS statistical package, version 22 (IBM).

Results

Patients

Between April 2017 and April 2019 a total of 200 patients were enrolled and randomized in a 1:1 fashion to receive either CB (n=100: 50 PAF, 50 pers. AF) or LB (n=100: 50 PAF, 50 pers. AF) PVI. At the end of the 12 months of follow-up period, all patients had completed follow up visits and have been assessed for the primary end point. After randomization, patient characteristics were not different between both groups. In brief, age (65 ± 9 vs. 66.5), male sex (58% vs. 54%), BMI (28.3 ± 5.0 vs. 28.0 ± 5.6), LA size (39.1 ± 5.3 vs. 39.8 ± 5.2) was comparable between both groups. All detailed patient characteristics are summarized in table 1.

Primary Endpoint

No patient was lost to follow up and completed the 12 months follow up period. The primary study endpoint defined as freedom from ECG documented ATa after 12 months (including 3 months blanking period) was not different between both groups: 80.0% (CB) vs. 78.0% (LB), $p=ns$, respectively. Overall, the clinical success rate in this mixed study patient population consisting of PAF and persist. AF patients was 79% after 12 months. The Kaplan Meier



estimates comparing both balloon devices are shown in figure 2. In detail, type of ATa recurrence was not different between both groups (CB: AF: n=15, AT: n=2, AFL: n=1 vs. LB: AF: n=17, AT: n=4, AFL: n=1).

Secondary Endpoints

Procedural data

In all patients the procedural endpoint of spiral catheter documented PVI (entrance block) was obtained. Balloon only PVI was achieved in 98% (CB) vs. 95% (LB) of patients, respectively. Per PV, the CB single shot rate (82%) and LB single pass isolation rate (96%) were high ($p < 0.0001$). LB single pass isolation of all PVs was obtained in 83% of patients. Additional touch up RF ablation was required in both groups: CB: n=2 PVs (RIPV: n=2) and LB: n=5 PVs (RIPV: n=3, LSPV: n=1, LIPV: n=1). Balloon defects occurred in 8% of LB cases. To restore sinus rhythm electrical cardioversion was performed in 37% and 43% in the CB and LB group, respectively. No acute PV re-conduction was observed at the end of the procedure in both groups. Procedure time but not fluoroscopy exposure were significantly shorter in the CB group (50.9 ± 21.0 min vs. 96.0 ± 20.4 min, $p < 0.0001$) (7.4 ± 4.4 min vs. 8.4 ± 3.2 min, $p = 0.083$). More procedural details are summarized in table 2.

Clinical outcome in paroxysmal and persistent AF

The 12 months success rate in paroxysmal AF patients (n=100) comparing the CB (n=50) vs. LB (n=50) was overall 83% and not different between both groups: 82% (CB) vs. 84% (LB), p-value=ns. In persistent AF, the overall 12 months success rate was 75% and not different between both groups: 78% (CB) vs. 72% (LB), p-value=ns. Both Kaplan Meier survival curves are shown in figure 2. No repeat procedure was performed within the 3 month blanking period.

Complications

No major complications such as death, atrio-esophageal fistula, pericardial tamponade or vascular laceration requiring surgery were observed. However, in the LB group 1 TIA (day 1 after the procedure was noted which resolved without clinical sequelae. In the CB group no stroke or TIA occurred. In addition, no persistent PNP but 8 transient PNP occurred compared to 2 persistent PNP and no transient PNP in the LB group. All further details with regards to adverse events are summarized in table 3.

Discussion

This present study reports to best of our knowledge the first randomized comparison of second/third generation cryoballoon and laserballoon in AF ablation. Main study findings comprise (1) favorable and not different rhythm outcome between both devices after 12 months in patients with paroxysmal and persistent AF, (2) significantly shorter procedure times using the CB compared to LB and (3) comparable benign procedural complication profile.

Clinical Efficacy

The procedural endpoint of PVI was obtained in all patients. Importantly, the rate of balloon only PVI was comparably high between both groups (CB: 98% vs. LB: 95%). Of note, sole PVI in PAF as well as in persistent AF patients resulted in a similar favorable rhythm outcome regardless of the utilized balloon device. Both observed success rates (PAF: >80%, persistent AF: >70%) are consistent with previously published controlled and non-controlled studies using intermittent Holter ECG as the follow up mode^{11 12 9 5 13 14}. If compared to the historical non-randomized first generations CB vs. LB balloon study¹⁵ the introduction of contemporary balloon generations was associated with an improved clinical outcome. Our data confirm initial

single arm experiences using the second generation CB or the new generation more compliant LB. However, lack of continuous monitoring as performed e.g. in the Circa Dose trial⁹ may overestimate the rate of freedom from any ATa. Still, this limitation would have equally affected both groups. Importantly, due to the centers high patient adherence no one was lost during follow up and all underwent the standardized follow up protocol.

Procedural Parameters and Technical Aspects

In contrast to the LB, the non-compliant CB system represents a true single shot PVI tool. The LB offers direct PV visualization which is a prerequisite to deploy a contiguous circular chain of overlapping point by point ablation lesions. Compared to the CB this offers the potential advantage of precise regional energy titration (e.g. anterior vs. posterior wall) but may be more time consuming. Procedure and fluoroscopy times for both devices are short compared to RF ablation¹⁶ and consistent with novel generations balloon experience^{17 18 14 19}. Of note, this trial allowed the use of latest CE marked CB and LB balloon generations and therefore demonstrates the incremental value of technological progress in the field of AF ablation. Interestingly, in this presented “head to head” comparison we could demonstrate a significantly shorter CB vs. LB procedure time (50.9min vs. 96.0min; $p < 0.0001$). In part, this may be explained with the meticulous effort to visualize PV potentials during CB ablation. PV potential visualization along with fast real time isolation enables individualized energy dosing and omitting empiric bonus freezes²⁰. Regardless of the beauty of real time PVI visualization this electrogram based strategy allows substantial streamlining of the CB procedure. In contrast, the LB lacks that option for real time PV spike visualization during ablation. It houses neither an internal lumen to insert a mapping catheter nor balloon mounted electrodes. Thus, ablation effects have to be controlled following circular PV ablation which increases procedure times if no first round PVI was

obtained. It is well established, that successful “first round” LB PVI is typically enabled if perfect PV occlusion can be obtained (broad contact zone, 360° view onto the PV). However, laser ablation in regions with non-perfect balloon contact/spilling blood and regions with LET increase may require balloon re-positionings/rotations to avoid so-called “blind spot” ablation. These maneuvers may add to increased procedure times. The more compliant second generation LB has been associated with favorable PV occlusion characteristics and requires less balloon rotations. This device is associated with high rates of “first round” PVI¹¹. Of note, very recently a third LB generation (X3) housing an integrated motor unit has recently become available in Germany. Very early clinical experience indicates shorter LB procedure times²¹.

Of note, fluoroscopy exposure was equally low and not different between both CB and LB devices (7.4min vs. 8.4min, p=0.083). This encouraging observation may question the mandatory need for a 3D mapping system if a standardized balloon PVI ablation approach is followed.

Safety

The observed safety data in this trial confirm the reported low chance of cardiac tamponade and neurological events if a balloon device was utilized. Of note no cardiac tamponade, AE-fistula or death occurred. There was one neurological event (1/200 patients, TIA: LB) which resolved without clinical sequelae. The overall risk for balloon specific complication such as persistent PN palsy was 1.5%. Using meticulous precautions to early identify PN palsy the risk of transient PNP was higher for the CB (8%) vs. LB (0%). In contrast, the risk for a persistent PNP was CB (0%) vs. LB (3%) for the LB device. As reported before, all persistent PNP resumed function after 3 months.

Pulmonary vein isolation and additional ablation

A recent large scale randomized trial in persistent AF failed to detect a benefit of different RF ablation strategies on top of acute PVI²². Despite general uncertainty regarding persistent AF ablation endpoints, potential lesion recovery including the PVs remain a key element for ATa recurrence. Importantly, both CB and LB balloon ablation results in reproducible high rates of durable PVI^{23 24 25}. Therefore, the overall 12 months success rate of 79% sinus rhythm in our mixed study cohort is consistent with previous data and may be explained by an equally high fraction of durable PVI using both balloon devices. As expected the success rate was higher in PAF compared to persistent AF. However, no difference was found comparing both balloons. Interestingly, a recently published retrospective Japanese balloon study also reported a similar rhythm outcome in persistent AF (CB: 81% vs. Hotballoon: 85%)¹³. The 12 months success rate of sole PVI in our persistent AF sub-group (75%, CB 72%, LB 78%) emphasizes the utmost need for ablation technologies producing durable PVI in a single procedure. Sophisticated (high power) ablation index guided RF ablation demonstrated promising safety and clinical outcome^{16 26 27} but randomized data is lacking. Of note, very promising energy sources such as electroporation²⁸ or novel devices toggling electroporation/high power RF ablation²⁹ will become available soon and may fill in for that gap. Multiple studies aim to address what to ablate beyond the PVs. The concept of substrate ablation based on pre-procedural MRI atrial fibrosis visualization³⁰ is currently investigated in the (DECAAF 2) trial and may impact future patient selection and ablation strategies. The ongoing randomized ASTRO AF study compares the role of empirical CB LAA isolation vs. substrate modification based on endocardial 3D mapping in the setting of permanent PVI. Therefore, at this point in time use of a standardized and predictable balloon PVI may qualify as the index AF ablation in PAF and persistent AF. If

required RF guided re-PVI + additional ablation in a second procedure may avoid empiric overtreatment.

Limitations

This prospective randomized CB vs. LB pilot single center study in AF ablation lacks sample size calculation. So far, there is no prospective data comparing contemporary CB vs. LB systems. We proposed that a descriptive comparison of 200 patients using latest balloon technologies should generate clinically relevant information since a trial including >680 patients deemed non-realistic. The high rate of single shot PVI in our study (ICE T concept) contributed to fast CB procedures but may depend on the centers experience. More data from a larger patient cohort and different centers is required to confirm our initial pilot trial data. Importantly, LB procedure times may be shortened in future if the latest X3 LB proves safety and feasibility in human.

Conclusions

Both cryoballoon and laserballoon ablation technologies represent very effective and safe tools for PVI resulting in similar favorable rhythm outcome in patients with paroxysmal and persistent AF. Use of the cryoballoon is associated with significantly shorter procedure times but not fluoroscopy exposure.

Sources of Funding: None

Disclosures: Julian KR Chun reports personal fees, speaking honoraria from Medtronic and Cardiofocus. Stefano Bordignon reports personal fees, speaking honoraria from Medtronic and Cardiofocus. Boris Schmidt reports personal fees, speaking honoraria from Medtronic and Cardiofocus. All others have none

References:

1. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, et al; ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893-2962.
2. Dukkipati SR, Cuoco F, Kutinsky I, Aryana A, Bahnson TD, Lakkireddy D, Woollett I, Issa ZF, Natale A, Reddy VY, HeartLight Study Investigators. Pulmonary Vein Isolation Using the Visually Guided Laser Balloon: A Prospective, Multicenter, and Randomized Comparison to Standard Radiofrequency Ablation. *J Am Coll Cardiol*. 2015;66:1350–1360.
3. Providencia R, Defaye P, Lambiase PD, Pavin D, Cebron J-P, Halimi F, Anselme F, Srinivasan N, Albenque J-P, Boveda S. Results from a multicentre comparison of cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: is cryoablation more reproducible? *Europace*. 2016;euw080.
4. Kuck K-H, Brugada J, Fürnkranz A, Metzner A, Ouyang F, Chun KRJ, Elvan A, Arentz T, Bestehorn K, Pocock SJ, et al, FIRE AND ICE Investigators. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med*. 2016;374:2235-2245.
5. Schmidt B, Neuzil P, Luik A, Osca Asensi J, Schrickel JW, Deneke T, Bordignon S, Petru J, Merkel M, Sediva L, et al. Laser Balloon or Wide-Area Circumferential Irrigated Radiofrequency Ablation for Persistent Atrial Fibrillation: A Multicenter Prospective Randomized Study. *Circ Arrhythm Electrophysiol*. 2017;10:e005767.
6. Tohoku S, Chen S, Last J, Bordignon S, Bologna F, Trolese L, Zanchi S, Bianchini L, Schmidt B, Chun KRJ. Phrenic nerve injury in atrial fibrillation ablation using balloon catheters: Incidence, characteristics, and clinical recovery course. *J Cardiovasc Electrophysiol*. 2020;31:1932-1941.
7. Chun K-RJ, Schmidt B, Metzner A, Tilz R, Zerm T, Köster I, Fürnkranz A, Koektuerk B, Konstantinidou M, Antz M, et al. The “single big cryoballoon” technique for acute pulmonary vein isolation in patients with paroxysmal atrial fibrillation: a prospective observational single centre study. *Eur Heart J*. 2009;30:699–709.
8. Chun KJ, Bordignon S, Gunawardene M, Urban V, Kulikoglu M, Schulte-Hahn B, Nowak B, Schmidt B. Single transeptal big Cryoballoon pulmonary vein isolation using an inner lumen mapping catheter. *Pacing Clin Electrophysiol PACE*. 2012;35:1304–1311.
9. Andrade JG, Champagne J, Dubuc M, Deyell MW, Verma A, Macle L, Leong-Sit P, Novak P, Badra-Verdu M, Sapp J, et al, For the CIRCA-DOSE Study Investigators. Cryoballoon or Radiofrequency Ablation for Atrial Fibrillation Assessed by Continuous Monitoring: A Randomized Clinical Trial. *Circulation*. 2019;140:1779–1788.

10. Bordignon S, Chun K-RJ, Gunawardene M, Urban V, Kulikoglu M, Miehm K, Brzank B, Schulte-Hahn B, Nowak B, Schmidt B. Energy titration strategies with the endoscopic ablation system: lessons from the high-dose vs. low-dose laser ablation study. *Europace*. 2013;15:685-689.
11. Nagase T, Bordignon S, Perrotta L, Bologna F, Tsianakas N, Chen S, Konstantinou A, Chun JKR, Schmidt B. Analysis of procedural data of pulmonary vein isolation for atrial fibrillation with the second-generation laser balloon. *Pacing Clin Electrophysiol*. 2019;42:837-845.
12. Fürnkranz A, Bordignon S, Dugo D, Perotta L, Gunawardene M, Schulte-Hahn B, Nowak B, Schmidt B, Chun JKR. Improved 1-year clinical success rate of pulmonary vein isolation with the second-generation cryoballoon in patients with paroxysmal atrial fibrillation. *J Cardiovasc Electrophysiol*. 2014;25:840-844.
13. Wakamatsu Y, Nakahara S, Nagashima K, Fukuda R, Nishiyama N, Watanabe R, Arai M, Otsuka N, Kurokawa S, Sato H, et al. Hot balloon versus cryoballoon ablation for persistent atrial fibrillation: Lesion area, efficacy, and safety. *J Cardiovasc Electrophysiol*. 2020;31:2310-2318.
14. Boveda S, Metzner A, Nguyen DQ, Chun KRJ, Goehl K, Noelker G, Deharo J-C,  Andrikopoulos G, Dahme T, Lellouche N, et al. Single-Procedure Outcomes and Quality-of-Life Improvement 12 Months Post-Cryoballoon Ablation in Persistent Atrial Fibrillation. *JACC Clin Electrophysiol*. 2018;4:1440-1447.
15. Bordignon S, Chun KJ, Gunawardene M, Fuernkranz A, Urban V, Schulte-Hahn B, Nowak B, Schmidt B. Comparison of Balloon Catheter Ablation Technologies for Pulmonary Vein Isolation: The Laser Versus Cryo Study: Laser- Versus CryoBalloon for PVI. *J Cardiovasc Electrophysiol*. 2013;24:987-994.
16. Philips T, Taghji P, El Haddad M, Wolf M, Knecht S, Vandekerckhove Y, Tavernier R, Duytschaever M. Improving procedural and one-year outcome after contact force-guided pulmonary vein isolation: the role of interlesion distance, ablation index, and contact force variability in the 'CLOSE'-protocol. *Europace*. 2018;20:f419-f427.
17. Ciconte G, Sieira-Moret J, Hacioglu E, Mugnai G, Di Giovanni G, Velagic V, Saitoh Y, Conte G, Irfan G, Baltogiannis G, et al. Single 3-minute versus Double 4-minute Freeze Strategy for Second-Generation Cryoballoon Ablation: A Single-Center Experience. *J Cardiovasc Electrophysiol*. 2016;27:796-803.
18. Iacopino S, Mugnai G, Takarada K, Paparella G, Ströker E, De Regibus V, Coutino-Moreno HE, Choudhury R, Abugattas de Torres JP, Brugada P, et al. Second-generation cryoballoon ablation without the use of real-time recordings: A novel strategy based on a temperature-guided approach to ablation. *Heart Rhythm*. 2017;14:322-328.

19. Metzner A, Reissmann B, Rausch P, Mathew S, Wohlmuth P, Tilz R, Rillig A, Lemes C, Deiss S, Heeger C, et al. One-year clinical outcome after pulmonary vein isolation using the second-generation 28-mm cryoballoon. *Circ Arrhythm Electrophysiol*. 2014;7:288–292.
20. Chun KRJ, Stich M, Fürnkranz A, Bordignon S, Perrotta L, Dugo D, Bologna F, Schmidt B. Individualized cryoballoon energy pulmonary vein isolation guided by real-time pulmonary vein recordings, the randomized ICE-T trial. *Heart Rhythm*. 2017;14:495–500.
21. Heeger C-H, Tiemeyer CM, Phan H-L, Meyer-Saraei R, Fink T, Sciacca V, Liosis S, Brüggemann B, Große N, Fahimi B, et al. Rapid pulmonary vein isolation utilizing the third-generation laserballoon - The PhoeniX registry. *Int J Cardiol Heart Vasc*. 2020;29:100576.
22. Verma A, Jiang C, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, et al, STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med*. 2015;372:1812–1822.
23. Chen S, Schmidt B, Bordignon S, Tohoku S, Urbanek L, Plank K, Willems F, Throm C, Konstantinou A, Hilbert M, et al. Cryoballoon pulmonary vein isolation in treating atrial fibrillation using different freeze protocols: The "ICE-T 4 minutes vs 3 minutes" propensity-matched study (Frankfurt ICE-T 4 vs. 3). *J Cardiovasc Electrophysiol*. 2020;31:1923–1931.
24. Dukkipati SR, Neuzil P, Kautzner J, Petru J, Wichterle D, Skoda J, Cihak R, Peichl P, Dello Russo A, Pelargonio G, et al. The durability of pulmonary vein isolation using the visually guided laser balloon catheter: multicenter results of pulmonary vein remapping studies. *Heart Rhythm*. 2012;9:919–925.
25. Bologna F, Bordignon S, Perrotta L, Dugo D, Nagase T, Chen S, De Lazzari M, Chun JK, Schmidt B. Incidence and pattern of conduction gaps after pulmonary vein isolation with the endoscopic ablation system. *J Interv Card Electrophysiol*. 2020;57:465–471.
26. Hussein A, Das M, Riva S, Morgan M, Ronayne C, Sahni A, Shaw M, Todd D, Hall M, et al. Use of Ablation Index-Guided Ablation Results in High Rates of Durable Pulmonary Vein Isolation and Freedom From Arrhythmia in Persistent Atrial Fibrillation Patients: The PRAISE Study Results. *Circ Arrhythm Electrophysiol*. 2018;11:e006576.
27. Chen S, Schmidt B, Bordignon S, Urbanek L, Tohoku S, Bologna F, Angelkov L, Garvanski I, Tsianakas N, Konstantinou A, et al. Ablation index-guided 50 W ablation for pulmonary vein isolation in patients with atrial fibrillation: Procedural data, lesion analysis, and initial results from the FAFA AI High Power Study. *J Cardiovasc Electrophysiol*. 2019;30:2724–2731.
28. Reddy VY, Neuzil P, Koruth JS, Petru J, Funosako M, Cochet H, Sediva L, Chovanec M, Dukkipati SR, Jais P. Pulsed Field Ablation for Pulmonary Vein Isolation in Atrial Fibrillation. *J Am Coll Cardiol*. 2019;74:315–326.
29. Reddy VY, Anter E, Rackauskas G, Peichl P, Koruth JS, Petru J, Funasako M, Minami K, Natale A, Jais P, et al. Lattice-Tip Focal Ablation Catheter That Toggles Between

Radiofrequency and Pulsed Field Energy to Treat Atrial Fibrillation: A First-in-Human Trial. *Circ Arrhythm Electrophysiol.* 2020;13:e008718.

30. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, Kholmovski E, Burgon N, Hu N, Mont L, et al. Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation: The DECAAF Study. *JAMA.* 2014;311:498-506.

Table 1: Patients baseline characteristics

	CB Group	LB Group
Sample size, N	100	100
Age, years	65.0±9.2	66.5±9.4
Male, n	58%	54%
BMI (kg/m ²)	28.3±5.0	28.0±5.6
Hypertension, n	65%	68%
Diabetes II, n	12%	9%
TIA/Stroke, n	2%	4%
Heart failure history, n	1%	2%
Coronary artery disease, n	12%	21%
CHA ₂ DS ₂ -VASc Score	2.0±1.2	2.3±1.4
LA (mm)	39.1±5.3	39.8±5.2
LVEF (%)	61.5±6.1	61.5±5.6
Failed AADs, n	1±0.5	1±0.5

BMI: Body Mass Index, AF: atrial fibrillation, TIA: transient ischemic attack, LA: left atrium, LVEF: left ventricular ejection fraction, AAD: antiarrhythmic drug

Table 2: Procedural data cryoballoon vs. laserballoon

	CB GROUP (N=100)	LB GROUP (N=100)	P VALUE
Real time PVI per vein	90%	-	
Mean time-to-isolation, s	46±29	-	
Mean temperature at isolation, °C	-33±11	-	
Minimal temperature, °C	-49±6	-	
Single shot PVI rate, per vein, %	82%	-	
Total freeze per patient, n	5±1.3	-	
Mean application # per vein, n	-	26±6	
First-pass PVI per vein, n	-	95.7%	
First-pass PVI per patient, n	-	83%	
Minimal ablation energy, watt	-	9.7±2.6	
Maximal ablation energy, watt	-	12±0.8	
Procedural time, min.	50.9±21.0	96.0±20.4	<0.0001
Fluoroscopy time, min.	7.4±4.4	8.4±3.2	0.083
ECV during procedure, n	37 (37%)	43 (43%)	0.386
LCPV (short common vein), n	8 (8%)	9(9%)	0.8
Touch-up ablation using RF, n	2 (RIPV) (2%)	5 (3 RIPV, 1 LSPV, 1 LIPV) (5%)	0.26
Balloon defect, n	0 (0%)	8 (8%)	0.05
LET rise (>39°C) or fall (<15°C), n	18 (18%) LET fall	26 (26%) LET rise	0.17
Additional linear ablation beyond PVI, n	3 CTI ablation (3%)	5 CTI ablation (5%)	0.48



CTI: cavotricuspid isthmus ECV: electrical cardioversion, LCPV: left common pulmonary vein, LET: luminal esophageal temperature, PVI: pulmonary vein isolation, RF-radiofrequency

Table 3: Comparison of procedural adverse events

	CB GROUP	LB GROUP	P
Complications			
Puncture site bleeding requiring intervention, n (%)	0	0	
Vascular laceration, n (%)	0	0	
Tamponade, n (%)	0	0	
Transient PNP, n (%)	7 (7%)	0	0.014
Persistent PNP, n (%)	0 (0%)	2 (both recovery in 3 moths)	0.5
Myocardial infarction, n (%)	0	0	
Stroke, n (%)	0	1 (1%), day 1 after PVI, but complete recovery before discharge	0.99
TIA, n (%)	0		
Atrial-esophageal fistula, n (%)	0	0	
Death, n (%)	0	0	

PNP: phrenic nerve palsy, TIA: transient ischemic attack

Figure Legends:

Figure 1: Flow chart of study showing 1:1 randomization to either Cryoballoon or Laserballoon PVI. Of note, each group consists of 100 patients (PAF: n=50, persistent AF: n=50). AF-atrial fibrillation, CB-cryoballoon, CMAP-compound motor action potential, LB-laserballoon, LET-luminal esophageal temperature, PAF- paroxysmal atrial fibrillation, persAF-persistent atrial fibrillation, PN-phrenic nerve, PV-pulmonary vein, PVI-pulmonary vein isolation, RAO-right anterior oblique, * indicates PVI,

Figure 2: Kaplan Meier curves demonstrating non different rhythm outcome in the overall patient cohort. CB-cryoballoon, LB-laserballoon, ATa – atrial tachyarrhythmia A. Kaplan Meier curves demonstrating non different rhythm outcome in the paroxysmal AF patient cohort. CB-cryoballoon, LB-laserballoon, ATa – atrial tachyarrhythmia. B. Kaplan Meier curves demonstrating non different rhythm outcome in the persistent AF cohort. CB-cryoballoon, LB-laserballoon, ATa – atrial tachyarrhythmia

What Is Known?

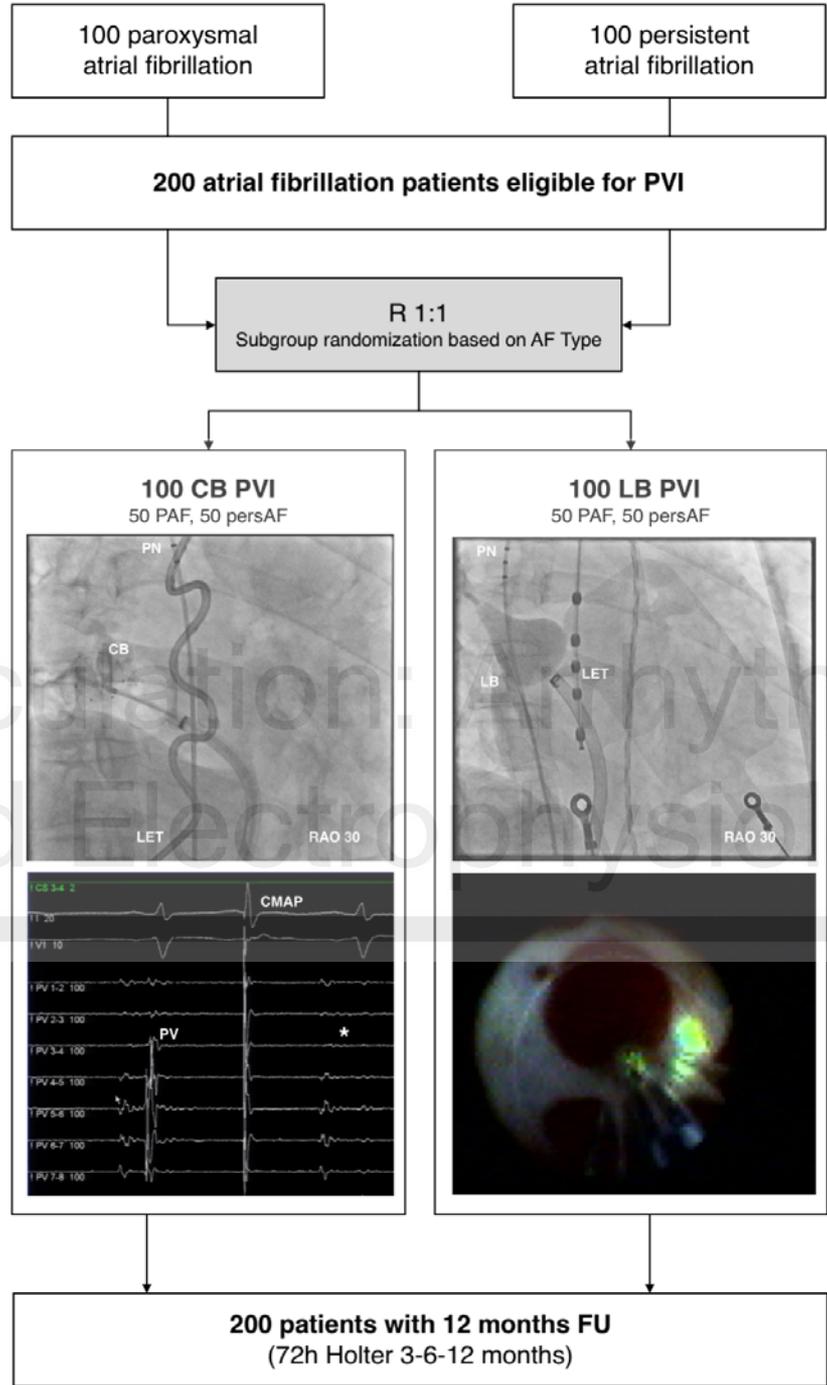
- Pulmonary vein isolation (PVI) is key in catheter ablation of atrial fibrillation (AF)
- Cryo- and Laserballoon PVI has attracted increased attention due to short, safe and less operator dependent procedures along with predictable patient.
- Both balloon devices have been successfully adopted into clinical routine but lack 185 randomized comparisons.

What the Study Adds?

- This prospective randomized study supports the concept of facilitated and efficient balloon PVI in catheter ablation of atrial fibrillation (AF).
- Both, cryo- and laserballoon result in similar favorable procedural safety and rhythm outcome after 12 months
- Procedure times are significantly shorter for the cryoballoon, whereas fluoroscopy exposures are not different.



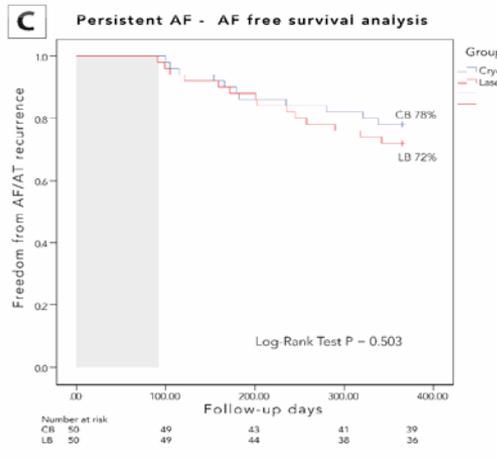
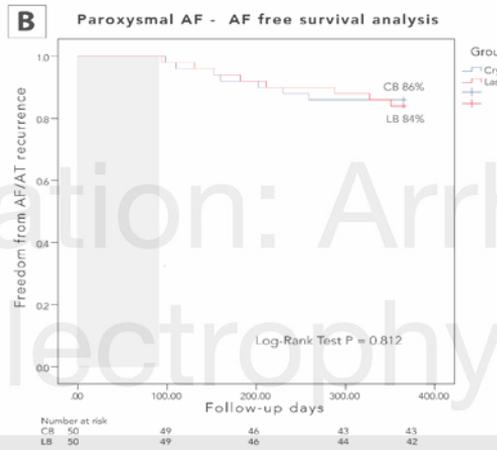
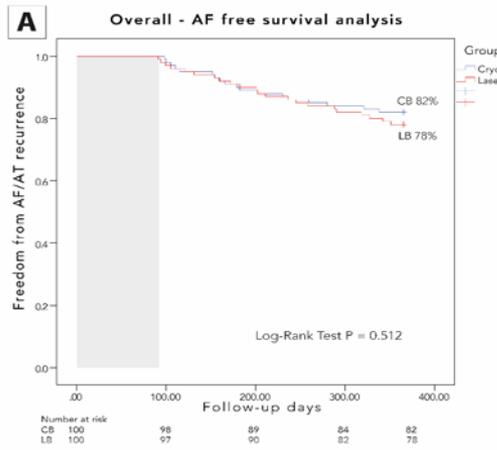
Circulation: Arrhythmia and Electrophysiology



Circulation: Arrhythmia and Electrophysiology



Circulation: Arrhythmia and Electrophysiology



CRYO

100 Cryoballoon PVI
- 50 paroxysmal AF
- 50 persistent AF

50.9±21.0 min*
Procedure time

7.4±4.4 min
Fluoroscopy time

Complications
- 0 PNP
- 7 transient PNP
- 0 Tamponade

200 AF patients
- 100 paroxysmal AF
- 100 persistent AF

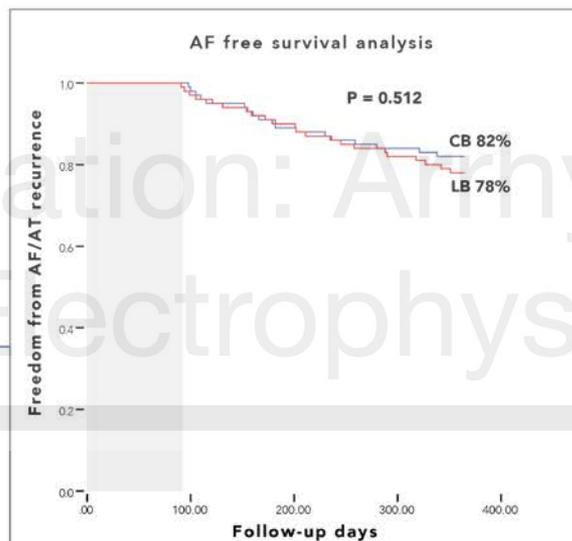
1:1
randomization

100 Laserballoon PVI
- 50 paroxysmal AF
- 50 persistent AF

96.0±20.4 min*
Procedure time

8.4±3.2min
Fluoroscopy time

Complications
- 2 PNP
- 1 TIA
- 0 Tamponade



LASER



* p<0.0001

Downloaded from <http://ahajournals.org> by on January 11, 2021