Title: Optimal single procedure strategy of pulmonary vein isolation with cryoballoon or radiofrequency and non-pulmonary vein triggers ablation for non-paroxysmal atrial fibrillation

Giichi Nitta[a], MD, Junichi Nitta[b], MD, PhD, Osamu Inaba[a], MD, PhD, Akira Sato[a], MD, Yukihiro Inamura[a], MD, PhD, Tomomasa Takamiya[a], MD, PhD, Masahiko Goya[c], MD, PhD, Tetsuo Sasano[c], MD, PhD

[a]Department of Cardiology, Japanese Red Cross Saitama Hospital, 1-5 Shintoshin, Chuo-ku, Saitama 330-8553, Japan

[b]Department of Cardiology, Sakakibara Heart Institute, 3-16-1 Asahi-cho, Fuchu-city, Tokyo 183-0003, Japan

[c]Department of Cardiovascular Medicine, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113-8519, Japan

Corresponding author:

Giichi Nitta, MD

Department of Cardiology, Japanese Red Cross Saitama Hospital

1-5 Shintoshin, Chuo-ku, Saitama 330-8553, Japan

Tel.: 81488521111

Fax: 81488523120

E-mail: gi1nitta@yahoo.co.jp

Declaration of interest: none

Funding sources: None.

Abstract

Introduction: Limited data exist on pulmonary vein isolation (PVI) using cryoballoon (CB) or radiofrequency (RF) ablation and additional non-pulmonary vein triggers ablation for non-

paroxysmal atrial fibrillation (non-PAF). The objective of this study was to assess the outcomes of first-stage catheter ablation for non-PAF patients.

Methods and Results: Initial PVI was performed on 734 non-PAF patients (age: 64±10 years; male: 584) between September 2014 and June 2018 [315 (43%), CB ablation; 419 (57%), RF catheter]. A logistic regression model was used to match 257 pairs (514 patients) according to propensity scores (CB group or RF group). After PVI, additional non-PV triggers ablation was performed if induced by isoproterenol. We analyzed the clinical outcomes of both groups. The mean procedural time was significantly shorter in the CB group (125 [range, 89–165] min) than in the RF group (190 [160–224] min; $P < 0.001$). The 1-year Kaplan-Meier event rate revealed similar atrial fibrillation-free survival rate between the groups (CB: 77.9%, RF: 82.3%; log-rank $P = 0.111$). The additional ablation percentage for non-PV foci (CB: 39%, RF: 41%; $P = 0.653$) and the complications incidence (CB: 5%, RF: 4%; $P = 0.670$) were also similar.

Conclusion: In non-PAF patients, PVI using CB or RF ablation and non-PV triggers ablation achieved comparable outcomes. The safety and efficacy of the combination strategy of PVI and non-PV triggers ablation was demonstrated.

Keywords: Catheter ablation, non-paroxysmal atrial fibrillation, success rate, cryoballoon, radiofrequency, non-pulmonary vein trigger

Introduction

Atrial fibrillation (AF) is associated with considerable morbidity and mortality possibly causing stroke or heart failure. Progression from paroxysmal AF (PAF) to non-PAF worsens clinical outcomes.[1] Catheter ablation (CA) for AF is an established sinus rhythm maintenance treatment without antiarrhythmic drugs (AADs).[2,3] Pulmonary vein isolation (PVI) is a standard strategy to eliminate AF triggers originating from the pulmonary vein (PV), and additional ablation for non-PV triggers has also been proven effective. The main methods of PVI are radiofrequency (RF) or cryoballoon (CB) ablation. RF ablation is applied by a point-by-point heating technique, whereas CB ablation is applied by a simple-step freezing technique. Kuck et al. reported the non-inferiority of CB ablation over RF ablation regarding PAF efficacy and safety.[4] Recent studies have demonstrated the efficacy of PVI and ablation of additional non-PV triggers with RF for non-PAF.[5,6,7] Nevertheless, the PVI with CB ablation combination strategy for non-PAF has not been established.[8-12] We hypothesized that this single procedure of PVI with CB or RF and non-PV triggers ablation beyond PVI for non-PAF patients could be safe and effective because it is already established for PAF.

Methods

Study design and patient selection

This single-center retrospective cohort study (September 2014-June 2018) included 2131 patients with AF undergoing initial PVI. AF was classified as PAF or non-PAF, and non-PAF was further divided into persistent AF (continuous AF >7 days, <1 year) or long-standing persistent AF (uninterrupted AF ≥1 year), defined by the current guidelines and depending on AF duration.[2,3] All non-PAF patients were eligible. Patients who underwent repeat CA or surgical ablation or CA for procedures other than RF or CB ablation for initial PVI; without exact follow-up data; or on hemodialysis were excluded. Exclusion criteria were left atrium thrombus (LA) or left atrial appendage (LAA), abnormal thyroid function, or any procedural contraindications. All patient data were obtained from an institutional database.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. This study was approved by the Japanese Red Cross Saitama Hospital's institutional review board. Written informed consent was obtained from all patients.

Procedural management

Procedural management at our hospital has been reported.[7, 10-17] Blood tests, chest radiography, and electrocardiography were performed preoperatively. Transthoracic echocardiography and contrast-enhanced computed tomography (CT) with three-dimensional LA construction were performed as cardiac function and structural abnormality-assessment screening tests and to help

the physicians choose between CB and RF ablation based on the PV or LA anatomies. Physicians estimated that PVI completion would be difficult with the CB ablation occlusion technique in patients with a common PV stem, with altered PV diameter, and with remodeling-related LA or LA antrum enlargement. All non-PAF patients underwent transesophageal echocardiography for intra-cavitary thrombi absence confirmation, especially with LA or LAA, within a week preoperatively. Oral anticoagulants were taken for at least 1 month, and AADs were discontinued for at least 1 week preoperatively. Warfarin was continued throughout the procedure for achieving an international normalized ratio of 2–3; oral anticoagulant administration was also continued. Patients continued taking oral anticoagulants for at least 3 months and proton-pump inhibitors for 2 months post-procedure. All procedures included initial PVI as the procedural endpoint and were performed with patients under deep midazolam and pentazocine-induced sedation and with continuous propofol infusion. A 6-French (Fr) 20-pole 4-site mapping catheter (2-, 8-, 2-, and 8-pole for the superior vena cava [SVC], right atrium, coronary sinus [CS] ostium, and CS, respectively) (BeeAT Cath; Japan Lifeline, Tokyo, Japan) was inserted through the right subclavian vein into the CS as a pacing, recording, and intracardiac defibrillation diagnostic catheter during CA. The mapping catheter's distal portion was placed in the CS and cavotricuspid isthmus; with the proximal portion in the crista terminalis and SVC. The CA protocol was described recently.[7,14,17] In patients undergoing PVI with RF, an 8.5-Fr long sheath

(SL0; Abbott Medical, Minneapolis, MN, USA) and 11.5-Fr steerable sheath (Agilis; Abbott Medical) were inserted through the right femoral vein, whereas an 8.5-Fr long sheath (SL0) and a 15-Fr steerable sheath (FlexCath Advance; Medtronic, Minneapolis, MN, USA) were inserted in patients undergoing PVI with CB ablation. The arterial line was inserted through the right femoral artery to monitor blood pressure. A transseptal puncture was performed using the modified Brockenbrough fluoroscopic guidance technique and an RF needle (powered transseptal needle; Japan Lifeline). Subsequently, a heparin bolus and continuous infusion were administered to achieve an activated clotting time of 300–350 s during the procedure. A temperature probe (SensiTherm Multi Probe; Abbott Medical) was inserted through the nasal cavity and positioned within the esophagus to monitor esophageal temperatures during the procedure.

Cryoballoon ablation

Post-transseptal puncture, a 15-Fr steerable long sheath (FlexCath Advance; Medtronic) was inserted into the LA. A 28-mm second-generation CB (Arctic Front Advance; Medtronic) was placed in the LA via the steerable sheath by inserting a spiral 20-mm mapping catheter (Achieve; Medtronic) to the summit. A 10-polar circular mapping catheter (Inquiry; Abbott Medical) was positioned in the SVC via the other 8.5-Fr long sheath (SL0). The CB was inflated near the

ostium of each PV, and a circular mapping catheter was positioned into the PV. The degree of PV occlusion was confirmed by contrast medium injection. Freezing was started following CB application with a cycle of 180–240 s. During the freezing of the right PVs, phrenic nerve pacing was stimulated, and freezing was immediately terminated in the case of phrenic palsy, if the CB temperature fell below -60°C or that of the esophagus fell below 15°C. The PVI procedure endpoint was defined as proof of the bidirectional conduction block between each PV and LA indicated by the absence of both local PV potentials (entrance block) and local capture of the PV during LA pacing (exit block) confirmed by the spiral mapping catheter in each PV and the 20-pole 4-site mapping catheter in the CS. One or more bonus freezing was performed at the physician's discretion when PVI was not completed or the required PVI complete time was >60 s. In cases of PVI failure with the CB, additional PV touch-up ablation was performed using a non-irrigation RF catheter (Thermocool [Biosense Webster], Flexibility [Abbott Medical], CoolPath [Abbott Medical], or Ablaze [Japan Lifeline]).

Radiofrequency ablation

Post-transseptal puncture, the 8.5-Fr long sheath (SL0) and 11.5-Fr steerable sheath (Agilis; Abbott Medical) were inserted into the LA. Pulmonary venography and esophagography were performed with contrast medium injection for the anatomical position and the PV, LA, and

esophagus relationship assessment. A 10- or 20-polar circular mapping catheter (Inquiry; Abbott Medical or Lasso; Biosense Webster) was positioned in the LA via an 8.5-Fr long sheath (SL0) while an irrigated ablation catheter with a 3.5-mm tip, with or without contact-force sensing (Thermocool [Biosense Webster]; Flexibility [Abbott Medical]; and CoolPath [Abbott Medical]) was positioned. All RF procedures were performed under three-dimensional electroanatomic mapping system (CARTO system; Biosense Webstar or Ensite NavX system; Abbott Medical) guidance. Before starting CA, cardioversion was attempted for sinus rhythm-restoration in most patients. Extensive encircling PVI (EEPVI) or PVI plus LA posterior wall isolation was performed at the physician's discretion. PVI plus LA posterior wall isolation included wide antral circumferential PVI with posterior lines extending to the LA posterior wall mid portion. A single vertical LA posterior wall line was drawn with the right posterior wall line adjacent to the left posterior wall line on the left or right side of the esophagus to avoid procedural esophageal injury. This approach of PVI plus LA posterior wall isolation (PWI) can potentially isolate a larger PV antrum area and a part of the LA posterior wall compared to that of EEPVI and PVI with the CB. RF energy was the output of the point-by-point technique under fluoroscopic guidance, the three-dimensional mapping system, and the local voltage on the intracardiac electrocardiogram. The energy (25–35 W) or ablation time (20–30 s) was adjusted according to the regions (each aspect of the PV or LA posterior wall). If dormant conduction of the PV was

confirmed after intravenous adenosine administration, additional electrical reconnection ablation was performed. The endpoint of EEPVI or PVI plus LA PWI was defined as proof of the bidirectional conduction block and PVI with the CB. This method has been described previously.[7,14,15]

Induction and additional ablation for non-PV triggers

Upon completion of PVI (CB or RF), non-PV trigger induction was attempted by continuous high-dose intravenous isoproterenol infusion and atrial burst pacing. Non-PV triggers were defined as the origin of the atrial premature beats, which initiate AF or focal atrial tachycardia (AT) and appear to have a short-run pattern (> 3 beats). After induction, both groups underwent additional ablation for non-PV triggers. The isoproterenol protocol for inducing non-PV triggers has been reported.[7,13-16] In some cases of non-PV triggers from the LA being induced or if additional touch-up RF ablation for the PV was needed post-CB ablation, additional PVI plus PWI with the RF catheter was performed at the physician's discretion.

Follow-up

All patients continued anticoagulants (≥ 3 months), depending on their $CHADS_2$ score. Atrial tachyarrhythmia within a blanking period within 3 months post-procedure was not regarded as a

recurrence instance. Any atrial tachyarrhythmia lasting 30 s following the blanking period was regarded as recurrence. Maintaining sinus rhythm without AAD use was defined as clinical success. All patients were followed up at our hospital for 2–3 weeks post-discharge, every 1–3 months up to 12 months, and every 6 months thereafter. Intensive interviews were obtained and 12-lead electrocardiograms performed at each time-point, with 24-h Holter monitor recordings performed at 3 and 12 months. Patients were asked to call or visit our hospital on experiencing arrhythmia recurrence symptoms. CT was performed to evaluate PV stenosis 12 months post-CA. Our primary endpoint was freedom from AF/AT recurrence at 1 year following the initial procedure in both groups, and the recurrence factors were assessed.

Statistical analyses

Propensity score matching using logistic regression was performed to reduce basal characteristic differences between CB or RF ablation patients based on age, sex, type of AF, presence of hypertension, diabetes mellitus, cerebral infarction, and congestive heart failure, LA diameter (LAD), and body mass index (BMI). Nearest-neighbor matching without replacement was performed, and score-matched pairs identical to the first two decimal places were used in the analyses. To compare baseline characteristics, Mann-Whitney U test, Student's t-test, and chi-square test were performed. Data are summarized as mean±standard deviation or median [25^{th} and 75^{th} percentiles (%)]. The Kaplan-Meier method was used to calculate 1-year event rate estimates, and the log-rank test was used to analyze between-group treatment efficacy. Predictors

of AF recurrence were evaluated using univariate and multivariate Cox hazard regression analyses. Values were assessed using linear univariate and multivariate regression analyses. The associated variables in the univariate analysis ($P \leq 0.10$) were entered into the final multivariate model. Analyses were performed using the R software program (version 3.6.1; The R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). All *P*-values were two-sided, and $P < 0.05$ was considered significant.

Results

Patient characteristics

A total of 734 non-PAF patients (467 [64%], persistent AF; 267 [36%], long-standing AF) underwent initial PVI during the study period. Among them, 419 (57%) with AF underwent RF ablation and 315 (43%) underwent CB ablation. After performing propensity score matching, 257 pairs with RF (RF group) or CB (CB group) ablation were matched (Figure 1). Both groups were similar (Table 1). Further basal characteristics classification according to the AF type is shown in Supplementary Appendix (Table S1-S2).

Procedural results

Table 2 shows the procedural and complication occurrence characteristics. The non-PV triggers induction and additional ablation required were similar between the groups (RF: 41%, CB: 39%; $P = 0.653$). Of the induced non-PV triggers, the LA triggers were higher in the CB group ($P =$

0.073). Additionally, cavo-tricuspid isthmus ablation for common type atrial flutter was similar between the groups (RF: 16%, CB: 15%; $P = 0.902$; Table 2).

The total procedural (190 [160–224] min vs. 125 [89–165] min, $P < 0.001$) and radiation (73 [57–92] min vs. 38 [23–61] min, $P < 0.001$) times were significantly shorter in the CB group than in the RF group, with both groups reporting similar complication rates (RF: 4%, CB: 5%; $P = 0.670$). No deaths occurred during the procedure, with complete patient recovery post-CA during the follow-up period (Table 3).

Clinical outcomes

The median follow-up period was significantly shorter in the CB group than in the RF group (615 vs. 836 days; $P < 0.001$). Early recurrence within 3 months post-procedure was observed more frequently in the CB group than in the RF group (38% vs. 27%; $P = 0.011$). AT/AF recurrence at 1 year was similar between the groups (RF: 18%, CB: 22%; $P = 0.267$) and throughout the entire follow-up period (RF: 25%, CB: 31%: $P = 0.202$). The number of patients with repeat ablation post-AF recurrence was also similar between the groups (RF: 18%, CB: 20%, $P = 0.499$; Table 3).

The AF-free survival rate was similar between the groups (1-year Kaplan-Meier event rate, RF: 82.3% and CB: 77.9%; log-rank $P = 0.111$; Figure 2A). After classification into persistent and

long-standing AF based on AF duration, AF-free survival rates were similar (persistent AF, RF: 86.1%, CB: 80.7%; *P*=0.157; Figure 2B; long-standing persistent AF, RF: 74.4%; CB: 71.6%; *P*=0.354; Figure 2C, D). Seven patient (CB: 4, RF: 3; *P*=0.98) deaths during the entire follow-up period were unrelated to the procedure (Table 3).

Atrial arrhythmia recurrence predictors

The AT/AF recurrence predictor in univariate analysis was longer AF duration (*P*<0.001), and other factors such as enlarged LAD (*P*=0.068) or non-PV induction (*P*=0.061) showed no association. In contrast, age (*P*=0.246), sex (*P*=0.115), employment of CB (*P*=0.125), PVI plus LA posterior isolation (*P*=0.124), and $CHADS_2$ score (*P*=0.476) were not associated. In the Cox proportional hazard model, longer AF duration (hazard ratio [HR]: 1.01, 95% confidence interval [CI]: 1.00–1.02, $P < 0.001$) was an independent predictor of atrial arrhythmia recurrence among non-PAF patients post-CA (Supplementary Appendix, Table S7).

Discussion

To our knowledge, this is the first study that demonstrates comparable first-stage CA outcomes in non-PAF patients undergoing PVI with CB or RF ablation and additional non-PV triggers ablation. The post-procedure success rate was similar between the groups, with the appropriate patient selection and sample size. Our study substantiated the safety and efficacy of both

procedures, confirming our hypothesis. Recent studies reported the CB group procedural time to be shorter than the RF group procedural time.[4,18-21] The baseline LA size in this cohort was not relatively enlarged for non-PAF, compared with other recent studies.[10,20] The method of selecting PVI with CB or RF according to the LA size was reported, and CB ablation was recommended for AF patients without enlarged LA regarding the short procedure time and its efficacy. [13] Our study also indicated that the physician's preprocedural employment of CB or RF under heart anatomy guidance could be helpful to achieve the comparable success rates among the non-PAF patients without enlarged LA by remodeling. These CB data and strategy with a less operator-dependent technique variability and shorter procedure time contribute to making CB ablation for non-PAF patients possible at lower centers.

In our study, additional ablation for non-PV triggers was routinely performed, and induction of non-PV triggers was similar between the groups. Almost 40% of non-PAF patients experienced induced non-PV triggers, and additional non-PV ablation with RF was performed post-PVI using RF or CB ablation. The non-PV foci induction from the LA was higher in the CB group than in the RF group, which may be reflected by the potentially larger isolation area of the LA in RF ablation (PVI plus LA posterior isolation).[7] Generally, non-PV triggers were observed in 10–30% PAF patients and more often in non-PAF, female patients, or patients with low BMI.[6,16,27,28] The

non-PV trigger ablation efficacy has been reported.[5,6,29] This knowledge of the induced non-PV trigger frequency necessitates the CA strategy development for non-PAF patients beyond the PVI procedure. This study suggests two methods beyond PVI: a first-stage procedure with RF ablation or a time-saving procedure with CB ablation for PV and RF ablation for non-PV triggers. Recent reports on CB ablation strategies beyond PVI have expanded applications including LA PWI, SVC isolation, and LAA isolation, enabling us to perform the first-stage procedure.[22-26] Further studies are required after initial CA in non-PAF patients to assess differences in recurrence factors or electrophysiological findings of repeat ablation such as PV reconnection or other recurrent triggers between the groups.

In conclusion, the determining factors influencing recurrence when physicians perform the CA procedure for non-PAF patients is important. Among non-PAF patients, longer AF duration was an independent predictor of atrial arrhythmia recurrence, whereas the use of CB or RF ablation and PVI plus LA PWI was not. Sawhney et al. also reported longer AF duration and enlarged LAD as factors affecting recurrence in non-PAF patients undergoing CB ablation.[10]

The results of long-standing persistent AF patients are shown in the sub-analysis (Supplementary Appendix, Table S8-S10); post-procedure success rates were lower and induction of non-PV triggers was higher in long-standing persistent AF (>50% of long-standing persistent AF required

additional non-PV ablation, than those in persistent AF. These data could aid in CA performance guidance in patients with long-standing persistent AF. Further large-scale studies on CA in a similar patient population are required to establish and develop the strategy. This study had limitations. The exact AF duration could not be confirmed in any patient, although the AF types were classified. Some were presumed or registered with AF duration based on data from the latest medical check-up or those of the primary care physician. Continuous observational period monitoring was not performed, which could have caused us to miss arrhythmia recurrence possibly reflected in the relatively better success rates. Additionally, isolation areas between the RF and CB groups were potentially different. In most RF group patients, areas were isolated from a part of the LA posterior wall in addition to the PV, whereas those in the CB group were not.

The long-standing persistent AF duration between RF and CB ablation was significantly different, possibly reflected in the selection bias at the physician's discretion or restriction of CB usage for PAF at that time. The total fluoroscopy time was higher in the RF group than in the CB group, contrary to other reports.[4,11,21] This possibly reflects our hospital's tendency to depend on fluoroscopic guidance and insufficiency of three-dimensional mapping to assess the exact location of a catheter affected by respiratory fluctuation under deep sedation.

Conclusions

The combination strategy of PVI with CB or RF and non-PV triggers ablation achieved comparable outcomes in non-PAF patients. The non-PV triggers were observed in almost 40% of the non-PAF patients. The safety and efficacy of the combination strategy was demonstrated.

Acknowledgments

None.

References

1. Gareth J, Christian S, Janice S, et al. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation. Heart Rhythm 2017;14:801-807.
2. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on

clinical practice guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. Circulation 2019;140:e125-151.

3. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373-498.

4. Kuck KH, Brugada J, Fürnkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med 2016;374:2235-2245.

5. Liang J, Elafros M, Muser D, et al. Pulmonary vein antral isolation and nonpulmonary vein trigger ablation are sufficient to achieve favorable long-term outcomes including transformation to paroxysmal arrhythmias in patients with persistent and long-standing persistent atrial fibrillation. Circ Arrhythm Electrophysiol 2016;9:e004239.

6. Chang H, Lo L, Lin Y, et al. Long-term outcome of catheter ablation in patients with atrial fibrillation originating from nonpulmonary vein ectopy. J Cardiovasc Electrophysiol 2013;24:250-258.

7. Takamiya T, Nitta J, Inaba O, et al. One-year outcomes after pulmonary vein isolation plus posterior wall isolation and additional non-pulmonary vein trigger ablation for persistent atrial fibrillation with or without contact force sensing: A propensity score-matched comparison. J Interven Cardiac Electrophysiol 2020;59:585-593.

8. Boveda S, Providência R, Defaye P, et al. Outcomes after cryoballoon or radiofrequency ablation for persistent atrial fibrillation: a multicentric propensity-score matched study. J Interv Card Electrophysiol 2016;47:133-142.

9. Hoffmann E, Straube F, Wegscheider K, et al. Outcomes of cryoballoon or radiofrequency ablation in symptomatic paroxysmal or persistent atrial fibrillation. Europace 2019;21:1313-1324.

10. Sawhney V, Schilling RJ, Providencia R, et al. Cryoablation for persistent and longstanding persistent atrial fibrillation: results from a multicentre European registry. Europace 2020;22:375-381.

11. Gallagher MM, Yi G, Gonna H, et al. Multi-catheter cryotherapy compared with radiofrequency ablation in long-standing persistent atrial fibrillation: a randomized clinical trial. Europace 2020;euaa289.

12. Su WW, Reddy VY, Bhasin K, et al. Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: results from the multicenter STOP Persistent AF trial. Heart Rhythm 2020;17:1841-1847.

13. Ikenouchi T, Inaba O, Takamiya T, et al. The impact of left atrium size on selection of the pulmonary vein isolation method for atrial fibrillation: Cryoballoon or radiofrequency catheter ablation. Am Heart J 2021;231:82-92.

14. Inamura Y, Nitta J, Inaba O, et al. Differences in the electrophysiological findings of repeat ablation between patients who first underwent cryoballoon ablation and radiofrequency catheter ablation for paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2019;30:1792-1800.

15. Takamiya T, Nitta J, Sato A, et al. Pulmonary vein isolation plus left atrial posterior wall isolation and additional nonpulmonary vein trigger ablation using dose isoproterenol for longstanding persistent atrial fibrillation. J Arrhythmia 2019;35:215-222.

16. Kato N, Nitta J, Sato A, et al. Characteristics of the nonpulmonary vein foci induced after second-generation cryoballoon ablation for paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 2020;31:174-184.

17. Ikenouchi T, Nitta J, Nitta G, et al. Propensity-matched comparison of cryoballoon and radiofrequency ablation for atrial fi brillation in elderly patients. Heart Rhythm 2019;16:838-845.

18. Straube F, Dorwarth U, Ammar-Busch S, et al. First-line catheter ablation of paroxysmal atrial fibrillation: outcome of radiofrequency vs. cryoballoon pulmonary vein isolation. Europace 2016;18:368-375.

19. Ravi V, Poudyal A, Pulipati P, et al. A systematic review and meta-analysis comparing second-generation cryoballoon and contact force radiofrequency ablation for initial

ablation of paroxysmal and persistent atrial fibrillation. J Cardiovasc Electrophysiol 2020;31:2559-2571.

20. Tondo C, Iacopino S, Pieragnoli P, et al. Pulmonary vein isolation cryoablation for patients with persistent and long-standing persistent atrial fibrillation: Clinical outcomes from the real-world multicenter observational project. Heart Rhythm 2018;15:363-368.

21. Mörtsell D, Arbelo E, Dagres N, et al. Cryoballoon vs. radiofrequency ablation for atrial fibrillation: a study of outcome and safety based on the ESC-EHRA atrial fibrillation ablation long-term registry and the Swedish catheter ablation registry. Europace 2019;21:581-589.

22. Aryana A, Biase L, Pujara D, et al. Long-term durability of posterior wall isolation using the cryoballoon in patients with persistent atrial fibrillation: a multicenter analysis of repeat catheter ablations. J Interv Cardiac Electrophysiol 2020 Sep 30. doi: 10.1007/s10840-020-00887-8. [Online ahead of print]

23. Shigeta T, Okishige K, Nishimura T, et al. Clinical investigation of the durability of the lesions created by left atrial linear ablation with a cryoballoon. J Cardiovasc Electrophysiol 2020;31:875-884.

24. Nishimura T, Yamauchi Y, Aoyagi H, et al. The clinical impact of the left atrial posterior wall lesion formation by the cryoballoon application for persistent atrial fibrillation:

Feasibility and clinical implications. J Cardiovasc Electrophysiol 2019;30:805-814.

25. Aryana A, Baker J, Espinosa Ginic MA, et al. Posterior wall isolation using the cryoballoon in conjunction with pulmonary vein ablation is superior to pulmonary vein isolation alone in patients with persistent atrial fibrillation: A multicenter experience. Heart Rhythm 2018;15:1121-1129.

26. Rottner L, Fink T, Kuck KH. Cryoballoon ablation beyond paroxysmal atrial fibrillation. Curr Opin Cardiol 2019;34:23-28.

27. Takigawa M, Takahashi A, Kuwahara T, et al. Long-term outcome after catheter ablation of paroxysmal atrial fibrillation: impact of different atrial fibrillation foci. Int J Cardiol 2017;227:407-412.

28. Inamura Y, Nitta J, Inaba O, et al. Presence of non-pulmonary vein foci in patients with atrial fibrillation undergoing standard ablation of pulmonary vein isolation: Clinical characteristics and long-term ablation outcome. Int J Cardiol Heart Vasc 2021;32:100717.

29. Lin WS, Tai CT, Hsieh MH, et al. Catheter ablation of paroxysmal atrial fibrillation initiated by non-pulmonary vein ectopy. Circulation 2003;107:3176-3183.

Table 1 Baseline characteristics of patients after propensity score matching.

	RF (n=257)	CB (n=257)	*P*
Age (years)	63.3±9.9	63.4±10.3	0.906
Male sex	216 (84%)	206 (80%)	0.300
BMI (kg/m^2)	25.4±4.3	25.0±4.0	0.284
Persistent AF (<1 year)	174 (68%)	179 (70%)	0.704
Long-standing AF	83 (32%)	78 (30%)	0.704
Duration of AF (months)	6 (3–24)	6 (2–14)	0.159
HT	148 (58%)	145 (56%)	0.859
DM	44 (17%)	39 (15%)	0.632
CI	18 (7%)	17 (7%)	0.98
CHF	40 (16%)	41 (16%)	0.98
$CHADS_2$	1.12±0.96	1.11±1.04	0.895
$CHADS_2$-VASC	1.96±1.30	1.94±1.44	0.872
BNP level (pg/mL)	104 (6–179)	100 (58–180)	0.726
EF (%)	58.5±11.9	59.8±12.3	0.205
LAD (mm)	41.4±5.9	41.0±6.0	0.552
Cre level (mg/dl)	0.90 (0.78–1.03)	0.87 (0.78–1.00)	0.350

*Values are presented as mean±standard deviation or median (25th and 75th percentiles [%]).

[+]AF: atrial fibrillation, BMI: body mass index, BNP: brain natriuretic peptide, CB: cryoballoon, CHF: congestive heart failure, CI: cerebral infarction, Cre: creatinine, DM: diabetes mellitus, EF: ejection fraction, HT: hypertension, LAD: left atrial diameter, RF: radiofrequency.

Table 2 Characteristics of procedures and occurrence of complications.

	RF (n=257)	CB (n=257)	*P*
PVI complete	257 (100%)	257 (100%)	0.98
PV touch-up	-	35 (14%)	-
CTI	40 (16%)	38 (15%)	0.902
LA posterior isolation	246 (96%)	30 (12%)	-
Add non-PV ablation	105 (41%)	100 (39%)	0.653
SVC	45 (18%)	45 (18%)	0.98
RA	36 (14%)	31 (12%)	0.600
LA	28 (11%)	43 (17%)	0.073
IAS	35 (14%)	37 (14%)	0.899
Mitral isthmus	7 (3%)	4 (2%)	0.381
CFAE	18 (7%)	13 (5%)	0.362
Complication	10 (4%)	12 (5%)	0.67
Cardiac tamponade	3	2	0.98
Hematoma/fistula	0	1	0.98
Blood pneumothorax	0	0	0.98
Esophageal injury	2	0	0.411
Phrenic nerve injury	3	7	0.351
Cerebral vascular disease	2	2	0.98

Severe bleeding	0	1	0.98
Pulmonary vein stenosis	4	0	0.045
Death	0	0	0.98

*Values are presented as mean±standard deviation.

+CFAE: continuous fractionated atrial electrogram, CTI: cavotricuspid muscle, IAS: interatrial septum, LA: left atrium, PVI: pulmonary vein isolation, RA: right atrium, SVC: superior vena cava.

Table 3 Outcomes of procedures in non-PAF patients.

	RF (n=257)	CB (n=257)	*P*
Procedure time (min)	190 (160 –224)	125 (89–165)	<0.001
Radiation time (min)	73 (57–92)	38 (23–61)	<0.001
Early recurrence (<3 months)	65 (27%)	92 (38%)	0.011
Recurrence at 1 year	45 (18%)	56 (21.8)	0.267
Recurrence during the whole period	65 (25%)	78 (31%)	0.202
Perform 2nd session	45 (18%)	52 (20%)	0.499
Observational period (d)	836 (547–1127)	615 (403–1079)	<0.001
Death during the follow-up	3 (1.2%)	4 (1.6%)	0.98

*Values are presented as mean±standard deviation or median (25th and 75th percentiles [%]).

[+]CB: cryoballoon, PAF, paroxysmal atrial fibrillation, RF: radiofrequency.

Figure Legends

Figure 1 Study population and patient enrolment.

AF: atrial fibrillation, CB: cryoballoon, non-PAF: non-paroxysmal atrial fibrillation, PVI: pulmonary vein isolation, RF: radiofrequency ablation.

Figure 2 Kaplan-Meier curve analysis.

Kaplan-Meier AF/AT-free survival curves of patients maintaining sinus rhythm without AADs after the first procedure. A) RF and CB rates in non-PAF patients, and B) patients with persistent AF. Subgroup analyses of C) patients with long-standing persistent AF in the RF and CB groups and D) the AF types.

AADs: antiarrhythmic drugs, AF: atrial fibrillation, AT: atrial tachycardia, CB: cryoballoon, PAF: paroxysmal atrial fibrillation, RF: radiofrequency.