

**Cryoballoon vs radiofrequency contact force ablation for paroxysmal atrial fibrillation:
a propensity score analysis**

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Abstract

Background. Radiofrequency and cryoballoon pulmonary vein isolation are common approaches for paroxysmal atrial fibrillation (AF) treatment, showing similar results in recent multicenter studies, including heterogeneous tools and protocols. The aim of this study is to compare prospectively in a single, high volume Centre the outcome of paroxysmal AF ablation performed specifically by second generation cryoballoon or contact force radiofrequency ablation.

Methods. Consecutive patients scheduled for paroxysmal AF transcatheter ablation have been included and prospectively followed up. Aiming to reduce potential bias deriving from baseline characteristics, a propensity score matching analysis has been performed to analyze safety and efficacy outcomes.

Results. Out of consecutive patients undergoing AF transcatheter ablation between January 2015 and December 2016, 46 patients approached by cryoablation were matched 1:1 by propensity score to a similar population treated by last generation radiofrequency ablation. Freedom from AF after 12 months (76% vs 78%, $p=0.804$) and incidence of complications (4% vs. 6%, $p=0.168$) did not differ between the two groups. Radiological exposure was higher for the cryoballoon group (11 vs. 4 min, $p<0.001$), while procedural duration did not differ ($p=0.174$). Aiming to assess the potential impact of a learning curve in patients undergoing cryoablation, the first third of patients ($n=15$) were compared to the remaining, reporting longer radiological exposure ($p<0.001$), but similar safety and efficacy.

Conclusion. In this propensity score analysis, last generation cryoballoon and radiofrequency catheters for AF ablation present similar efficacy and safety. Cryoablation requires longer fluoroscopy exposure compared to radiofrequency, although this is reduced by increased experience.

Introduction

Atrial fibrillation (AF) transcatheter ablation is a therapeutic option for rhythm control strategy in patients symptomatic from AF, which is receiving continuously wider recommendations due to its safety and efficacy on the long term compared to antiarrhythmic drug treatment. In particular, AF transcatheter ablation can be proposed for paroxysmal AF when antiarrhythmic drugs fail or are not tolerated, or even as an alternative to antiarrhythmic drug treatment when patients wish not to undergo chronic pharmacological treatment (1).

Conversely to persistent AF, in which the optimal transcatheter ablation approach is still under investigation, as common practice protocols still reach suboptimal results (2-4), the mainstay for paroxysmal AF ablation is pulmonary veins (PV) isolation (5). PV isolation can be effectively achieved through different devices (punctual, circular or balloon catheters) and energy sources (radiofrequency, cryoenergy, laser). Recently, a large multicentre randomized trial enrolling patients with paroxysmal AF compared the two most commonly used energy sources, reporting no difference in terms of 1-year outcome alternatively through radiofrequency or cryoballoon ablation (6). However, in the latter trial the tools employed and compared were not uniform, as a significant amount of patients were not treated by the last generation irrigated radiofrequency catheters, with contact force sensing, (a feature that helps to confirm stable contact with the tissue during radiofrequency application, resulting in reduced procedural and fluoroscopy times and potentially improved safety (7-8)), while few patients were treated with the first-generation cryoballoon.

The aim of our study is to compare prospectively in a single, high volume Centre the safety and efficacy of PV isolation for the treatment of paroxysmal AF by second generation cryoballoon or last generation, contact force, radiofrequency catheters.

Methods

Consecutive patients suffering from paroxysmal AF, as classified by the most recent ESC guidelines (1), referred to the two Electrophysiology Labs (“Città della Salute e della Scienza” Hospital, Turin, Italy, and “Cardinal Massaia” Hospital, Asti, Italy) of our Cardiology Department, between January 2015 and December 2016, for a first procedure of transcatheter ablation have been included in this prospective study. All patients signed written informed consent to undergo the procedure. Clinical characteristics of the population, procedural details and follow-up data have been routinely collected and prospectively included in a data registry.

Ablation procedure

Patients were routinely admitted to the hospital one day before the ablation. The ablation method, radiofrequency or cryoballoon, was decided casually. According to the principle of planning one cryoablation procedure per week, among patients with paroxysmal AF and no previous catheter ablation attempts, patients referred to cryoablation were selected randomly by the administratives of the hospital; the remaining were referred for radiofrequency ablation. Exclusion criteria were: previous ablations, contraindications to anticoagulation, cardiac thrombi.

Oral anticoagulants were continued during the procedure: Warfarin, to maintain an international normalized ratio (INR) between 2 and 3 at the time of the procedure; direct oral anticoagulants were withheld only the morning of ablation and restarted in the evening. Before ablation, a transesophageal echocardiogram was performed in all patients to rule out cardiac thrombi. Magnetic resonance or computerized tomography scan was performed routinely to assess left atrial (LA) dimension, morphology and PVs pattern.

After femoral vascular access, a decapolar electrode catheter was positioned in the coronary sinus. The LA was accessed by transseptal puncture or through a patent foramen ovale, when present. After transseptal puncture, intravenous unfractionated heparin was administered to maintain an

activated clotting time (ACT) of above 350 seconds.

For radiofrequency ablation, a multipolar catheter (Lasso, Biosense Webster, CA, USA) and an irrigated-tip ablation catheter with contact force-sensing (Thermocool SmartTouch or Thermocool SmartTouch SF, Biosense Webster, CA, USA) were advanced into the LA through the same transseptal access. A 3-dimensional reconstruction of the LA and PVs ostia, with the use of an electroanatomic mapping system (Carto 3, Biosense Webster, CA, USA) was performed in all patients and merged to pre-procedural imaging (cardiac CT or MR). The mainstay of the ablation procedure was to obtain complete antral PVs isolation. Contact force was continuously assessed during ablation, and optimal contact was defined as a contact force range between 5-15 g, with stability set as at least 30% of a 6 seconds time interval over a 3 mm spot. Effective isolation was defined by complete elimination of PVs potentials, documented by the circular multipolar catheter.

For patients treated by cryoablation, after accessing the LA with a single transseptal puncture, the cryoballoon (Arctic Front Advance, Medtronic, Minneapolis, USA) including the circular mapping catheter (Achieve, Medtronic, Minneapolis, USA) was advanced in the LA. A 3-dimensional reconstruction of the LA and PVs ostia, with the use of an electroanatomic mapping system (EnSite Precision, St. Jude Medical, Minneapolis, USA) was performed in all patients through the decapolar mapping catheter (Livewire, St Jude Medical, Minneapolis, USA), aiming to identify the PVs ostia, and merged to pre-procedural imaging to reduce radiation exposure. After PVs cannulation with the Achieve catheter, the cryoballoon was placed at each PV ostia, and after confirmation of optimal occlusion through contrast dye injection, cryoenergy was delivered. The protocol included a single, 3-minute lesion in case of optimal parameters (minimal temperature lower than -40°C in 60 seconds and/or and time to isolation shorter than 45 seconds), followed by a bonus freeze of 4 minutes in case of suboptimal parameters, until complete PV isolation is obtained. Right-sided PVs cryoablation was performed during subclavicular vein pacing through the decapolar mapping catheter and continuous phrenic nerve capturing to prevent phrenic nerve palsy. Pacing was performed just

above capture threshold (9), and cryoenergy delivery was interrupted in case of phrenic nerve capture loss, waiting for recovery before continuation of the procedure. Effective isolation was defined by complete elimination of PVs potentials, determined by the circular multipolar catheter.

In case of ineffective isolation of any PV following multiple attempts, touch-up with an alternative punctual radiofrequency ablation catheter) was considered to achieve PV isolation. If concomitant typical atrial flutter was documented, radiofrequency cavo-tricuspid isthmus ablation was performed.

Following the procedure patients were discharged on oral anticoagulation for at least one month, including an antiarrhythmic drug if considered appropriate and tolerated.

Outcomes and follow up

The main outcomes of the study are: acute success in PV isolation, defined as PV isolation 20 minutes after the end of ablation with the pre-defined catheter; safety, measured as the incidence of major complications, defined as life-threatening complications or those requiring interventions or prolonging hospital stay; fluoroscopy time and procedural durations; one-year freedom from arrhythmic recurrences.

Recurrences were detected by routine ambulatory visits (performed at 3, and 12 months and then yearly), with collection of patients' characteristics, symptoms, ECG and 24/48 hours Holter ECG recordings. Arrhythmic recurrences were defined as the presence of documented sustained AF, atypical atrial flutter or atrial tachycardia lasting more than 30 seconds, respecting a blanking period of 3 months following ablation (defined as "early recurrences").

Information concerning pharmacological treatment during follow-up, pattern and duration of eventual arrhythmic recurrences were collected in the same registry during follow-up visits.

Statistical analysis

To reduce the effect of selection bias in the assignment of patients to either group propensity score matching was run on the following baseline characteristics: age, sex, weight, AF duration, hypertension, ischemic heart disease, hypertrophic cardiomyopathy, valvular cardiomyopathy, LA volume and left ventricular ejection fraction (LVEF). Of note, other potential predictors of outcome after AF ablation, as atypical PV pattern, congenital heart disease and obstructive sleep apnea were not included as rare or not specifically stratified in the present population. None of other baseline variables not included in the propensity score (e.g. pharmacological baseline therapy) did anyway report statistically significant values in the two groups. After propensity-score estimation, the two groups were matched 1:1 without replacement (nearest-neighbor algorithm), with a caliper equal to 0.15 of the standard deviation of the logit of the propensity score.

Out of consecutive patients undergoing a first AF transcatheter ablation between January 2015 and December 2016, 46 patients approached by cryoablation were matched 1:1 by propensity score to a similar population treated by radiofrequency ablation. In this model, the P-value of the Hosmer–Lemeshow of goodness of fit was 0.168.

Continuous variables are reported as mean (standard deviation, SD) or median (range), and categorical variables as number (%). Continuous data were compared by one-way ANOVA test, after normal distribution was confirmed. Categorical variables were compared in cross-tabulation tables by Pearson's chi-square test or Fisher's Exact Test. Kaplan Meier curves were used to estimate AF recurrence-free survival over time, stratified by the energy source used.

All tests of significance were two-tailed, and a p value <0.05 was considered statistical significant.

All analyses were performed using SPSS 21.0 (IBM, Armonk, NY, USA).

Results

Baseline characteristics of the two populations after propensity score matching, including overall 92 patients, are described in Table 1. None of the baseline characteristics was different among the two groups. Considering acute efficacy in PV isolation, all patients in the radiofrequency group experienced effective isolation, while in the cryoablation group 3 patients (overall 4 PVs) did not; in these patients PV isolation was finally achieved by radiofrequency touch-up (Table 2).

After a mean follow-up of 12 ± 5 months, no significant difference in AF recurrences was found between the two groups (24% in radiofrequency vs. 22% in cryoablation group, $p=0.804$) (Figure 1). Early recurrences presented a non-significant trend towards relationship to long-term relapses only among the radiofrequency group ($p=0.220$). Radiological exposure was higher for patients in the cryoablation group (11 min vs. 4 min in the radiofrequency group, $p<0.001$; 31.08 Gy/cm^2 in cryoablation vs. 8.42 Gy/cm^2 in radiofrequency group, $p<0.001$), while procedural duration did not differ between the two groups (133 min in radiofrequency vs. 124 min in cryoablation group, $p=0.174$). Concerning complications, the overall incidence was comparable between the two approaches (4% in radiofrequency vs. 6% in cryoablation group, $p=0.168$) (Table 2). However, the pattern of complications was slightly different: in cryoablation group, 2 patients experienced vascular access complications and 1 experienced transient hemoptysis; in radiofrequency group, 1 patient experienced a vascular access complication and 1 pericardial effusion. No life-threatening complications were reported in both groups.

Pulmonary vein anatomy and outcome

The influence of PV anatomy on the outcome of cryoballoon or radiofrequency PV isolation has been analyzed. In particular, 11 (12%) patients presented “atypical” PV anatomy (left common trunk and/or right intermediate PV): no difference in the acute outcome of PV isolation nor in the incidence of follow-up arrhythmic recurrences ($p=0.154$) was found among patients with “atypical” PV anatomy treated by cryoballoon compared to those treated by radiofrequency (Table

3). The only difference was a trend toward lower acute efficacy in achieving isolation of the right inferior PV by cryoballoon compared to radiofrequency (96% vs. 100%, $p=0.307$). Despite similar procedural duration ($p=0.341$), fluoroscopy time was longer for patients treated by cryoballoon compared to radiofrequency ($p<0.001$), also in this subsetting of patients.

Cryoablation learning curve

Of note, this case sample represents the first experience of our Group with cryoballoon ablation. Therefore, aiming to assess the effect of the learning curve on the outcome of cryoballoon ablation, the first third of procedures ($n=15$), were compared to the following ones (Table 4). No difference was found in terms of freedom from AF recurrences ($p=0.720$) and complications ($p=0.327$). However, longer fluoroscopy time was reported within the first cryoablation procedures (15 vs. 9 min, $p<0.001$), along with a non-significant trend towards longer procedural duration (133 vs. 119 min, $p=0.120$) and more need for intraprocedural touch-up due to failure of cryoballoon PV isolation (12% vs. 3%, $p=0.230$), especially related to isolation of the right inferior PV.

Discussion

Efficacy and safety outcomes

The present is a single, high-volume Department prospective study evaluating the outcome of a propensity score adjusted population of paroxysmal AF patients alternatively treated by radiofrequency or cryoballoon ablation of the latest generation. Second generation cryoballoon and radiofrequency contact force catheters proved similar 1-year freedom from AF recurrences after ablation. In the present experience ablation efficacy is overall high compared to previous literature; interestingly this result was achieved exposing patients to a limited dose of fluoroscopy and without affecting safety.

Previous studies have, in fact, compared radiofrequency and cryoballoon AF ablation, as the Fire and Ice multicenter randomized trial (6), however including a large amount of patients treated by previous generation catheters. Another German multicenter registry (10) and a recent meta-analysis (11), also assessed this topic; however, by not including specifically last generation catheters, as second generation cryoballoon has shown improved outcome compared to the first (12), and improved outcome has also been documented in published experiences on contact force catheters compared to the previous generations (13-14), these studies potentially encompass bias. On the other side a study by Squara et al. (15), including patients treated only with second generation cryoballoon and contact force radiofrequency catheters, reported results similar to ours in terms of both efficacy and complications; due to the observational design, however, several differences among baseline population characteristics were reported, and their impact on the results is unknown.

Of note, isolated early recurrences, frequently described as a transient irritative consequence of transcatheter ablation (16), presented a non-significant difference among the two groups. It is known that radiofrequency relates to a traumatic effect on the atrial tissue structure, resulting in local inflammation and isolated early recurrences during the first months following the procedure.

Cryoablation, conversely, presents a more gentle biological effect, potentially limiting irritative effects (17). However, in the present experience patients in both groups suffered isolated early recurrences, suggesting the presence of a certain amount of myocardial inflammation, probably related to the physical contact with the tissue requested to achieve PVs occlusion, also following cryoballoon ablation.

Interestingly, atypical PV patterns were not related to worse acute or mid-term outcome in radiofrequency nor in cryoballoon groups. This finding confirms, as previously described by other Authors (18-19) also with alternative “one-shot” ablation tools (20), that experienced operators, guided by pre-procedural anatomy definition, can manage all PV anatomies indifferently with mostly all commonly used ablation tools. The only mark related to PV anatomy is that in 3 patients the right inferior PV could not be isolated by cryoballoon. Although not resulting statistically significant, and being most probably related to the learning curve in cryoballoon ablation (therefore potentially reducible by operators’ experience), this finding warrants consideration.

Concerning safety, the overall incidence of complications did not differ between the two technologies. None of the patients experienced life-threatening complications; more in details, in the cryoballoon group there were mainly vascular access-related complications, likely due to the larger diameter of the cryoballoon catheter. These results confirm the findings of previous larger studies, reporting a similar overall incidence of complications (6,13,14,21). Of note, none of our patients experienced phrenic nerve palsy. The explanation may rely on the phrenic nerve monitoring method, as we performed just above threshold subclavicular vein pacing (9) during right-sided PV isolation: this, in our opinion, results in an earlier alert that corresponds to only tangential nerve damage, strongly limiting, if not eliminating, the potential risk of persistent phrenic nerve palsy.

Fluoroscopy and procedural times

Radiofrequency ablation procedures were characterized by significantly shorter fluoroscopy times, compared to cryoballoon ablation. This finding has already been reported (6), while other studies found no significant difference between the two technologies (12-13). The generally lower exposure related to radiofrequency ablation can likely be explained by the strong synergy of this approach with the electroanatomic mapping systems, enabling, in highly trained Centers, “nearly-zero fluoroscopy” ablation procedures (22-23). Conversely, cryoablation usually requires X-ray monitoring for manipulation, or at least, as in our study, for confirming PV occlusion by venography. Therefore, despite a significant reduction in fluoroscopy time was described with second generation catheters and increased operators experience, X-ray exposure probably cannot be reduced below a certain level (24).

Overall procedural duration did not differ between the two technologies. Previous studies reported shorter procedural duration for cryoablation, as the balloon-based technology may help to obtain isolation faster than point-by-point technologies (6,12-15). The divergence of our study in this respect most likely relies on two factors. The first is that a 3-dimensional reconstruction of the LA and PVs ostia was performed, to minimize radiation exposure, also in the cryoballoon ablation group. This indeed permits to navigate the circular mapping catheter outside the distal cryoballoon without continuous fluoroscopy but requires additional mapping time. In our opinion, this investment in time is anyway counterbalanced by the clear reduction of radiation exposure that reflects in reduced risks for both patients and operators (25-26).

The second is the inclusion of the first operator’s experience with cryoballoon, although in a Department highly trained in radiofrequency, point-by-point AF ablation. The role of the learning curve in cryoballoon ablation may therefore have impacted the results of this study producing longer procedural time, along with the need in some patients of touch-up radiofrequency applications to reach PV isolation. Given this, safety and freedom from AF recurrences among the

first cryoablation patients did not differ from the following ones. This finding underlines the relatively steep learning curve with cryoballoon ablation (27), most probably impacting on top of the need of touch-up to complete PV isolation (in particular regarding the right inferior PV), only secondary endpoints, as fluoroscopy time and, procedural duration. In fact, the large extension of cryoballoon-induced fibrosis at PV ostia (28) renders PV isolation potentially more reproducible and durable (29) with second generation cryoballoon compared to point-by-point radiofrequency ablation, resulting in a favorable outcome even in case of limited experience.

Limitations

First, the limited study size may bound the strength of the results, in particular referring to statistical relevance of infrequent features such as procedural complications. Additionally, the non-randomized design does not exclude the risk of bias in scheduling patients for each of the alternative procedures; although propensity score matching limits this issue, the optimal study design remains a randomized controlled trial. On the other side, the uniformity related to enrollment in a single Department potentially reduces bias introduced by multiple Centers preferences and procedural heterogeneities, leading to a standardized work flow in patients' clinical evaluation, selection, procedural details and follow-up evaluations.

Finally, the extensive use of mapping systems to reduce radiological exposure implies a slight prolongation in procedural duration along with a variable (center-dependent) increase in procedural costs. However, the low incidence of complications, in particular the absence of thromboembolic events or tamponade, underlines the high safety profile of the procedure.

Conclusion

Second generation cryoballoon and last generation radiofrequency contact force ablation are equally effective in the mid-term for the treatment of paroxysmal AF, interestingly this result may be achieved by exposing patients to employing a very limited dose use of fluoroscopy and with very high safety profile.

Cryoablation may rarely fail to isolate right inferior PV and requires longer fluoroscopy exposure compared to radiofrequency ablation,, both this aspects, however, relate to operators' experience.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

References

1. Kirchhof P, Benussi S, Kotecha D et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-2962.
2. Gaita F, Caponi D, Scaglione M et al. Long-term clinical results of 2 different ablation strategies in patients with paroxysmal and persistent atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2008;1(4):269-75.
3. Verma A, Mantovan R, Macle L et al. Substrate and Trigger Ablation for Reduction of Atrial Fibrillation (STAR AF): a randomized, multicentre, international trial. *Eur Heart J*. 2010;31(11):1344-56.
4. Verma A, Jiang CY, Betts TR et al; STAR AF II Investigators. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med*. 2015;372(19):1812-22.
5. Calkins H, Kuck KH, Cappato R et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace*. 2012;14(4):528-606.
6. Kuck KH, Brugada J, Fürnkranz A et al; FIRE AND ICE Investigators. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med*. 2016;374(23):2235-45.
7. Stabile G, Solimene F, Calò L et al. Catheter-tissue contact force values do not impact mid-term clinical outcome following pulmonary vein isolation in patients with paroxysmal atrial fibrillation. *J Interv Card Electrophysiol*. 2015;42(1):21-6

8. Stabile G, Solimene F, Calò L et al. Catheter-tissue contact force for pulmonary veins isolation: a pilot multicentre study on effect on procedure and fluoroscopy time. *Europace*. 2014;16(3):335-40.
9. Ghosh J, Singarayar S, Kabunga P, McGuire MA. Subclavian vein pacing and venous pressure waveform measurement for phrenic nerve monitoring during cryoballoon ablation of atrial fibrillation. *Europace*. 2015;17(6):884-90.
10. Schmidt M, Dorwarth U, Andresen D et al. Cryoballoon vs. radiofrequency ablation in paroxysmal atrial fibrillation--One-year outcome data. *Heart Rhythm*. 2016;13(4):836-44.
11. Cardoso R, Mendirichaga R, Fernandes G et al. Cryoballoon versus Radiofrequency Catheter Ablation in Atrial Fibrillation: A Meta-Analysis. *J Cardiovasc Electrophysiol*. 2016;27(10):1151-1159.
12. Fürnkranz A, Bordignon S, Dugo D et al. 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(8):840-4.
13. Reddy VY, Dukkipati SR, Neuzil P et al. Randomized, Controlled Trial of the Safety and Effectiveness of a Contact Force-Sensing Irrigated Catheter for Ablation of Paroxysmal Atrial Fibrillation: Results of the TactiCath Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) Study. *Circulation*. 2015;132(10):907-15.

14. Stabile G, Solimene F, Calò L et al. Catheter-tissue contact force for pulmonary veins isolation: a pilot multicentre study on effect on procedure and fluoroscopy time. *Europace*. 2014;16(3):335-40.
15. Squara F, Zhao A, Marijon E et al. Comparison between radiofrequency with contact force-sensing and second-generation cryoballoon for paroxysmal atrial fibrillation catheter ablation: a multicentre European evaluation. *Europace*. 2015;17(5):718-24.
16. Oral H, Knight BP, Ozaydin M et al. Clinical significance of early recurrences of atrial fibrillation after pulmonary vein isolation. *J Am Coll Cardiol*. 2002;40(1):100-4.
17. Andrade JG, Khairy P, Dubuc M. Catheter cryoablation: biology and clinical uses. *Circ Arrhythm Electrophysiol*. 2013;6:218–27.
18. Khoueiry Z, Albenque JP, Providencia R et al. Outcomes after cryoablation vs. radiofrequency in patients with paroxysmal atrial fibrillation: impact of pulmonary veins anatomy. *Europace*. 2016;18(9):1343-51.
19. Anselmino M, Scaglione M, Blandino A et al. Pulmonary veins branching pattern, assessed by magnetic resonance, does not affect transcatheter atrial fibrillation ablation outcome. *Acta Cardiol*. 2010;65(6):665-74.
20. Stabile G, Anselmino M, Soldati E et al. Effect of left atrial volume and pulmonary vein anatomy on outcome of nMARQ™ catheter ablation of paroxysmal atrial fibrillation. *J Interv Card Electrophysiol*. 2017;48(2):201-207.

21. Mugnai G, Irfan G, de Asmundis C et al. Complications in the setting of percutaneous atrial fibrillation ablation using radiofrequency and cryoballoon techniques: A single-center study in a large cohort of patients. *Int J Cardiol.* 2015;196:42-9.
22. Scaglione M, Biasco L, Caponi D et al. Visualization of multiple catheters with electroanatomical mapping reduces X-ray exposure during atrial fibrillation ablation. *Europace.* 2011;13(7):955-62.
23. Gaita F, Guerra PG, Battaglia A, Anselmino M. The dream of near-zero X-rays ablation comes true. *Eur Heart J.* 2016;37(36):2749-2755.
24. Reissmann B, Maurer T, Wohlmuth P et al. Significant reduction of radiation exposure in cryoballoon-based pulmonary vein isolation. *Europace.* 2017 Apr 7. [Epub ahead of print]. doi: 10.1093/europace/eux066.
25. Andreassi MG, Piccaluga E, Guagliumi G, Del Greco M, Gaita F, Picano E. Occupational Health Risks in Cardiac Catheterization Laboratory Workers. *Circ Cardiovasc Interv.* 2016;9(4):e003273.
26. Casella M, Dello Russo A, Pelargonio G et al. Near zero fluoroscopic exposure during catheter ablation of supraventricular arrhythmias: the NO-PARTY multicentre randomized trial. *Europace.* 2016;18(10):1565-1572.
27. Velagić V, de Asmundis C, Mugnai G et al. Learning curve using the second-generation cryoballoon ablation. *J Cardiovasc Med (Hagerstown).* 2017;18(7):518-527.

28. Kenigsberg DN, Martin N, Lim HW, Kowalski M, Ellenbogen KA. Quantification of the cryoablation zone demarcated by pre- and postprocedural electroanatomic mapping in patients with atrial fibrillation using the 28-mm second-generation cryoballoon. *Heart Rhythm*. 2015;12(2):283-90.
29. Ciconte G, Velagić V, Mugnai G et al. Electrophysiological findings following pulmonary vein isolation using radiofrequency catheter guided by contact-force and second-generation cryoballoon: lessons from repeat ablation procedures. *Europace*. 2016;18(1):71-7.

Tables and Figures

Table 1. Baseline characteristics of the study population after propensity score matching.

	Radiofrequency (n=46)	Cryoballoon (n=46)	p-value
Age, years (SD)	59 (9)	59 (9)	0.946
Males, n (%)	38 (82)	36 (78)	0.471
Weight, kg (SD)	79 (12)	78 (11)	0.730
Height, cm (SD)	175 (9)	174 (8)	0.804
AF during ablation, n (%)	14 (30)	9 (20)	0.229
AF duration, months (SD)	51 (57)	57 (51)	0.585
AF burden, episodes/year	6 (10)	4 (7)	0.213
Hypertension, n (%)	21 (46)	21 (46)	1.00
Hyperthyroidism, n (%)	1 (2)	2 (4)	0.557
Hypothyroidism, n (%)	2 (4)	4 (9)	0.398
Diabetes, n (%)	3 (7)	3 (7)	1.000
Heart failure, n (%)	2 (4)	1 (2)	0.557
Previous TIA/stroke, n (%)	1 (2)	0 (0)	0.315
Gastropathy, n (%)	8 (18)	13 (28)	0.182
Sick sinus syndrome, n (%)	4 (8)	5 (11)	0.238
Hypertrophic cardiomyopathy, n (%)	0 (0)	0 (0)	-
Coronary artery disease, n (%)	3 (7)	3 (7)	1.000
Valvular cardiomyopathy, n (%)	1 (2)	1 (2)	1.000
Obstructive sleep apnea, n (%)	0 (0)	0 (0)	-
Antiarrhythmic drugs (baseline),	38 (83)	43 (93)	0.135
Class Ic, n (%)	27 (59)	29 (63)	0.669
Amiodarone, n (%)	7 (15)	9 (20)	0.582
Sotalol, n (%)	3 (7)	6 (13)	0.292
Quinidine, n (%)	1 (2)	0 (0)	0.315
Oral anticoagulants (baseline),	37 (81)	38 (83)	0.887
Warfarin, n (%)	27 (59)	31 (67)	0.388

DOAC, n (%)	10 (22)	7 (15)	0.420
Beta-blockers (baseline), n (%)	24 (52)	26 (57)	0.675
LA volume, ml (SD)	69 (21)	70 (15)	0.816
LVEF, % (SD)	61 (6)	61 (5)	0.858

SD: standard deviation; AF: atrial fibrillation; TIA: transient ischaemic attack. DOAC: direct oral anticoagulants; LA: left atrium; LVEF: left ventricular ejection fraction.

Table 2. Procedural characteristics and follow-up findings of the study population. PV isolation refers to acute isolation with the originally employed ablation catheter (without crossover)

	Radiofrequency (n=46)	Cryoballoon (n=46)	p-value
LSPV isolation, n (%)	46/46 (100)	46/46 (100)	1.000
LIPV isolation, n (%)	44/44 (100)	42/43 (98)	0.398
RSPV isolation, n (%)	46/46 (100)	45/46 (98)	0.315
RIPV isolation, n (%)	46/46 (100)	44/46 (96)	0.307
Right isthmus, n (%)	12 (26)	5 (11)	0.011
Procedural time, min (SD)	133 (35)	124 (30)	0.174
Fluoroscopy time, min (SD)	4.1 (3)	11 (5)	<0.001
Radiation exposure, Gy/cm ² (SD)	8.42 (5.02)	31.08 (11.41)	<0.001
Complications, n (%)	2 (4)	3 (6)	0.168
Follow-up, months (SD)	12 (6)	12 (5)	0.655
Recurrences, n (%)	11 (24)	10 (22)	0.804
Recurrences with drugs, n (%)	7 (15)	5 (11)	0.536
Early recurrences, n (%)	5 (10)	2 (4)	0.220
Antiarrhythmic drugs (follow-up),	26 (57)	36 (78)	0.116
Class Ic, n (%)	17 (37)	23 (50)	0.207
Amiodarone, n (%)	6 (13)	6 (13)	1.000
Sotalol, n (%)	3 (7)	8 (17)	0.108
Oral anticoagulants (follow-up),	16 (35)	22 (47)	0.204
Warfarin, n (%)	9 (20)	14 (30)	0.229
DOAC, n (%)	7 (15)	8 (17)	0.778
Beta-blockers (baseline), n (%)	28 (61)	23 (50)	0.201

SD: standard deviation; AF: atrial fibrillation; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein; DOAC: direct oral anticoagulants.

Table 3. Procedural details and follow-up of patients presenting “atypical” PV anatomies (left common trunk and/or right intermediate accessory PV), stratified according to the type of ablation procedure.

	Overall (n=11)	Radiofrequency (n=6)	Cryoballoon (n=5)	p-value
Left common trunk, n (%)	5 (45)	2 (33)	3 (60)	-
Left common trunk isolation, n (%)	11 (100)	(100)	(100)	-
Right intermediate PV, n (%)	7 (64)	5 (83)	2 (40)	-
Right intermediate PV isolation, n (%)	7 (100)	(100)	(100)	-
RSPV isolation, n (%)	11/11 (100)	6/6 (100)	5/5 (100)	-
RIPV isolation, n (%)	11/11 (100)	6/6 (100)	5/5 (100)	-
All PVs isolation, n (%)	11/11 (100)	6/6 (100)	5/5 (100)	-
Procedural time, min (SD)	118 (20)	125 (25)	112 (16)	0.341
Fluoroscopy time, min (SD)	7 (5)	11.7 (3.5)	2.7 (1.8)	<0.001
Complications, n (%)	0 (0)	0 (0)	0 (0)	-
Recurrences, n (%)	2 (18)	0 (0)	2 (33)	0.154
Recurrences with drugs, n (%)	1 (9)	0 (0)	1 (17)	0.338
Early recurrences, n (%)	3 (27)	1 (20)	2 (33)	0.303

PV: pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein; SD: standard deviation.

Table 4. Comparison between the acute and mid-term outcome of the first 15 patients treated with cryoballoon ablation (learning curve) and the following 30 patients (ordinary procedures). PV isolation refers to acute isolation with the originally employed ablation catheter (without crossover)

	Learning curve (n=15)	Ordinary procedures (n=31)	p-value
Age, years (SD)	61.9 (8)	57.1 (9)	0.087
Males, n (%)	9 (60)	27 (87)	0.057
AF duration, months (SD)	46.9 (46)	61.7 (53)	0.366
Hypertension, n (%)	8 (53)	13 (42)	0.467
Diabetes, n (%)	2 (13)	1 (3)	0.193
Heart failure, n (%)	0 (0)	1 (3)	0.482
Coronary artery disease, n (%)	1 (7)	2 (7)	0.978
Valvular cardiomyopathy, n (%)	1 (7)	1 (3)	0.592
LA volume, ml (SD)	72 (16)	69 (16)	0.533
LVEF, % (SD)	62 (3)	61 (6)	0.860
LSPV isolation, n (%)	16/16 (100)	31/31 (100)	-
LIPV isolation, n (%)	14/15 (93)	28/28 (100)	0.734
RSPV isolation, n (%)	14/15 (93)	31/31 (100)	0.146
RIPV isolation, n (%)	13/15 (87)	30/31 (97)	0.193
RF use, n (%)	2/15 (13)	1/31 (3)	0.168
Procedural time, min (SD)	132 (29)	120 (30)	0.230
Fluoroscopy time, min (SD)	15 (5)	8.9 (3)	<0.001
Radiation exposure, Gy/cm ² (SD)	44.15 (19.13)	21.74 (9.72)	<0.001
Complications, n (%)	1 (7)	3 (10)	0.327
Recurrences, n (%)	3 (20)	7 (22)	0.842
Recurrences with drugs, n (%)	1 (7)	4 (13)	0.524

SD: standard deviation; AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LSPV: left superior pulmonary vein; LIPV: left inferior pulmonary vein; RSPV: right superior pulmonary vein; RIPV: right inferior pulmonary vein; RF: radiofrequency.

Figure legends

Figure 1. Kaplan-Meier estimate of overall freedom from arrhythmic recurrences after 1 year (A), and patients AF-free with antiarrhythmic drug treatment (B), according to the technology used for catheter ablation.

